



FDA Adverse Event Reporting System (FAERS)

FOIA Case Report Information

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The FOIA case report information may include both Electronic Submissions (Esubs) and Report Images (Non-Esubs). Case ID(s) will be displayed under separate cover pages for the different submission types.

Cover page Case ID(s) with an asterisk (*) indicate an invalid status and are not captured in the body of the report.

Esub Case ID(s) Submitted:

17634805	17654740	17657617	17669369	17670483	17683901	17684186
17684845	17696939	17702433	17728918	17729811	17732903	17733286
17734738	17736244	17736889	17737377	17742574	17744530	17749423
17754876	17759164	17759274	17761274	17761778	17763817	17763825
17763830	17764633	17769300	17770111	17773731	17773868	17778290
17778672	17779081	17779155	17780019	17780160	17780331	17785405
17785409	17787108	17787203	17787343	17788916	17789436	17791424
17792471	17795162	17796109	17796734	17796912	17797597	17798009

Run by: STEPPERH

Date - Time: 12-NOV-2020 16:09 PM

Total number of cases (Esub): 207

Total number of inactive cases: 0

17798212	17798241	17798503	17798851	17799090	17800626	17805686
17807391	17807469	17808058	17808090	17808203	17808608	17809848
17809905	17810896	17811201	17811943	17811956	17812256	17813329
17814749	17814753	17815379	17815826	17816151	17816709	17816816
17816827	17817430	17819799	17819809	17820249	17820893	17820959
17820998	17821297	17822236	17822237	17822402	17822482	17823846
17824668	17826266	17826274	17826277	17826772	17829521	17834089
17834132	17835460	17835846	17840537	17840870	17845906	17848643
17849592	17851578	17852173	17852176	17865779	17867692	17868071
17868106	17868158	17868210	17868227	17868233	17869068	17870754
17871741	17872273	17872325	17872379	17872487	17875733	17876548
17876602	17877278	17877952	17878542	17883177	17883279	17883333
17883540	17883989	17884171	17884243	17884300	17885880	17886220
17887554	17888179	17888202	17888264	17888592	17888635	17889550
17890000	17890402	17890478	17893215	17894004	17894015	17894259
17894337	17896282	17896309	17900139	17901141	17907664	17907863
17912668	17913003	17914494	17917099	17917244	17917275	17920856

Run by: STEPPERH

Date - Time: 12-NOV-2020 16:09 PM

Total number of cases (Esub): 207

Total number of inactive cases: 0

17921018	17923666	17925339	17925741	17926239	17926454	17930403
17930404	17932524	17932932	17939291	17939900	17940899	17942818
17942975	17943117	17943910	17943996	17944026	17944035	17944049
17944529	17944967	17945414	17947493	17948725	17950145	17951119
17954076	17954786	17955137	17959552			

Run by: STEPPERH

Date - Time: 12-NOV-2020 16:09 PM

Total number of cases (Esub): 207

Total number of inactive cases: 0



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17634805

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 23-Mar-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 10-May-2020 Mfr Rcvd Date: 05-May-2020 Mfr Control #: IT-ROCHE-2575241 Application #: 125276

Patient Information:

Age: 73 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		8 MG/KG/Q12H	Intravenous (not otherwise specified)	Date of most recent dose of tocilizumab prior to onset of SAE: 23/Mar/2020	COVID-19 pneumonia	23-Mar-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	0 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC
 Respiratory failure NA

Event/Problem Narrative:

AER 2575241 is a clinical study case, received on 25/Mar/2020 from a physician in Italy. It concerns a 73 year old male patient (patient number: (b) (6)) who developed fatal respiratory failure whilst enrolled in (b) (6) (b) (6)

The patient's concurrent conditions included delirium, hypertension, hypernatremia and hyponutrition. Concomitant medication included morphine and enoxaparin. No medical history and past drugs were reported.

On 18/Mar/2020, the patient was in non-invasive ventilation. (b) (6) On (b) (6) despite the tocilizumab infusion, he experienced respiratory failure and the respiratory condition deteriorated until death. On (b) (6) he died due to respiratory failure. It was not reported if an autopsy was performed or not. The vital signs before treatment were: PA147/80mmHg, heart rate 120 bpm, body temperature 38.6 degree C. ECG was normal. Blood count revealed high WBC count. PCR was 43mg/l, D-dimer 10655 and IL-6 455pg/mL.



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The physician assessed the fatal respiratory failure as possibly related to tocilizumab.

The company assessed the causality of fatal respiratory failure as unrelated with tocilizumab considering the event is more related with underlying disease of COVID-19 pneumonia rather than suspect drug. Concurrent conditions of hypernatremia and hyponutrition can be additional confounding factors for the event.

No further information was provided.

Additional information received on 05/May/2020. The following information was added: The patient detail updated (birth date, age and sex), concurrent condition hypertension. new conmade morphine and enoxaparin, therapy start date of tocilizumab updated and event description updated (On 18/Mar/2020, the patient was non-invasive ventilation. The vital signs before treatment were: PA147/80mmHg, heart rate 120 bpm, body temperature 38.6 degree C. ECG was normal. Blood count revealed high WBC count. PCR was 43mg/l, D-dimer 10655 and IL-6 455pg/mL).

Relevant Medical History:

HYPONUTRITION

Disease/Surgical Procedure

Delirium

Hypernatraemia

Hypertension

Start Date

End Date

Continuing?

Medical History Product(s)

Start Date

End Date

Indications

Events

Relevant Laboratory Data:

Test Name

Result

Unit

Normal Low Range

Normal High Range

Info Avail



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FOIA Case Report Information

Case ID: 17634805

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ENOXAPARIN							
2	MORPHINE							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17654740

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ITA
Event Date: 12-Mar-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 13-May-2020
Mfr Rcvd Date: 07-May-2020
Mfr Control #: IT-ROCHE-2577032
Application #: 125276

Patient Information:

Age: 67 YR
Sex: Male
Weight: 96 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		768 MG/	Unknown		COVID-19	11-Mar-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	1 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Off label use	NA
Product use in unapproved indication	NA
Respiratory distress	NA

Event/Problem Narrative:

AER 2577032 is a spontaneous case, received on 30/Mar/2020 from a physician in Italy and concerns a 67 year old male patient who was intentionally treated with tocilizumab for an unapproved indication (off label use) and died due to worsening respiratory distress whilst being treated with tocilizumab.

The patient's concurrent conditions included parkinson's disease and hypertension. Past drug included kaletra, rocefin, linezolid and clexane. No concomitant medications and past history were reported.

On (b) (6) he received positive result for nasopharyngeal swab for COVID-19 diagnosis. He experienced the following symptoms related to the Covid-19 infection of fever, cough, PaO2/FiO2 was 171. He was hospitalized. On (b) (6) C-Reactive Protein (CRP) test 15.2 mg/dl. On (b) (6) (CRP) test results 14.4 mg/dl and interleukin-6 (IL-6) test was 49.5 pg/ml. On (b) (6) he was treated with one dose of tocilizumab 768 mg (8mg/kg, his weight 96 kgs) in 100 ml of physiological solution. On same day, he started therapy with tocilizumab



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FOIA Case Report Information

Case ID: 17654740

(lot number: unknown) , 768 mg (route and frequency not reported) used for covid-19 infection (for an unapproved indication: off label use). On (b) (6) he died (b) (6) of receiving tocilizumab for worsening of a pre-existing respiratory distress. He was affected by concomitant parkinson's disease and hypertension. It was unknown if an autopsy was performed or not. On same day (CRP) test results 9.1 mg/dl and IL-6 test was above 1000. The physician reported that there was not correlation between the fatal event and tocilizumab.

The physician report a causality of fatal event worsening respiratory distress as unrelated to tocilizumab.

No further information was provided.

This case is cross-referenced with AER 2566804 (same reporter).

AER 2577032 was identified as a duplicate of AER 2570860 and AER 2571121. All information from AER 2570860 and AER 2571121 were added to AER 2577032, which remains the active case.

Additional information was received on 07/May/2020.The following information was added to the case: Past drug (kaletra, rocefin, linezolid and clexane), reporter causality updated from (not reported to not related) and lab test (C-reactive protein (CRP) test, interleukin-6 (IL-6) test, PaO2/FiO2, nasopharyngeal swab, chest CT and chest X ray) was added. Event description updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension			
Parkinson's disease			

Medical History Product(s)	Start Date	End Date	Indications	Events
CLEXANE				
KALETRA	(b) (6)			
ROCEFEN	(b) (6)			
LINEZOLID	(b) (6)			



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FOIA Case Report Information

Case ID: 17654740

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
C-reactive protein					N
C-reactive protein					N
C-reactive protein					N
Computerised tomogram thorax	-				N
Chest X-ray					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17657617

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: PHL
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 04-May-2020
Mfr Rcvd Date: 24-Apr-2020
Mfr Control #: PH-ROCHE-2578150
Application #: 125276

Patient Information:

Age:
Sex: Female
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2578150 is a spontaneous case, received on 31/Mar/2020 from a physician in Philippines. It concerns a female patient (age not reported) who was intentional treated with tocilizumab for unlabeled indication (off label use) and died whilst being treated with tocilizumab (Actemra).

The patient's medical history, past drugs, concurrent conditions and concomitant medications were not reported.

On an unknown date, the patient started therapy with tocilizumab (dosage regimen and lot number not reported) for covid-19 (off label use). The patient died on an unknown date. It was not reported if an autopsy was performed or not.

At the time of report, the therapy ongoing status with tocilizumab was not reported.

The physician did not report a causality between death and tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17657617

No further information was provided.

Additional information was received on 24/Apr/2020. Following information was added in the case: Query reply received. All available information has been provided and there is no consent for further follow up.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17657617

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17669369

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: PHL Event Date: Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 06-May-2020 Mfr Rcvd Date: 24-Apr-2020 Mfr Control #: PH-ROCHE-2579746 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Off label use	NA

Event/Problem Narrative:

AER 2579746 is a spontaneous case, received on 04/Apr/2020 from a physician in Philippines. It concerns a patient of unknown demographics who died and used tocilizumab (Actemra)for off-label use.

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On an unknown date, the patient started therapy with tocilizumab (lot number: unknown and therapy details not reported) for COVID-19 infection (intentional use for unlabeled indication; off label use). On an unknown date, the patient was died. The cause of death was not reported. It was unknown if an autopsy was performed or not. On 24/Apr/2020, it was reported that, all available information has been provided and there was no consent for further follow up.

The physician did not report a causality between death and tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17669369

No further information was provided.

Additional information was received on 24/Apr/2020. The following information was added to the case: Event description updated (On 24/Apr/2020, it was reported that it was reported that, all available information has been provided and there was no consent for further follow up).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17669369

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17670483

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 03-Apr-2020
Outcomes: DE,LT,
Application Type: BLA
FDA Rcvd Date: 06-Aug-2020
Mfr Rcvd Date: 31-Jul-2020
Mfr Control #: US-SA-2020SA095091
Application #: 761037

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	400 mg, 1X	COVID-19	31-Mar-2020	31-Mar-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	11164 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Alanine aminotransferase increased	NA
Alanine aminotransferase increased	NA
Aspartate aminotransferase increased	NA
COVID-19	NA
Multiple organ dysfunction syndrome	NA



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FOIA Case Report Information

Case ID: 17670483

Event/Problem Narrative:

Initial information received on 06-Apr-2020 and 08-Apr-2020 regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference number 2020-28919 on 06-Apr-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6)

Patient ID: (b) (6) Site: (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

A 59-year-old, male patient, of unreported ethnicity, with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6) The patient experienced (Multi-organ failure related to COVID-19 (Multiple organ dysfunction syndrome): Life threatening; Severity: Grade 4; Outcome: Not Recovered/Not Resolved; Event resolved on: Unknown) on (b) (6) and (Death due to COVID-19 (COVID-19): Death; Severity: Grade 5; Outcome: Fatal; Event resolved on: (b) (6)) on (b) (6) (Elevated ALT (Alanine aminotransferase increased): Life-threatening; Serious AESI (ALT or AST increase); Severity: Grade 4; Outcome: Not Recovered/Not Resolved; Event resolved on: Ongoing) and (Elevated AST [Aspartate aminotransferase increased]: Life-threatening; Serious AESI (ALT or AST increase); Severity: Grade 4; Outcome: Not Recovered/Not Resolved; Event resolved on: Ongoing) on (b) (6) and (Elevated ALT (Alanine aminotransferase increased): Non-serious AESI (ALT or AST increase); Severity: Grade 2; Outcome: Recovered/resolved; Event resolved on: (b) (6)) on (b) (6) after receiving study drug.

No relevant medical history was reported.

Concomitant medications reported included hydroxychloroquine and azithromycin.

On 20-Mar-2020, the patient started experiencing earliest symptoms of pneumonia, evidence of which was present based on subsequently performed chest X-ray or computerized tomography (CT) scan. On (b) (6) limited chest X-ray exam showed possible early infiltrates, and the patient was admitted to hospital. Electrocardiogram (ECG) performed showed presence of sinus tachycardia.

On (b) (6) baseline lung auscultation and rales/crackles were present. The patient had fever, with the highest temperature recorded within 24 hours prior to dosing of 102.2 degrees Fahrenheit (F), measured orally. SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test was performed from the nasopharyngeal swab, and patients SARS-CoV-2 Virus result was positive. The patient was using supplemental oxygen by non-rebreather face mask, and his peripheral capillary oxygen saturation (SpO2) was 97%. Patient vital signs reported for blood pressure (BP) was 116/72 mmHg, pulse rate was 106 beats per minute (bpm), respiratory rate was 19 respirations per minute (rpm), highest temperature measured during the day 96.6 F, and the patient was alert. Patients blood chemistry test results reported for alanine aminotransferase (ALT) was 44 U/L (reference range: 1-45), aspartate aminotransferase (AST) was 83 U/L (reference range: 1-40), lactate dehydrogenase (LDH) was 402 U/L (reference range: 60-200), total bilirubin was 0.6 mg/dl (reference range: 0.1-1.2).

Haematology results reported for platelets was 239/uL (reference range 150-400), white blood cells (WBC) count was 11.69/nL (reference range 3.9-10.6), and neutrophils (absolute) was 10.13/nl (reference range: 1.9-8.7). On (b) (6) patients SpO2 decreased to 90%, blood pressure increased to 148/85, pulse rate was 92 and highest temperature measured was 98.1. Patients ALT increased to 82, AST decreased



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to 41, WBC to 8.34, and neutrophils to 7.08.

On (b) (6) patients ALT was 112 and AST 71.

On (b) (6) patients WBC increased to 13.13 and neutrophils to 11.31. On the same day, increased levels of ALT and AST were detected. On the same day, 2 days 7 hrs 10 min after the administration of the investigational product ALT level was 196 and AST 127. Patients SpO2 was 90%, blood pressure to 144/88, temperature 99.3, pulse rate was 106 and respiratory rate 22. No corrective treatment was applied in response to the events.

On (b) (6) ALT decreased to 181 and AST to 78, and the event of increased AST was deemed resolved. Patients SpO2 was 91%, blood pressure to 133/82, temperature was 98.3, pulse rate was 93, and respiratory rate 20.

On (b) (6) patients SpO2 decreased to 87%, blood pressure to 109/79, temperature was 99.2, pulse rate was 98 and respiratory rate 20. ALT further decreased to 142, and AST to 55 and the event of elevated ALT was deemed resolved.

On (b) (6) ALT was 130 and AST 51. Blood and urine infection testing was performed, and the results were negative.

On (b) (6) the patient was intubated, and his SpO2 was 85%, with the invasive mechanical ventilation. Patients blood pressure increased to 131/87, temperature was 97.7, pulse to 127 and respiratory rate 20. ALT was 132 U/L, and AST increased to 79 U/L. At 16:28, arterial blood gas (ABG) test was performed, and the results were: pH 7.48, partial pressure of carbon dioxide (PaCO2) 39.2 mmHg, arterial partial pressure of oxygen (PaO2) 40.9 mmHg, and arterial oxygen saturation (SaO2) 80.1%. By 20:21, pH decreased to 7.24, and PaCO2 increased to 79.9. The patient experienced shock and started receiving norepinephrine, vasopressin and epinephrine at unspecified doses, intravenously.

On (b) (6) patients SpO2 increased to 100%, and respiratory rate to 25. Blood pressure decreased to 92/64, pulse rate to 126, and temperature 97.8. Repeated chest X-ray showed bilateral infiltrates, greater in left lung than the right, especially seen in the periphery. At 10:54, 7 days 18 hrs 4 min after the administration of the investigational product elevated levels of AST and ALT were detected again. ALT increased to as much as 2545 and AST to 2372. No corrective treatment was applied in response to the events. Patients condition deteriorated, and 7 days 7 hrs 10 min after the administration of the investigational product he was experiencing multi-organ failure secondary to COVID- 19, for which unspecified medication/therapy was applied. At 18:55, pH was 7.01, PaCO2 79.1 mmHg, PaO2 53.5 mmHg, and SaO2 69.6%. Echocardiogram was performed.

On (b) (6) patients SpO2 was 96%, blood pressure 123/69, pulse 105, respiratory rate 30 and temperature 99.7. Both ALT and AST were 7000, LDH 1800 and total bilirubin 1.6.

On (b) (6) patients SpO2 was 93%, blood pressure 124/75, pulse decreased to 94, temperature 97.5, respiratory rate 30 and the patient was unresponsive. Both ALT and AST were >7000 and LDH was >1800.

On (b) (6) patients SpO2 was 95%, blood pressure 154/53, respiratory rate 22, temperature 98 and pulse again increased to 123. ALT remained >7000, but AST decreased to 2890.

On (b) (6) patients SpO2 decreased to 95%, blood pressure to 91/42, pulse to 56, respiratory rate was 26 and temperature increased to 101.6, measured both axillary and orally. Patients ALT was 4859 and AST 3146. Platelet count decreased to 21, WBC count increased to 18.01 and neutrophil absolute count increased to 14.64. At 09:34, (b) (6) days 16 hrs 44 min after the administration of the investigational product, the patient died due to COVID-19. Autopsy was not performed.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

On 30-Jul-2020, the event Elevated AST was downgraded from non-serious AESI to non-serious non-AESI and inactivated, as there were no



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reports for the patient.

Action taken with study drug in response to the events was not applicable.

Causality assessment is as follows: (b) (6)

Death due to COVID-19 Investigator Causality = Not Related; Company Causality = Not Related Investigator causality rationale: COVID-19.

Multiple organ dysfunction syndrome: Investigator Causality = Not Related; Company Causality = Not Related Investigator causality rationale:

Complications of COVID-19.

Company causality rationale: A 59-year-old male patient with severe or critical COVID-19 experienced multi-organ failure secondary to COVID-19 and subsequent death (b) (6) days after receiving the study drug. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug is cause for both events which are, therefore, assessed as unrelated to the study drug or to any clinical trial procedure.

Aspartate aminotransferase increased (b) (6): Investigator Causality = Not Related; Company Causality = Related Investigator causality rationale: Due to COVID-19.

Alanine aminotransferase increased (b) (6): Investigator Causality = Not Related; Company Causality = Related

Investigator causality rationale: COVID-19.

Alanine aminotransferase increased (b) (6): Investigator Causality = Related; Company Causality = Related

Investigator causality rationale: The timing of the ALT elevation suggests relatedness with the study investigational product (IP).

Company causality rationale: A 59-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced two episodes of elevated ALT and elevated AST. Confounding factor for all three events is concomitant use of azithromycin and hydroxychloroquine. Based on a plausible temporal association between study drug administration and the reported events and known potential effect of study drug on functional liver enzymes, causality for all four events is assessed as related to study drug and not related to any clinical trial procedure. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 09-Apr-2020 and 12-Apr-2020 (processed together) The Investigator provided the following updates: events added (elevated AST, elevated ALT (b) (6)), multi-organ failure related to COVID-19, death due to COVID-19, clinical course and concomitant medication updated.

Follow up: 29-May-2020 and 03-Jun-2020 The Investigator provided the following updates: fatal event re-coded to correct preferred term (COVID-19), concomitant medications, lab data, and clinical course updated.

Follow up: 13-Jun-2020 The Investigator provided the following updates: seriousness criteria, outcome of event Multi-organ failure related to COVID-19 updated.

Correction on 31-Jul-2020: The following was corrected based on internal review - Severity of the event Elevated ALT (onset: (b) (6)).

Follow up: 30-Jul-2020 The Investigator provided the following updates: event Elevated AST (onset (b) (6)) was downgraded and clinical course updated.

Relevant Medical History:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17670483

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension	2014	(b) (6)	NO
Intubation			
Shock			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	112	U/L	1	45	N
Blood pH	7.48	UNK			Y
Diastolic blood pressure	87	mmHg			N
Systolic blood pressure	124	mmHg			N
Body temperature	97.7	degF			Y
Body temperature	101.6	degF			Y
Chest X-ray					Y
Pulse rate	92	beats/min			N
Pulse rate	106	beats/min			N
Oxygen saturation	85	%			N
White blood cell count	11.69	10 ⁹ /L	3.9	10.6	N
Alanine aminotransferase	82	U/L	1	45	N
Alanine aminotransferase	132	U/L	1	45	N
Aspartate aminotransferase	127	U/L	1	40	N
Aspartate aminotransferase	55	U/L	1	40	N
Auscultation					Y
Creatine phosphokinase	130	UNK			Y
Systolic blood pressure	154	mmHg			N
Systolic blood pressure	91	mmHg			N
Pulse rate	98	beats/min			N
Neutrophil count	7.08	10 ⁹ /L	1.9	8.7	N
Oxygen saturation	87	%			N
Oxygen saturation	93	%			N
pH	7.01	UNK			Y
PaO2	53.5	mmHg			N
Respiratory rate	26	breaths/min			N
White blood cell count	8.34	10 ⁹ /L	3.9	10.6	N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17670483

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	181	U/L	1	45	N
Lactate dehydrogenase	1800	U/L	60	200	N
Diastolic blood pressure	53	mmHg			N
Systolic blood pressure	109	mmHg			N
Systolic blood pressure	131	mmHg			N
Systolic blood pressure	92	mmHg			N
Body temperature	99.3	degF			Y
Pulse rate	126	beats/min			N
Oxygen saturation	90	%			N
Oxygen saturation	69.6	%			Y
Respiratory rate	19	breaths/min			N
Respiratory rate	22	breaths/min			N
White blood cell count	18.01	10 ⁹ /L	3.9	10.6	N
Alanine aminotransferase	44	U/L	1	45	N
Alanine aminotransferase	130	U/L	1	45	N
Alanine aminotransferase			1	45	Y
Alanine aminotransferase			1	45	Y
Aspartate aminotransferase	71	U/L	1	40	N
Aspartate aminotransferase	2372	U/L	1	40	N
Aspartate aminotransferase	2890	U/L	1	40	N
Diastolic blood pressure	69	mmHg			N
Blood test					N
Body temperature	98.1	degF			Y
Body temperature	99.7	degF			Y
Pulse rate	106	beats/min			N
Pulse rate	123	beats/min			N
Neutrophil count	10.13	10 ⁹ /L	1.9	8.7	N
Neutrophil count	14.64	10 ⁹ /L	1.9	8.7	N
Oxygen saturation	91	%			N
Platelet count	239	10 ⁹ /L	150	400	N
Respiratory rate	30	breaths/min			N
Alanine aminotransferase	7000	U/L	1	45	N
Aspartate aminotransferase	78	U/L	1	40	N
Aspartate aminotransferase	3146	U/L	1	40	N
Bilirubin	1.6	mg/dL	0.1	1.2	N
Blood pH	7.24	UNK			Y
Blood pH	7.01	UNK			Y



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17670483

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Diastolic blood pressure	88	mmHg			N
Body temperature	96.6	degF			Y
Body temperature	99.2	degF			Y
Body temperature	97.8	degF			Y
Body temperature	97.5	degF			Y
Pulse rate	127	beats/min			N
Pulse rate	105	beats/min			N
Pulse rate	94	beats/min			N
Oxygen saturation	100	%			N
Oxygen saturation	95	%			N
PCO2	39.2	mmHg			Y
pH	7.24	UNK			Y
Urine analysis					N
Alanine aminotransferase	142	U/L	1	45	N
Alanine aminotransferase	4859	U/L	1	45	N
Aspartate aminotransferase	41	U/L	1	40	N
Diastolic blood pressure	64	mmHg			N
Diastolic blood pressure	42	mmHg			N
Systolic blood pressure	133	mmHg			N
Systolic blood pressure	123	mmHg			N
Chest X-ray					Y
CT scan					Y
Oxygen saturation	90	%			N
Respiratory rate	20	breaths/min			N
Alanine aminotransferase	196	U/L	1	45	N
Aspartate aminotransferase	51	U/L	1	40	N
Aspartate aminotransferase	79	U/L	1	40	N
Aspartate aminotransferase		1		40	Y
Bilirubin	0.6	mg/dL	0.1	1.2	N
Lactate dehydrogenase	402	U/L	60	200	N
Lactate dehydrogenase		60		200	Y
Diastolic blood pressure	72	mmHg			N
Diastolic blood pressure	79	mmHg			N
Systolic blood pressure	116	mmHg			N
Systolic blood pressure	144	mmHg			N
ECG					Y
Oxygen saturation	96	%			N
Oxygen saturation	95	%			N
pH	7.48	UNK			Y



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17670483

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Platelet count	21	10 ⁹ /L	150	400	N
PaO2	40.9	mmHg			N
Respiratory rate	22	breaths/min			N
SARS-CoV-2 test					Y
Alanine aminotransferase	2545	U/L	1	45	N
Aspartate aminotransferase	83	U/L	1	40	N
Aspartate aminotransferase	7000	U/L	1	40	N
Diastolic blood pressure	85	mmHg			N
Diastolic blood pressure	82	mmHg			N
Diastolic blood pressure	75	mmHg			N
Systolic blood pressure	148	mmHg			N
Body temperature	98.3	degF			Y
Body temperature	98	degF			Y
Chest X-ray					Y
Pulse rate	93	beats/min			N
Pulse rate	56	beats/min			N
Neutrophil count	11.31	10 ⁹ /L	1.9	8.7	N
Oxygen saturation	97	%			N
Oxygen saturation	80.1	%			Y
PCO2	79.9	mmHg			Y
PCO2	79.1	mmHg			Y
Respiratory rate	20	breaths/min			N
Respiratory rate	20	breaths/min			N
Respiratory rate	25	breaths/min			N
Respiratory rate	30	breaths/min			N
White blood cell count	11.96	10 ⁹ /L	3.9	10.6	N
White blood cell count	13.13	10 ⁹ /L	3.9	10.6	N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ADENOSINE	6 MG/1X	Intravenous (not otherwise specified)	6 mg, 1X		07-Apr-2020	07-Apr-2020	7774 MIN



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17670483

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
2	ADENOSINE	6 MG/1X	Intravenous (not otherwise specified)	12 mg, 1X	Arrhythmia	07-Apr-2020	07-Apr-2020	7774 MIN
3	AMIODARONE	.5 MG/	Intravenous (not otherwise specified)	0.5 mg, continous infusion	Arrhythmia	08-Apr-2020	09-Apr-2020	6334 MIN
4	AMIODARONE	400 MG/Q12H	Oral	400 mg, q12h		09-Apr-2020	12-Apr-2020	6334 MIN
5	AZITHROMYCIN	500 MG/QD	Oral	500 mg, qd	COVID-19	30-Mar-2020	30-Mar-2020	19294 MIN
6	AZITHROMYCIN	250 MG/QD	Oral	250 mg, qd		31-Mar-2020	03-Apr-2020	19294 MIN
7	CARDIZEM [DILTIAZEM]	15 MG/1X	Intravenous (not otherwise specified)	15 mg, 1X	Arrhythmia	07-Apr-2020	07-Apr-2020	7774 MIN
8	CEFTRIAXONE				Leukocytosis			9214 MIN
9	CEFTRIAXONE	1000 MG/QD	Intravenous (not otherwise specified)	1000 mg, qd	Bacterial pneumonia, unspecified	06-Apr-2020	06-Apr-2020	9214 MIN
10	EPINEPHRINE	.5 MG/1X	Intravenous (not otherwise specified)	0.5 mg, 1X	Shock	07-Apr-2020	07-Apr-2020	5 DAY
11	FENTANYL	250 UG/	Intravenous (not otherwise specified)	250 ug, continous infusion	Sedation	07-Apr-2020	12-Apr-2020	5 DAY
12	HYDROXYCHLOROQUIN E	400 MG/Q12H	Oral	400 mg, q12h	COVID-19	29-Mar-2020	03-Apr-2020	20734 MIN
13	METHYLPREDNISOLON E	40 MG/Q12H	Intravenous (not otherwise specified)	40 mg, Q12H	Pneumonia	08-Apr-2020	11-Apr-2020	6334 MIN
14	MIDAZOLAM		Intravenous (not otherwise specified)	2 mg/mL, continuous infusion	Sedation	07-Apr-2020	12-Apr-2020	5 DAY
15	NOREPINEPHRINE		Intravenous (not otherwise specified)	1-30 mcg/min, continuous infusion	Shock	07-Apr-2020	12-Apr-2020	5 DAY
16	VASOPRESSIN		Intravenous (not otherwise specified)	0.04 units/min, continuous infusion	Shock	07-Apr-2020	12-Apr-2020	5 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17670483

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17683901

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 08-Apr-2020 Outcomes: DE,OT, Application Type: BLA
 FDA Rcvd Date: 12-Jun-2020 Mfr Rcvd Date: 04-Jun-2020 Mfr Control #:US-SA-2020SA100547 Application #: 761037

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	REGN mAb1 400 mg	COVID-19	02-Apr-2020	02-Apr-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	8578 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC
 Acute respiratory distress syndrome NA
 Bacteraemia NA

Event/Problem Narrative:

Initial information from the Company sponsored study (b) (6) was received on 13-Apr-2020.
 Patient ID: (b) (6) Site: (b) (6) Country: United States.

Study title: (b) (6)
 (b) (6)

A 74-year-old, Caucasian, male patient with severe or critical COVID-19 was enrolled in study (b) (6)
 (b) (6)

(u) (b) (b) (6) The patient experienced serious AESI (adverse event of special interest), namely, bacteremia on (b) (6) and SAE (serious adverse event), namely, ARDS (acute respiratory distress syndrome) on (b) (6) after receiving study drug.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17683901

Relevant medical history included pneumonia and acute hypoxic respiratory failure
No relevant concomitant medications were reported.

On 20-Mar-2020, the patient experienced earliest symptoms of pneumonia.

On 27-Mar-2020, chest X-ray was performed without results available. Electrocardiogram was normal.

On 28-Mar-2020, SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test was performed from the nasopharyngeal swab, and the patient was SARS-CoV-2 Virus positive. Electrocardiogram was normal.

On 30-Mar-2020 chest X-ray was performed without results available.

On 31-Mar-2020 blood pressure was 115/61 mmHg, heart rate was 61 bpm (beats per minute) and respiratory rate 20 rpm (respirations per minute).

On (b) (6) the patient was admitted to intensive care unit (ICU). Patient was placed on invasive ventilation and use of vasopressors. Oxygen saturation SpO₂ was 96% with oxygen flow rate set to 100%. Chest X-ray was performed without results available.

On (b) (6) vitals had the following values: oxygen saturation SpO₂ was 89%, blood pressure was 100/63 mmHg, pulse was 49 bpm (beats/min), respiratory rate 18 rpm (respirations/min) and body temperature was 36.5°C. Laboratory test had following results: Alanine Aminotransferase (ALT) 38 U/L (12-59), Aspartate Aminotransferase (AST) 67 U/L (15-37), and total bilirubin was 0.7 (mg/dL (0-1.1)). Results of the haematology tests were white blood cells count (WBC) 6.78/nL (4.5-11), neutrophils (absolute) 5.64/nL (2-6.6) while the platelets count was 166/nL.

On (b) (6) SpO₂ varied from 83% to 99% until (b) (6) WBC and neutrophils increased to 13.32 and 11.98, respectively.

On (b) (6) and 05-Apr-2020 chest X rays were performed however no results were provided.

On (b) (6) ALT elevated to 113 and AST to 96.

On (b) (6) (b) (6) days 22 hrs 58 min after the first dose of IP, patient's blood was positive for Gram positive cocci and the patient was diagnosed with bacteraemia (grade 2). This event was assessed medically significant and serious AESI. Source was central line. WBC was 10.85 and neutrophils 9.30.

On (b) (6) the patient started receiving vancomycin at a dose of 1000 mg, two times per day, intravenously, as corrective treatment for bacteraemia. Central line was removed and new one placed. WBC was 11.45 and neutrophils 9.07. Temperature was 99.1.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17683901

On (b) (6) WBC was 13.04 and neutrophils were 11.66. Partial pressure of oxygen (PaO₂) dropped (from 184 mmHg on (b) (6)) to 66 mmHg and temperature 106.6.

On (b) (6) the patient received vancomycin at dose of 1250 mg, every 12 hours, IV (b) (6) days 12 hrs 25 min days after the first dose of IP, the patient experienced acute respiratory distress syndrome (grade 5) and started to deteriorate. Patient's blood oxygen level was significantly low despite maximal therapy and intubation was required. The patient was started on Levophen max dose, added vasopressin and bolus of normal saline. Body temperature was 104. The patient lost pulse and received cardiopulmonary resuscitation (CPR) and advanced cardiac life support (ACLS), but could not be revived. The patient died on (b) (6). The cause of death was reported as ARDS. Autopsy was not performed.

The outcome was not recovered for the event of bacteremia and fatal for ARDS at the time of this report.

Action taken with study drug in response to the events was not applicable.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

Causality assessment is as follows:

For acute respiratory distress syndrome:

Relationship with IP according to investigator: No reasonable possibility

Investigator causality rationale: No alternative explanation.

Relationship with IP according to company: Not reportable.

Company causality rationale: A 74-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced acute respiratory distress syndrome which ended fatally, nine days after receiving the study drug. The event is assessed as not related to study drug or any clinical trial procedure since it is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and comorbidities such as pneumonia and acute hypoxic respiratory failure.

For bacteremia:

Relationship with IP according to investigator: Related

Investigator causality rationale: Related due to known risk of secondary infections with Anti-IL6 treatment. No other suspected causes.

Relationship with IP according to company: Reportable.

Company causality rationale: A 74-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced bacteraemia, (b) (6) days after receiving study drug. Patient's baseline WBC and neutrophil values were within reference ranges, however, they've further increased following study drug administration. Based on a plausible temporal association between study drug administration and the reported event and a known fact that higher rate of bacterial infections was observed in patients treated with sarilumab, especially opportunistic infections in already compromised patients, causality for the event assessed as related to study drug. The event is not related to any clinical trial procedure.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17683901

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 18-May-2020

The Investigator provided following updates: Event term (for event Bacteremia) updated, concomitant medications, cause of death and clinical course updated.

Follow up: 27-May-2020 and 29-May-2020 (processed together)

The Investigator provided the following updates: event outcome, seriousness criteria and cause of death updated.

Follow up: 04-Jun-2020 and 05-Jun-2020 (processed together)

The Investigator provided the following updates: outcome for the event Bacteremia updated, clinical course and time for ARDS updated

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Myocardial infarction	(b) (6)	(b) (6)	NO	
Melanoma	12-Feb-2019		YES	
Leukopenia	27-Mar-2020		YES	
Pneumonia	27-Mar-2020		YES	
Respiratory failure	27-Mar-2020		YES	
Thrombocytopenia	27-Mar-2020		YES	
Hypercholesterolemia			YES	
Hypertension			YES	
Obesity			YES	
Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17683901

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Chest X-ray					Y
Oxygen saturation	96	%			N
White blood cell count	13.04	cells/uL	4.5	11	Y
Alanine aminotransferase	113	U/L	12	59	Y
Aspartate aminotransferase	67	U/L	15	37	Y
Aspartate aminotransferase	96	U/L	15	37	Y
Systolic blood pressure	115	mmHg			N
Chest X-ray					Y
PaO2	66	mmHg			N
Body temperature	36.5	Cel			Y
Chest X-ray					Y
Chest X-ray					Y
Electrocardiogram					Y
Heart rate	68	beats/min			N
Body temperature	106.6	degF			Y
Bilirubin total	0.7	mg/dL	0	1.1	Y
Systolic blood pressure	100	mmHg			N
PaO2	184	mmHg			N
Alanine aminotransferase	38	U/L	12	59	Y
Chest X-ray					Y
Heart rate	49	beats/min			N
Absolute neutrophil count	11.98	cells/nL	2	6.6	Y
Coronavirus test positive					Y
Absolute neutrophil count	5.64	/nL	2	6.6	Y
Diastolic blood pressure	61	mmHg			N
Chest X-ray					Y
Respiratory rate	20	breaths/min			N
White blood cell count	6.78	cells/uL	4.5	11	Y
White blood cell count			4.5	11	Y
Body temperature	104	degF			Y
Diastolic blood pressure	63	mmHg			N
Chest X-ray					Y
Absolute neutrophil count	11.66	cells/nL	2	6.6	Y
Oxygen saturation	89	%			N
Platelet count	166	cells/nL	150	450	Y
Respiratory rate	18	breaths/min			N
White blood cell count	13.32	cells/uL	4.5	11	Y



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17683901

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN				Fever			12 DAY
2	ACETAMINOPHEN	650 MG/	Oral	650 mg, PRN	Fever	27-Mar-2020	11-Apr-2020	12 DAY
3	ASPIRIN 81	81 MG/QD	Oral	81 mg, QD	Cardiac disorder prophylaxis			
4	AZITHROMYCIN	500 MG/QD		500 mg, QD	Ant biotic therapy	27-Mar-2020	27-Mar-2020	17913 MIN
5	AZITHROMYCIN	250 MG/QD		250 mg, QD		28-Mar-2020	31-Mar-2020	17913 MIN
6	ENOXAPARIN	40 MG/QD		40 mg, QD		28-Mar-2020	11-Apr-2020	16473 MIN
7	ENOXAPARIN				DVT			16473 MIN
8	HYDROXYCHLOROQUIN E	200 MG/Q12H	Oral	200 mg, BID	Malaria	30-Mar-2020	03-Apr-2020	9 DAY
9	HYDROXYCHLOROQUIN E	400 MG/Q12H		400 mg, bid	COVID-19	29-Mar-2020	30-Mar-2020	9 DAY
10	HYDROXYCHLOROQUIN E	40 MG/Q12H		40 mg, BID		01-Apr-2020	05-Apr-2020	9 DAY
11	LEVOPHED		Intravenous (not otherwise specified)	2-50 mcg/min, CONT	Supportive care	01-Apr-2020		7 DAY
12	METHYLPREDNISOLON E	40 MG/Q12H		40 mg, BID	Steroid therapy	01-Apr-2020	05-Apr-2020	10713 MIN
13	METHYLPREDNISOLON E	20 MG/Q12H		20 mg, BID		05-Apr-2020	10-Apr-2020	10713 MIN
14	SOLU-MEDROL	Q12H	Intravenous (not otherwise specified)	20 to 40 mg, Q12H		01-Apr-2020		7 DAY
15	SOLU-MEDROL	125 MG/Q12H		125 mg, bid	COVID-19	31-Mar-2020	31-Mar-2020	7 DAY

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17684186

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 12-Apr-2020 Outcomes: DE,HO, Application Type: BLA

FDA Rcvd Date: 12-Nov-2020 Mfr Rcvd Date: 30-Oct-2020 Mfr Control #:US-SA-2020SA100314 Application #: 761037

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	200 mg, single	COVID-19	08-Apr-2020	08-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	103 Hour	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC

Cardio-respiratory arrest NA

Liver function test abnormal NA

Event/Problem Narrative:

Initial information received on 13-Apr-2020 regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference number 2020-31844 on 13-Apr-2020 and transmitted to Sanofi, in the scope of company sponsored study ^{(b) (6)}

Patient ID: ^{(b) (6)} Site: ^{(b) (6)} Country: United States.

Study title: ^{(b) (6)}
^{(b) (6)}

A 72-year-old, Black, male patient with severe or critical COVID-19 was enrolled in study ^{(b) (6)}
^{(b) (6)}

^{(u) (b)}
^{(b) (6)} The patient experienced Cardiopulmonary arrest due to hypoxia [Cardio-respiratory arrest] (initially reported



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17684186

as Cardiopulmonary arrest): Death; Onset: (b) (6) Severity: Grade 5; Outcome: Fatal on: (b) (6) Abnormal LFT'S [Liver function test abnormal]: Hospitalization; Serious AESI (ALT or AST increase); Onset date: (b) (6) Severity: Grade 4; Outcome: Not recovered / Not Resolved; Event resolved on: Ongoing, after receiving study drug.

Relevant medical history included hypertension.

Relevant concomitant medications include anakinra, acetylsalicylic acid, azithromycin, methylprednisolone, ceftriaxone and hydroxychloroquine.

On (b) (6) the patient experienced earliest symptoms of pneumonia without rales/crackles on lung auscultation present. The highest temperature that was recorded within 24 hours prior to dosing was 97.8 F (Fahrenheit), measured axillary. On the same date, the patient was admitted to intensive care unit and received oxygen supplementation therapy with non-rebreather mask.

On (b) (6) nasopharyngeal swab was taken for SARS-CoV-2 Virus test, and the patient was positive. Chest X-ray scans included streaky bilateral airspace opacities consistent with COVID 19 infection.

On (b) (6) the patients vital parameters were measured: SpO2 98%; blood pressure 148/87 mmHg; pulse 99 beats per minute (bpm); respiratory rate 24 respirations per minute (rpm); temperature 97.6 F (Fahrenheit), measured axillary, and the patient was confused. The following laboratory results were reported: urea 158 and creatinine 5.5 mg/dL (reference range 0.5-1.3). The following haematology tests were provided: platelets 277×10^9 (reference range 150- 400), and white blood cells (WBC) 20.99 K/uL (3.8-10.5).

On (b) (6) head CT scan was performed, and no acute intra-cranial haemorrhage, extra axial collection, hydrocephalus, mid-line shift or space occupying mass lesion. Alanine aminotransferase (ALT) was 130 U/L (4 - 33), Aspartate Aminotransferase (AST) 106 U/L (4 - 40) and total bilirubin was 2.3 mg/dL (0.2-1.2).

On (b) (6) the patients ALT measurement was 185 U/L, and AST was 122 U/L. Chest X-ray was performed and confirmed S/P ET (endotracheal tube) tube placement and central line placement.

On (b) (6) the patients pulse was 125 bpm and respiratory rate was 37 rpm. At 08:20, (b) (6) hours after taking study drug, the patient started experiencing elevated liver test enzymes, level of ALT was 4482 U/L and AST 10840 U/L. No corrective treatment was given in response to the event. Patient's creatinine was 7.05 mg/dL and total bilirubin was 3.0 mg/dL. The patients WBC were 17.86 K/uL. Chest X-ray was performed and confirmed S/P Shiley catheter placement.

On (b) (6) (b) (6) hours after taking study drug, the patient died due to cardiopulmonary arrest at 03:05. Autopsy was not performed.

Action taken with study drug in response to the events was not applicable.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17684186

Abnormal LFT'S had not resolved at the time of report.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

Causality assessment is as follows:

(b) (6)

Cardio-respiratory arrest: Severity = Grade 5; Investigator Causality = Not related; Company Causality = Not related

Investigator causality rationale: No alternate explanation provided.

Company causality rationale: A 72-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced cardiopulmonary arrest due to hypoxia and subsequent death (b) (6) days after receiving the study drug. The event cardiopulmonary arrest due to hypoxia is assessed as not related to study drug or any clinical trial procedure. The event is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and underlying hypertension.

Liver function test abnormal: Severity = Grade 4; Investigator Causality = Related; Company Causality = Related

Investigator causality rationale: No alternate explanation provided.

Company causality rationale: A 72-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced abnormal liver function test- a significant increase of AST and ALT (b) (6) days after receiving study drug. Based on a plausible temporal relationship between study drug administration and the reported event and known potential effect of study drug on functional liver enzymes, causality for the event abnormal LFT'S is assessed as related to study drug. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation. The event is confounded with concomitant use of azithromycin, methylprednisolone, ceftriaxone and hydroxychloroquine. The event abnormal LFT'S is not related to any clinical trial procedure.

Relationship to study conduct or study procedure: The Investigator assessed both events as not related to study conduct or study procedure.

Follow up: 24-Apr-2020

The Investigator provided the following updates: outcome and resolution date for event Abnormal LFT'S, concomitants medications, relevant concomitants, relevant tests and event course updated.

Follow up: 13-May-2020

The Investigator provided the following updates: earliest onset date for symptoms of pneumonia updated.

Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up: 20-May-2020

The Investigator provided the following updates: outcome for abnormal LFTs updated.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17684186

Follow up: 01-Jun-2020

The Investigator provided the following updates: severity of event abnormal LFTs updated.

Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up: 22-Jun-2020

The Investigator provided the following updates: event term for cardiopulmonary arrest due to hypoxia updated.

Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Expectedness Assessment per current IB (version 14):

Cardiopulmonary arrest due to hypoxia: unexpected

Abnormal LFT'S: unexpected

(b) (6)

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	Events
Hypertension			YES	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
White blood cells	20.99	10 ³ /uL			N
Alanine aminotransferase	130	U/L	4	33	N
Bilirubin total	2.3	mg/dL			N
Creatinine	5.5	mg/dL	0.5	1.3	N
Creatinine	7.05	mg/dL	0.5	1.3	N
Urea	158	UNK			Y
Platelet count	277	10 ⁹ /L	150	400	N
Body temperature	97.6	degF			Y



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17684186

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Body temperature	97.8	degF			Y
Chest X-ray					Y
Alanine aminotransferase	4482	U/L	4	33	N
Aspartate aminotransferase	122	U/L	4	40	N
Chest X-ray					Y
Respiratory rate	37	breaths/min			N
Aspartate aminotransferase	106	U/L	4	40	N
Chest X-ray					Y
Chest X-ray					Y
Respiratory rate	24	breaths/min			N
White blood cells	17.86	10 ³ /uL			N
Head CT					Y
Alanine aminotransferase	185	U/L	4	33	N
Aspartate aminotransferase	10840	U/L	4	40	N
Pulse rate	99	beats/min			N
Pulse rate	125	beats/min			N
Oxygen saturation	98	%			N
SARS-CoV-2 test					N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ANAKINRA	100 MG/QD	Subcutaneous	100 mg, qd	COVID-19	04-Apr-2020	07-Apr-2020	9 DAY
2	ASPIRIN [ACETYLSALICYLIC ACID]	81 MG/QD	Oral	81 mg, QD	DVT prophylaxis	12-Apr-2020	13-Apr-2020	1 DAY
3	AZITHROMYCIN 0.5-ETHANOL MONOHYDRATE	500 MG/QD	Oral	500 mg, QD	COVID-19	01-Apr-2020	02-Apr-2020	17465 MIN
4	CEFTRIAZONE	1000 MG/Q12H	Intravenous (not otherwise specified)	1000 mg, bid	COVID-19	03-Apr-2020	07-Apr-2020	10 DAY
5	FAMOTIDINE	20 MG/QOD	Intravenous (not otherwise specified)	20 mg, every 48 hours	COVID-19	12-Apr-2020	13-Apr-2020	1 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17684186

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
6	HYDROXYCHLOROQUIN E	200 MG/Q12H	Oral	200 mg, bid	COVID-19	02-Apr-2020	07-Apr-2020	11 DAY
7	METHYLPREDNISOLON E	40 MG/Q12H	Oral	40 mg, bid	COVID-19	04-Apr-2020	07-Apr-2020	9 DAY
8	NOREPINEPHRINE	16 MG/	Intravenous (not otherwise specified)	16 mg, infusion	Blood pressure	11-Apr-2020	13-Apr-2020	2 DAY

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17684845

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: URY
Event Date: 07-Apr-2020
Outcomes: DE,OT,
Application Type: BLA
FDA Rcvd Date: 07-May-2020
Mfr Rcvd Date: 28-Apr-2020
Mfr Control #: UY-ROCHE-2584714
Application #: 125276

Patient Information:

Age: 85 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		Q12H	Unknown	Unknown dose	COVID-19	06-Apr-2020	07-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Cardio-respiratory distress	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2584714 is a spontaneous case, received on 14/Apr/2020 from an other health care professional in Uruguay. It concerns a 85 year old male who used intentional of actemra for an unapproved indication which is covid-19, off-label use and cardiogenic acute respiratory distress (cardio respiratory distress) whilst being treated with tocilizumab (Actemra).

No medical history, past drug and concomitant medications were reported. Concurrent condition included ischemic dilated heart disease.

On 06/Apr/2020, patient started therapy with tocilizumab (lot number and dose not reported) once per 12 hours for covid-19 (off label use). On (b) (6) he died due to cardiogenic acute respiratory distress. It was unknown if an autopsy was performed or not.

At the time of death, therapy status of tocilizumab was not reported.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17684845

The other health care professional did not report the causality between cardiogenic acute respiratory distress and tocilizumab.

No further information was reported.

Follow-up information was received on 28/Apr/2020 following information was added to the case: Physician as reporter added. Therapy details for suspects were added. Event cardiogenic acute respiratory distress added. Concurrent condition included ischemic dilated heart disease. Event description updated.

Relevant Medical History:

ischemic dilated heart disease

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17684845

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17696939

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ROM Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 04-May-2020 Mfr Rcvd Date: 27-Apr-2020 Mfr Control #:RO-ROCHE-2586522 Application #: 125276

Patient Information:

Age: 66 YR Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ROACTEMRA			Intravenous (not otherwise specified)	(3 vials of 400 mg and 1 vial of 200 mg)	COVID-19			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	B293H04,B30174 H1				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2586522 is a spontaneous case, received on 16/Apr/2020 from a pharmacist via consumer in Romania and concerns a 66 year old patient (gender unspecified) who died whilst being treated with tocilizumab (Roactemra) intentionally for an unapproved indication as off label use.

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On an unspecified date, the patient started therapy with intravenous tocilizumab (lot number: B293H04, expiry date 30/Nov/2021; lot number: B30174H1, expiry date 30/Aug/2021) intentionally for an unapproved indication for sars-cov-2 infection as off label use. The total dose was 1200 mg, 3 vials of 400 mg and 1 vial of 200 mg. On an unspecified date, the patient died due to an unknown cause. It was not reported if an autopsy was performed or not. The reporter did not agree to provide additional information regarding this case.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17696939

At the time of death, the therapy status of tocilizumab was maintained.

The reporter did not report the causality between the event death nos and tocilizumab.

No further information was provided.

Additional information was received on 27/Apr/2020 and the following information was added to the case: The reporter did not agree to provide additional information regarding this case.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17696939

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17702433

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ROM Event Date: Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 04-May-2020 Mfr Rcvd Date: 27-Apr-2020 Mfr Control #:RO-ROCHE-2586553 Application #: 125276

Patient Information:

Age: 72 YR Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ROACTEMRA			Intravenous (not otherwise specified)	total dose was 1200 mg (2 vials of 400 mg and 2 vials of 200 mg).	COVID-19			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	B293H04,B3016H33				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2586553 is a spontaneous case, received on 16/Apr/2020 from a pharmacist in Romania. It concerns a 72 year old patient (gender unspecified) who died while being treated with tocilizumab (Roactemra).

No medical history, past drug, concurrent condition and concomitant medication were reported.

On an unknown date, the patient received intravenous tocilizumab (lot number: 400 mg: B293H04, expiry date: 30/Nov/2021; 200 mg: B3016H33, expiry date: 28/Feb/2021) for SARS-CoV-2 infection (intentionally use for unlabeled indication (off label use)). The total dose was 1200 mg (2 vials of 400 mg and 2 vials of 200 mg). On unspecified date, the patient died. The cause of death was unknown. It was not specified if an autopsy was performed or not. Later, upon further follow up attempts, the pharmacist did not agree to provide additional information.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17702433

At the time of death, therapy with tocilizumab was ongoing.

The reporter did not report a causality between death nos and tocilizumab.

No further information was provided.

Additional information received on 27/Apr/2020, following information was added to the case: Event description (the reporter pharmacist did not agree to provide additional information regarding this case).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** ROCHE **503B Compounding
Outsourcing Facility?:**



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17702433

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17728918

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: FRA
Event Date: 14-Apr-2020
Outcomes: DE,HO,
Application Type: BLA
FDA Rcvd Date: 23-Jun-2020
Mfr Rcvd Date: 19-Jun-2020
Mfr Control #: FR-ROCHE-2591165
Application #: 125276

Patient Information:

Age: 72 YR
Sex: Female
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		560 MG/QD	Intravenous (not otherwise specified)	20 mg/mL	COVID-19	02-Apr-2020	02-Apr-2020
2	TOCILIZUMAB		400 MG/M**2/QD	Intravenous (not otherwise specified)	20 mg/mL		04-Apr-2020	04-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN,UNK NOWN				
2	TOCILIZUMAB		NA	NA	UNKNOWN,UNK NOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Enterococcal infection	NA
Hypoxia	NA
Pneumonia bacterial	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17728918

Event/Problem Narrative:

AER 2591165 is a clinical study case, received on 24/Apr/2020 from a physician in France. It concerns a 72 year old female patient (patient number: (b) (6)) who developed hypoxemia, ventilator associated bacterial pneumonia and enterococcus faecalis infection whilst enrolled in (b) (6)
(b) (6)

Patient's concurrent conditions included hyperparathyroidism and overweight. concomitant medications included propofol, Sufenta, furosemide, atracurium, insulin, Lovenox, noradrenaline, Calciparine, lansoprazole. No medical history, past drugs were reported.

(b) (6)
(b) (6)
(b) (6)
(b) (6)
On (b) (6) First symptom of ventilator associated bacterial pneumonia to enterococcus faecalis occurred as septic shock clinical picture. Symptomatic measure taken, cefepime/amikacine and Voriconazole introduction, On (b) (6) First symptoms was occurred as failure of decubitus therapy and FiO2 = 100%. Symptomatic measure taken: nitrogen addition. On (b) (6) Bronchial aspiration procedure, an identification test for enterococcus faecalis identification showed presence of enterococcus faecalis. On (b) (6) identification of E. faecalis, introduction of amoxicillin. On (b) (6) Final diagnosis of ventilator associated bacterial pneumonia and enterococcus faecalis infection was performed. On (b) (6) she developed hypoxemia, Initial notification form pertaining to hypoxemia was provided with medical validation; onset date was modified to on (b) (6) (severe intensity grade 4) was reported. According to the hospitalization report from (b) (6) to (b) (6) she experienced an severe ARDS on viral SARS-COV-2 with refractory hypoxemia resistant to curare and a ventilator-associated pneumonia due to Enterococcus feacalis treated with amoxicilline. The evolution was unfavorable, she died on (b) (6) It was unknown if an autopsy was performed or not.

The investigator assessed the causality of ventilator associated bacterial pneumonia and Enterococcus faecalis infection as expected. and hypoxemia: unexpected by outcome and related to disease progression. Investigator mentioned that proportion of intubated/ventilated Covid positive patients that developed a ventilator associated pneumonia was not negligible outside any trial.

The company assessed the causality of events ventilator associated bacterial pneumonia and enterococcus faecalis infection as related to tocilizumab. Tocilizumab is a recombinant humanized monoclonal antibody of the immunoglobulin IgG1 subclass which acts on interleukin 6 receptors. Infections are commonly observed due to its immunomodulatory action. Considering mechanism of action of the drug, the company cannot exclude the possibility of a cause-and-effect relationship between administration of tocilizumab and the event.

No further information was provided.

Additional information was received on 08/May/2020. Following information was added to the case: Patient details(date of birth). Causality amended from not reporter to related.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17728918

Additional information was received on 08/Jun/2020. Following information was added to the case: New events ventilator associated bacterial pneumonia and enterococcus faecalis infection. Event description updated accordingly.

Additional information was received on 19/Jun/2020, following information was added to the case: (FR-DRCDAPHPP-202000504), onset date of enterococcus faecalis infection and ventilator associated bacterial pneumonia updated (b) (6) (previous (b) (6)), seriousness criteria updated to hospitalization, therapy details of IV tocilizumab (Roactemra) 8 mg/kg concentrate for solution for infusion added, concurrent conditions hyperparathyroidism and overweight added, lab details added, Date of death was confirmed on (b) (6) concomitant medications included propofol, Sufenta, furosemide, atracurium, insulin, Lovenox, noradrenaline, Calciparine, lansoprazole added, causality of events updated to related. event description updated. The sponsor considered this case as no longer a SUSAR. Nevertheless, this case was reported to ANSM regarding conditions of initial authorization of CORIMUNO-19 protocol.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hyperparathyroidism			
Overweight			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Bronchial aspiration procedure					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ATRACURIUM							
2	CALCIPARINE							



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17728918

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
3 FUROSEMIDE							
4 INSULIN							
5 LANSOPRAZOLE							
6 LOVENOX [ENOXAPARIN SODIUM]							
7 NORADRENALINE [NOREPINEPHRINE]							
8 PROPOFOL							
9 SUFENTA							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17729811

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 18-Mar-2020 Outcomes: DE,OT, Application Type: NDA
 FDA Rcvd Date: 05-Jun-2020 Mfr Rcvd Date: 05-Jun-2020 Mfr Control #: ES-PFIZER INC-2020171785 Application #: 021131

Patient Information:

Age: 21 YR Sex: Female Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LINEZOLID			Intravenous (not otherwise specified)	UNK	Acute respiratory insufficiency	18-Mar-2020	21-Mar-2020
2	AMBISOME [AMPHOTERICIN B]			Intravenous (not otherwise specified)	UNK	Acute respiratory insufficiency	18-Mar-2020	21-Mar-2020
3	HYDROXYCHLOROQUIN E		400 MG/QD	Oral	400 mg, 1x/day	COVID-19 pneumonia	18-Mar-2020	21-Mar-2020
4	TOCILIZUMAB			Intravenous (not otherwise specified)	Unknown	COVID-19 pneumonia	18-Mar-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	LINEZOLID	1 Day	No	NA				PFIZER	
2	AMBISOME [AMPHOTERICIN B]	1 Day	No	NA					
3	HYDROXYCHLOROQUIN E	1 Day	No	NA					
4	TOCILIZUMAB	1 Day	NA	NA					

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Acute kidney injury	NA
Hepatitis	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17729811

Hypocoagulable state	NA
Off label use	NA
Pancreatitis acute	NA
Product use in unapproved indication	NA

Event/Problem Narrative:

This is a spontaneous report from a contactable physician downloaded from the European Medicines Agency (EMA) EudraVigilance-WEB ES-AEMPS-620349.

A 21-year-old female patient started to receive linezolid (manufacturer unknown), and amphotericin b (AMBISOME, 50 mg), both intravenously from 18Mar2020 to 21Mar2020 at unspecified dose for acute respiratory insufficiency, hydroxychloroquine (manufacturer unknown), orally from 18Mar2020 to 21Mar2020 at 400 mg, once a day for pneumonia COVID-19, tocilizumab (manufacturer unknown), intravenously from 18Mar2020 and ongoing at unknown dose for pneumonia COVID-19.

Medical history included blood stem cell transplant from (b) (6) (Submitted for HPT (hematopoietic parent transplant) since 21Jan, an infusion of hematopoietic parents is carried out on 05Feb2020), and Fanconi's anemia. The patient concomitant medications were not reported. On 19Mar2020, the patient experienced acute pancreatitis, hepatitis, hypocoagulable state, failure kidney acute, all medically significant with outcome as not recovered. The action taken in response to the events for linezolid, amphotericin b, and hydroxychloroquine was permanently withdrawn on 21Mar2020, for tocilizumab was dose not changed.

The patient died on (b) (6). Reported cause of death was pulmonary trichosporonosis, respiratory insufficiency, septic shock. It is unknown if autopsy was done.

Pfizer is a marketing authorization holder of Linezolid in the country of incidence or the country where the product was purchased (if different). This may be a duplicate report if another marketing authorization holder of Linezolid has submitted the same report to the regulatory authorities.

No follow-up attempts possible. No further information expected.

Amendment: This follow-up report is being submitted to amend previously reported information: updated coding of coronavirus term, coronavirus infection, which was the indication of suspects hydroxychloroquine and tocilizumab, to the more specific COVID related term made available with the upgrade to MedDRA V 23.0, COVID-19 pneumonia.

Relevant Medical History:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17729811

Disease/Surgical Procedure

Blood stem cell transplant

Fanconi's anemia

Start Date

(b) (6)

End Date

Continuing?

UNKNOWN

Medical History Product(s)

Start Date

End Date

Indications

Events

Relevant Laboratory Data:

Test Name

Result

Unit

Normal Low Range

Normal High Range

Info Avail

Concomitant Products:

Product Name

**Dose/
Frequency**

Route

Dosage Text

Indications(s)

Start Date

End Date

**Interval 1st
Dose to Event**

Reporter Source:

Study Report?: No

Sender Organization: PFIZER

**503B Compounding
Outsourcing Facility?:**

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17732903

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: HUN
Event Date:
Outcomes: DE,OT,
Application Type: BLA
FDA Rcvd Date: 14-May-2020
Mfr Rcvd Date: 08-May-2020
Mfr Control #: HU-ROCHE-2588846
Application #: 125276

Patient Information:

Age: 37 YR
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
COVID-19 pneumonia	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2588846 is a spontaneous case, received on 21/Apr/2020 from a physician via company representative in Hungary. It concerns a 37 year old patient (gender unspecified) who was being treated with tocilizumab for COVID 19 - off label use (drug intentional use for unapproved indication) and experienced fatal COVID-19 pneumoitis.

The patient's medical history, past drugs, concurrent condition and concomitant medication were not reported.

On an unknown date, the patient started therapy with tocilizumab (lot number: unknown and dosage regimen: not reported) for COVID-19 (off label use: tocilizumab intentional use for Covid-19). On an unknown date in 2020, the patient experienced COVID-19 and died due to corona pneumoitis (captured as COVID-19 pneumonitis). It was reported that, the patient received tocilizumab beyond the time window. It was not reported if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17732903

The physician assessed the causality of COVID-19 pneumoitis as unrelated with tocilizumab.

No further information were provided.

Additional information was received on 05/May/2020. The following information was added to the case: cause of death (COVID-19 pneumonitis), Causality of the event (not related) and event description updated accordingly.

Additional information was received on 08/May/2020. The following information was added to the case (20HU063fu2): Patient's birth year (1983) added.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Coronavirus test					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17732903

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17733286

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: CAN Event Date: 24-Apr-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 18-Jun-2020 Mfr Rcvd Date: 17-Jun-2020 Mfr Control #: CA-ROCHE-2591648 Application #: 125276

Patient Information:

Age: 31 YR Sex: Male Weight: 132 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		200 MG/	Intravenous (not otherwise specified)	This was the most recent dose of blinded tocilizumab administered prior to AE onset at 18:45 hours.	COVID-19 pneumonia	21-Apr-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	3 Day	NA	NA	MJM22690,MJM80678,MJM39019,MJM29655				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC

Multiple organ dysfunction syndrome NA

Event/Problem Narrative:

AER 2591648 is a clinical study case, received on 25/Apr/2020 from a physician in Canada. It concerns a 31 year old male patient (patient number: (b) (6)) who died due to the multi-organ failure whilst enrolled in (b) (6) (b) (6)

Patient's medical history, past drugs were not reported. Concurrent conditions included heavy smoker, alcohol abuse with binge drinking, hypertension, dyslipidemia, obesity, paralysis, fluid overload, constipation, bleeding, hypotension, hyperglycemia and hypoxemia. Concomitant medications included fentanyl for sedation, insulin human (Humulin R), cisatracurium besilate (Nimbex) as paralytic agent, heparin as an ECLS anticoagulation, dexmedetomidine for sedation, labetalol, norepinephrine, tranexamic acid, furosemide, metoprolol, multivitamin for nutrition supplement, nicotine, senna alexandrina leaf (Senna Leaf), clonidine, pantoprazole for stress ulcer prophylaxis, rocuronium, quetiapine for sedation, hydromorphone as an analgesia, lorazepam as sedation, hydralazine and clonazepam for sedation.

(b) (6)



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17733286

(b) (6)
(b) (6) On 24/Apr/2020, he became hemodynamically unstable. His complete blood count revealed white blood cell count at 44.6 (unit not reported), while creatinine: 195 (unit not reported), lactate: 14.0 (unit not reported) and aspartate aminotransferase (AST): 50917 (unit not reported). His white blood cell count increased, blood pressure required support with multiple pressors, onset of metabolic acidosis, worsening of creatinine and liver enzymes. On (b) (6) he developed multi organ failure and septic shock. He was given fluid resuscitation, blood cultures samples were collected and antibiotics started. He was treated with vasopressin for hypotension, hydrocortisone for sepsis, vancomycin as an antibiotic, tobramycin as an antibiotic and piperacillin sodium; tazobactam sodium (Piptazo) as an antibiotic, meropenem as an anti-microbial, ascorbic acid (Vitamin C) for sepsis, micafungin (Micafungin) as an anti-fungal, thiamine (Thiamine) for nutrition supplement, amiodarone for ventricular tachycardia (VT), esmolol for tachycardia and midazolam for sedation. On (b) (6) he died due to multi organ failure. An autopsy was not performed. He was discontinued from the study due to fatal multi-organ failure.

The physician assessed the causality of fatal multi-organ failure as a serious adverse event of special interest: serious and or medically significant infections.

The physician assessed the causality of fatal multi-organ failure as related with blinded tocilizumab and concurrent illness.

The company assessed fatal multi organ failure as related to tocilizumab. The inflammatory response of cytokines overwhelms the immune system response to the infection, which can lead to damage of organs, including lungs, heart, and kidneys. Contributory factors include sepsis, hyperglycemia, dyslipidemia, hypertension and the underlying condition of COVID-19. However, the causal relationship with tocilizumab cannot be completely excluded.

No further information was provided.

This case is cross-referenced with AER 2590126 (same patient).

Additional information received on 22/May/2020. Following information was added in this case: Event updated to Multi-organ failure (Previously reported as septic shock with Multi-organ failure), concurrent condition (hypoxemia requiring mechanical ventilation and extracorporeal life support), dose and frequency of some concomitant drugs and event description were updated.

The event of fatal septic shock no longer meets expedited reporting requirements as septic shock is deleted from the case as the event term septic shock with Multi-organ failure is amended to Multi-organ failure.

Additional information received on 03/Jun/2020. Following information was added in this case: Patient's birth date updated (from (b) (6) to //1988).



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17733286

Additional information received on 05/Jun/2020. Following information was added in this case: new correspondence reporter as consumer and patient's weight updated.

Additional information was received on 17/Jun/2020, following information was added to the case: Event description (The patient was discontinued from the study due to fatal multi-organ failure) was added.

Analysis of similar events (PT- Multiple organ dysfunction syndrome)

On 29/04/2020 the Roche safety database was searched with MEDDRA preferred term of multiple organ dysfunction syndrome for Tocilizumab for the treatment of COVID-19 pneumonia. The search was based on both open label and blinded data. The following 07 previously submitted IND Safety report was found (Aer no.- 492910, Aer no.- 575719, Aer no.- 607093, Aer no.- 617545, Aer no.- 663497, Aer no.- 664294, Aer no.- 673045). In addition, 86 non IND reports of serious case with similar events were identified of which 15 were reported from clinical studies, 01 reported from Literature - Non-Interventional Study/Program, 02 reported from Literature - Study, 01 reported from spontaneous and 67 reported from Non-Interventional Study/Program which included 22 male ,56 female 01 unknown and rest with 7 unspecified gender. The age ranged from 33 years to 82 years with fatal outcome was reported in 73 cases, not reported in 7 cases, not recovered/not resolved in 01 case, Recovered/resolved in 3 cases and unknown in 2 cases. The investigator assessed the causality in relationship to the investigational drug as related in 19, unrelated in 28 and not reported/unspecified in rest of the cases. In the index case AER-2591648, event fatal multi organ failure occurred 3 days after initiating tocilizumab and 2 days after receiving last dose of tocilizumab for the indication of COVID-19 pneumonia. Other contributing/risk and etiological factors include sepsis, hyperglycemia, dyslipidemia, hypertension and the underlying condition COVID-19. Based on review of available data, there is some evidence suggesting that administration of Tocilizumab can be associated with fatal multi organ failure. After review of the clinical details of the index case and similar previous cases, the sponsor does not believe that changes to the conduct of the clinical trial are warranted in response to this case report at this time.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Alcohol abuse			
Constipation			
Dyslipidaemia			
Fluid overload			
Haemorrhage			



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17733286

Hyperglycaemia

Hypertension

Hypotension

Hypoxia

YES

Obesity

Paralysis

Tobacco user

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
White blood cell count	44.6	unit not reported			N
Aspartate aminotransferase	50917	unit not reported			N
Blood creatinine	195	unit not reported			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	CLONAZEPAM	.5 MG/BID	Unknown			23-Apr-2020	23-Apr-2020	1 DAY
2	CLONIDINE	.2 MG/TID	Unknown		Hypertension	17-Apr-2020	24-Apr-2020	7 DAY
3	DEXMEDETOMIDINE	1.5 UG/	Unknown	FOR SEDATION,		17-Apr-2020	24-Apr-2020	7 DAY
4	FENTANYL	150 UG/	Unknown			24-Apr-2020	27-Apr-2020	11 DAY
5	FENTANYL	250 UG/	Unknown	for sedation.		13-Apr-2020	17-Apr-2020	11 DAY
6	FUROSEMIDE	40 MG/QD	Unknown	for fluid overload		16-Apr-2020	21-Apr-2020	8 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17733286

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
7	HEPARIN	2100 IU/	Unknown	FOR ECLS ANTICOAGULATION		13-Apr-2020	27-Apr-2020	11 DAY
8	HUMULIN R	8 IU/	Unknown		Hyperglycaemia	13-Apr-2020	27-Apr-2020	11 DAY
9	HYDRALAZINE	20 MG/	Unknown		Hypertension	17-Apr-2020	24-Apr-2020	7 DAY
10	HYDROMORPHONE	8 MG/QID	Unknown	as analgesia		17-Apr-2020	24-Apr-2020	7 DAY
11	LABETALOL	.3 MG/	Unknown		Hypertension	21-Apr-2020	23-Apr-2020	3 DAY
12	LORAZEPAM	2 MG/TID	Unknown	for sedation.		17-Apr-2020	21-Apr-2020	7 DAY
13	METOPROLOL	100 MG/BID	Unknown		Hypertension	18-Apr-2020	23-Apr-2020	6 DAY
14	NICOTINE	7 MG/QD	Unknown		Tobacco user	17-Apr-2020	18-Apr-2020	7 DAY
15	NIMBEX [CISATRACURIUM BESILATE]	3 UG/	Unknown	AS PARALYTIC AGENT		13-Apr-2020	23-Apr-2020	11 DAY
16	NOREPINEPHRINE	.9 UG/	Unknown		Hypotension	23-Apr-2020	27-Apr-2020	1 DAY
17	PANTOPRAZOLE	40 MG/QD	Unknown	for stress ulcer prophylaxis		17-Apr-2020	26-Apr-2020	7 DAY
18	PROPOFOL	80 UG/	Unknown	for sedation,		13-Apr-2020	25-Apr-2020	11 DAY
19	QUETIAPINE	75 MG/TID	Unknown	for seadtion		17-Apr-2020	24-Apr-2020	7 DAY
20	ROCURONIUM	100 MG/TID	Unknown		Paralysis	17-Apr-2020	17-Apr-2020	7 DAY
21	SENNA LEAF	8.5 MG/	Unknown		Constipation	17-Apr-2020	24-Apr-2020	7 DAY
22	TRANEXAMIC ACID	2 MG/TID	Unknown		Haemorrhage	19-Apr-2020	19-Apr-2020	5 DAY

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17734738

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: FRA
Event Date: 05-Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 19-Oct-2020
Mfr Rcvd Date: 15-Oct-2020
Mfr Control #: FR-ROCHE-2591170
Application #: 125276

Patient Information:

Age: 61 YR
Sex: Female
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Tocilizumab		720 MG/	Intravenous (not otherwise specified)	Concentrate for solution for infusion 20 mg/ml	COVID-19	03-Apr-2020	05-Apr-2020
2	Tocilizumab		400 MG/	Intravenous (not otherwise specified)			05-Apr-2020	05-Apr-2020
3	Tocilizumab			Intravenous (not otherwise specified)	20 mg/ml		03-Apr-2020	05-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Tocilizumab		Unk	NA	ASKED BUT UNKNOWN,ASKE D BUT UNKNOWN				
2	Tocilizumab		Unk	NA	ASKED BUT UNKNOWN,ASKE D BUT UNKNOWN				
3	Tocilizumab		Unk	NA	ASKED BUT UNKNOWN,ASKE D BUT UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) **ReC**
Acute respiratory distress syndrome NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17734738

Pneumonia
Septic shock

NA
NA

Event/Problem Narrative:

AER 2591170 is a clinical study case, received on 24/Apr/2020 from a physician in France. It concerns a 61 year old female patient (patient number: (b) (6)) who developed ventilator-associated pneumonia, septic shock and acute respiratory distress syndrome whilst enrolled in (b) (6)

The patient's concurrent conditions included thyroid nodule, hypothyroidism, obesity and dislipidemia. Concomitant medications included levothyroxine, enoxaparin sodium (Lovenox), rosuvastatin, insulin aspart (Novorapid), cefepime and amoxicillin; clavulanic acid (Augmentin). Medical history and past drugs were not reported.

On (b) (6) the patient was hospitalized and was (b) (6) (b) (6) No intensive care unit (ICU) at admission. (b) (6) On the same day, she experienced first symptoms occurred of respiratory distress. First symptoms occurred on (b) (6), respiratory distress (severe acute respiratory distress syndrome). On an unspecified date, she was performed some additional test as viral swab which was positive for oro pharyngeal flora (report not provided). On (b) (6) she worsened with septic shock on late mechanical ventilator associated pneumonia on oropharyngeal flora. On (b) (6) she developed ventilator-associated pneumonia and septic shock (severity: grade 4). First symptoms occurred on (b) (6) which includes respiratory degradation, increase of catecholamines. Symptomatic measures were taken like antibiotherapy and increase of noradrenaline. No other etiology was considered. She initially improves but on (b) (6) worsening without improvement beside sedation and curarisation. On (b) (6), she was admitted for acute respiratory distress syndrome and COVID-19 viral pneumonia. Probabilistic antibiotherapy with meropenem and gentamicin was started, bronco alveolar fluid was negative. A new session of ventral decubitus was performed without improvement. At H+10 of ventral decubitus, she experienced cardio respiratory arrest, ultra sound confirmed the pneumothorax, emergency insufflation allowed a return to a sinus rhythm. CT scan revealed a diffuse SC emphysema with pneumoperitoneum, there was also an extension and an evolution towards the condensation of COVID-19 lesion with the onset of an excavated lesion of the right lower lobe. Super infection could not be excluded. She was transferred to ICU. Haematosiis continued to worsen and she died at 09:41 PM on (b) (6) It was not reported if an autopsy was performed or not. Investigator's assessment regarding final diagnosis was confirmed.

At the time of death, it was not reported whether the therapy with tocilizumab was ongoing or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17734738

The physician assessed the causality of event ventilator-associated pneumonia, septic shock as related with tocilizumab and disease progression while assessed acute respiratory distress syndrome as not related to tocilizumab but related to disease progression. The physician assessed that it was difficult to distinguish between acute respiratory distress syndrome from COVID ventilator-associated pneumonia and other element item could be linked, but COVID had the major part in the acute respiratory distress syndrome. Other etiologies considered by the investigator acute respiratory distress syndrome on COVID, pneumothorax, contributive to the death with infection.

No further information was provided.

Additional information received on 29/Apr/2020 and the following data was added to the case: concomitant medications (cefepime, Augmentin), lab data, etiology, causality of event acute respiratory distress syndrome (related to not related) and updated narrative accordingly.

Additional information was received on 02/Jun/2020, following information was added to the case: (2020-001246-18(EU)) therapy details for tocilizumab added, onset date of acute respiratory distress syndrome updated to (b) (6) (previous (b) (6)), event description updated.

Additional information was received on 29/Jun/2020, following information was added to the case: Event description (Investigator's assessment regarding final diagnosis was confirmed) updated.

Additional information was received on 21/Aug/2020, following information was added to the case: Therapy end date of tocilizumab (from (b) (6) to (b) (6)) and event description was updated.

Additional information was received on 15/Oct/2020, following information was added to the case: Tocilizumab therapy details and death date ((b) (6)) added.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Dyslipidaemia			
Hypothyroidism			
Obesity			
Thyroid mass			



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17734738

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Viral test					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	AUGMENTIN							
2	CEFEPIME							
3	LEVOTHYROXINE							
4	LOVENOX							
5	NOVORAPID							
6	ROSUVASTATIN							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17736244

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 13-Apr-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 26-May-2020 Mfr Rcvd Date: 21-May-2020 Mfr Control #: US-ROCHE-2586209 Application #: 125276

Patient Information:

Age: 44 YR Sex: Female Weight: 150 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		200 MG/	Intravenous (not otherwise specified)	Date of most recent dose of Tocilizumab prior to SAE onset: 03/Apr/2020, at 20:37	COVID-19 pneumonia	03-Apr-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	10 Day	NA	NA	MJM15677,MJM33295,MJM80781,MJM87355				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC

COVID-19 pneumonia NA

Event/Problem Narrative:

AER 2586209 is a clinical study case, received on 14/Apr/2020 from a physician in the USA. It concerns a 44 year old female patient (patient number: (b) (6)) who died due to COVID-19 pneumonia whilst enrolled in (b) (6) (b) (6)

The patient's concurrent conditions included acute kidney injury, adult respiratory distress syndrome, hypertension, gastroesophageal reflux disease, iron deficiency anemia, congestive heart failure, borderline pulmonary hypertension, morbid obesity, acute tubular necrosis, cardiomegaly, acute respiratory failure, acute hypoxemic respiratory failure, posterior reversible encephalopathy syndrome, respiratory failure, increase blood pressure, suspected respiratory infection, low blood pressure, lower respiratory infection, pain, upper respiratory infection, inflammation, irregular heartbeats and blood clots. Concomitant medications included magnesium sulfate, paracetamol (Acetaminophen), azithromycin, ceftriaxone, chlorhexidine, enoxaparin, etomidate, famotidine, fentanyl, furosemide, hydrocortisone sodium succinate, hydroxychloroquine, lorazepam, midazolam, morphine, macrogol (Polyethylene Glycol), vancomycin, propofol, chlorothiazide, vasopressin, norepinephrine, ketamine, dexmedetomidine, cisatracurium, rocuronium, chlorothiazide, heparin, lidocaine and alteplase. Medical history and



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17736244

past drugs were not reported.

(b) (6)
(b) (6) On 13/Apr/2020, she developed COVID-19 pneumonia. On the same day, white blood cell (WBC) was 13.44 (k/UL), red blood cell (RBC) was 3.57 (m/UL), hemoglobin was 9.8 (g/dL), hematocrit was 34.3 (%), mean corpuscular hemoglobin cone was 28.6 (g/dL), red cell distribution width (RDW) was 15.8 %, platelet count was 378 (k/UL), NRBC 4 (WBC) lymph % was 14.0 %, APTT was 41 3 (sec), anti-xa heprin was 0.43 (IU/mL), monitoring 0.81 (IU/mL), uric acid was 1.7 mg/dL, lactate dehydrogenase was 621 (u/l), ferritin was 354 (ng/ml), triglycerides was 535(mg/dl), glucose was 166 (mg/dL), 156 (mg/dL) and 169 (mg/dL), magnesium was 2.0 (mg/dl), vancomycin was 18.2 (ug/ml), comprehensive metabolic panel: sodium was 132 (mmol/l), CO2 was 21 (mmol/l), glucose was 163 (mg/dl), calcium was 8.3 (mg/dl), albumin was 2.4 (g/dlL), alkaline phosphatase was 347 (uL), aspartate aminotransferase (AST) was 96 (u/L) and alanine aminotransferase (ALT) was 58 (u/L). Patient was not oxygenating on maximal doses of the vent and maxed out on pressor, withdrawal of pressor and CRRT made her comfortable. She was placed supine, shortly following she had no spontaneous respiration, palpable carotid pulse, heart beat or breath sounds on auscultation. Subsequently, she died due to progression of COVID-19 pneumonia. An autopsy was not performed.

The physician assessed the causality of fatal COVID-19 pneumonia as not related to blinded tocilizumab, while related to disease under study.

The company assessed the fatal COVID-19 pneumonia as not related with blinded tocilizumab. As COVID-19, damages the walls and linings of the air sacs in lungs, which causes the inflammatory response of cytokines, overwhelming the immune system response to the infection, which can lead to damage of organs, including lungs, heart, and kidneys, leading to severe pneumonia or acute respiratory distress syndrome (ARDS). Other contributory factor includes the patient's concurrent conditions of adult respiratory distress syndrome, hypertension, iron deficiency anemia, congestive heart failure, borderline pulmonary hypertension, morbid obesity, acute tubular necrosis, cardiomegaly, acute respiratory failure, acute hypoxemic respiratory failure, posterior reversible encephalopathy syndrome, respiratory failure, increase blood pressure, suspected respiratory infection, low blood pressure, irregular heartbeats and blood clots. The causality of COVID-19 infection cannot be established with tocilizumab and considered as not related to the drug but more likely related to the current pandemic situation of COVID-19.

No further information was provided.

Additional information was received on 28/Apr/2020. The following information was added to the case: Secondary reporter, patient details, concurrent conditions (increase blood pressure, suspected respiratory infection, low blood pressure, lower respiratory infection, pain, upper respiratory infection, inflammation, irregular heartbeats and blood clots), concomitant medications (chlorothiazide, vasopressin, norepinephrine, ketamine, dexmedetomidine, cisatracurium, rocuronium, chlorothiazide, heparin, lidocaine, alteplase), event term amended to COVID-19 pneumonia (previously: worsening of severe hypoxia), (initial grade 4 and most extreme severity grade 5). Lot number of tocilizumab (MJM33295, MJM80781 and MJM87355), autopsy performed updated to no (previously: no) and event description (It was reported that death was attributed to progression of COVID-19 pneumonia. An autopsy was not performed).



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17736244

Additional information was received on 01/May/2020. Following information was added to the case: Patient's age and weight, onset date of COVID-19 pneumonia and therapy details of blinded tocilizumab.

Additional information was received on 05/May/2020. The following information was added to the case: Most extreme severity grade of the event (COVID-19 pneumonia) as grade 5.

Additional information was received on 19/May/2020, the following information was added to the case: reporter (consumer) added, COVID-19 pneumonia (initial grade 4) added, indication for concomitant medication azithromycin, ceftriaxone (lower respiratory infections) and vancomycin (upper respiratory infections) to suspected infection.

Additional information was received on 21/May/2020. The following information was added to the case: Reporter causality of the event (COVID-19 pneumonia) with suspect drug (tocilizumab) was updated to not related (previously not reported) and therapy ongoing status of tocilizumab at the time of death was added.

This case no longer meets expedited reporting requirements because the causality of event COVID-19 pneumonia was updated as unrelated to study drug tocilizumab.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension	01-Apr-2018		
Obesity	04-Apr-2018		
Pulmonary hypertension	04-Apr-2018		
Cardiomegaly	06-Apr-2018		
Iron deficiency anaemia	19-Apr-2018		
Gastroesophageal reflux disease	23-Apr-2018		
Respiratory failure	24-Apr-2018		
Posterior reversible encephalopathy syndrome	25-Apr-2018		
Acute respiratory failure	(b) (6)		



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17736244

Renal tubular necrosis (b) (6)

Acute kidney injury (b) (6)

Acute respiratory distress syndrome (b) (6)

Acute respiratory failure YES

Blood pressure increased

Cardiac failure congestive

Heart rate irregular

Hypotension

Inflammation

Lower respiratory tract infection

Pain

Respiratory tract infection

Thrombosis

Upper respiratory tract infection

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood lactate dehydrogenase	621	U/L	110	260	N
Platelet count			150	350	N
Blood calcium	8.3	mg/dL	8.7	10.5	N
Haematocrit	34.3	%	37.0	48.5	N
Blood magnesium	2.0	mg/dL	1.6	2.6	N
Red blood cell count			4	5.40	N
White blood cell count			3.90	12.70	N
Haemoglobin	9.8	g/dL	12	16	N
Lymphocyte count	14.0	%	18.0	48.0	N
Blood glucose	163	mg/dL	70	110	N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17736244

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood albumin	2.4	g/dL		5.2	N
Blood triglycerides	535	mg/dL	30	150	N
Blood sodium	132	mmol/L	136	145	N
Blood uric acid	1.7	mg/dL	2.4	5.7	N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/	Unknown			02-Apr-2020	13-Apr-2020	12 DAY
2	ACETAMINOPHEN	325 MG/	Unknown		Pain	01-Apr-2020	01-Apr-2020	12 DAY
3	ALTEPLASE	2 MG/QD	Unknown		Thrombosis	12-Apr-2020	12-Apr-2020	1 DAY
4	AZITHROMYCIN	250 MG/QD	Unknown			01-Apr-2020	01-Apr-2020	12 DAY
5	AZITHROMYCIN	500 MG/QD	Unknown			01-Apr-2020	01-Apr-2020	12 DAY
6	AZITHROMYCIN	250 MG/	Unknown		Lower respiratory tract infection	02-Apr-2020	05-Apr-2020	12 DAY
7	CHLORHEXIDINE	15 ML/	Unknown			01-Apr-2020	01-Apr-2020	12 DAY
8	CHLORHEXIDINE	30 ML/	Unknown			02-Apr-2020	12-Apr-2020	12 DAY
9	CHLORHEXIDINE	15 ML/BID	Unknown			01-Apr-2020	13-Apr-2020	12 DAY
10	CHLOROTHIAZIDE	1000 MG/BID	Unknown			02-Apr-2020	02-Apr-2020	11 DAY
11	CHLORTHIAZIDE	1000 MG/	Unknown			02-Apr-2020	02-Apr-2020	11 DAY
12	CISATRACURIUM	200 MG/	Unknown			01-Apr-2020	02-Apr-2020	12 DAY
13	Ceftriaxone	2 G/	Unknown		Lower respiratory tract infection	02-Apr-2020	05-Apr-2020	12 DAY
14	Ceftriaxone	2 G/QD	Unknown			01-Apr-2020	01-Apr-2020	12 DAY
15	DEXMEDETOMIDINE		Unknown			01-Apr-2020	02-Apr-2020	12 DAY
16	ENOXAPARIN	40 MG/QD	Unknown			01-Apr-2020	01-Apr-2020	12 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17736244

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
17 ENOXAPARIN	80 MG/	Unknown			02-Apr-2020	02-Apr-2020	12 DAY
18 ETOMIDATE	30 MG/	Unknown		Pain	01-Apr-2020	01-Apr-2020	12 DAY
19 FAMOTIDINE	40 MG/	Unknown			01-Apr-2020	13-Apr-2020	12 DAY
20 FAMOTIDINE	40 MG/QD	Unknown			01-Apr-2020	08-Apr-2020	12 DAY
21 FENTANYL	QD	Unknown			01-Apr-2020	01-Apr-2020	12 DAY
22 FENTANYL	150 UG/	Unknown		Pain	01-Apr-2020	01-Apr-2020	12 DAY
23 FENTANYL		Unknown	2500 unit		13-Apr-2020	13-Apr-2020	12 DAY
24 FENTANYL		Unknown			01-Apr-2020	05-Apr-2020	12 DAY
25 FUROSEMIDE	80 MG/QD	Unknown			01-Apr-2020	01-Apr-2020	12 DAY
26 FUROSEMIDE	280 MG/	Unknown			02-Apr-2020	02-Apr-2020	12 DAY
27 HEPARIN		Unknown	2500 unit		10-Apr-2020	13-Apr-2020	10 DAY
28 HEPARIN		Unknown			03-Apr-2020	04-Apr-2020	10 DAY
29 HYDROCORTISONE SODIUM SUCCINATE	100 MG/	Unknown		Inflammation	02-Apr-2020	02-Apr-2020	11 DAY
30 HYDROCORTISONE SODIUM SUCCINATE	100 MG/	Unknown			04-Apr-2020	04-Apr-2020	11 DAY
31 HYDROCORTISONE SODIUM SUCCINATE	300 MG/	Unknown			03-Apr-2020	03-Apr-2020	11 DAY
32 HYDROXYCHLOROQUIN E	400 MG/BID	Unknown			01-Apr-2020	02-Apr-2020	12 DAY
33 HYDROXYCHLOROQUIN E		Unknown			02-Apr-2020	02-Apr-2020	12 DAY
34 KETAMINE	500 MG/	Unknown		Anaesthesia	01-Apr-2020	02-Apr-2020	12 DAY
35 LIDOCAINE	10 MG/QD	Unknown		Heart rate irregular	07-Apr-2020	07-Apr-2020	6 DAY
36 LORAZEPAM	1 MG/	Unknown			13-Apr-2020	13-Apr-2020	



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17736244

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
37 MAGNESIUM SULFATE	2 G/	Unknown			08-Apr-2020	08-Apr-2020	5 DAY
38 MIDAZOLAM	4 MG/	Unknown			13-Apr-2020	13-Apr-2020	
39 MORPHINE	2 MG/	Unknown		Pain	13-Apr-2020	13-Apr-2020	
40 NOREPINEPHRINE	4 MG/	Unknown		Hypotension	01-Apr-2020	02-Apr-2020	12 DAY
41 NOREPINEPHRINE	4 MG/	Unknown			12-Apr-2020	12-Apr-2020	12 DAY
42 POLYETHYLENE GLYCOL [MACROGOL]		Unknown			06-Apr-2020	13-Apr-2020	7 DAY
43 PROPOFOL		Unknown		Anaesthesia	02-Apr-2020	13-Apr-2020	12 DAY
44 PROPOFOL	10 MG/	Unknown			02-Apr-2020	02-Apr-2020	12 DAY
45 PROPOFOL	10 MG/	Unknown			01-Apr-2020	01-Apr-2020	12 DAY
46 ROCURONIUM	100 MG/BID	Unknown			01-Apr-2020	01-Apr-2020	12 DAY
47 VANCOMYCIN	1000 MG/QD	Unknown			13-Apr-2020	13-Apr-2020	12 DAY
48 VANCOMYCIN	1250 MG/BID	Unknown		Upper respiratory tract infection	01-Apr-2020	02-Apr-2020	12 DAY
49 VANCOMYCIN	2000 MG/	Unknown		Respiratory tract infection	08-Apr-2020	08-Apr-2020	12 DAY
50 VANCOMYCIN	2000 MG/QD	Unknown			01-Apr-2020	01-Apr-2020	12 DAY
51 VASOPRESSIN	QD	Unknown	20 UNit		13-Apr-2020	13-Apr-2020	12 DAY
52 VASOPRESSIN		Unknown		Blood pressure increased	01-Apr-2020	04-Apr-2020	12 DAY

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17736889

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 19-May-2020 Mfr Rcvd Date: 11-May-2020 Mfr Control #:US-ROCHE-2591454 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2591454 is a spontaneous case, received on 24/Apr/2020 from a physician in the USA. It concerns a patient of unknown demographics who passed away whilst being treated with tocilizumab (Actemra) as drug actemra intentionally used for unlabeled indication (off-label use).

No medical history, past drug, concurrent condition or concomitant medication was reported.

On an unknown date, the patient started therapy with tocilizumab (lot number: unknown; dosing regimen not reported) for COVID-19 as drug actemra intentionally used for unlabeled indication(off-label use). On an unknown date, the patient passed away. The cause of death was unknown and it was not reported if an autopsy was performed or not.

The reporter assessed a causality between patient passed away as unrelated with tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17736889

No further information was reported.

Additional information was received on 11/May/2020 and following information was added to case: Causality of passed away was not related (previously mentioned as not reported).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17736889

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17737377

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: POL
Event Date: 2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 29-Jul-2020
Mfr Rcvd Date: 21-Jul-2020
Mfr Control #: PL-ROCHE-2591197
Application #: 125276

Patient Information:

Age: 67 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Tocilizumab		8 MG/KG/	Intravenous (not otherwise specified)	maximum of 800 mg	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Tocilizumab		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2591197 is a literature-non-interventional study case, received on 25/Apr/2020 from a physician in Poland and concerns a 67 year old male patient who was intentionally treated with tocilizumab for unlabeled indication (off label use) and died while enrolled in study of tocilizumab for patients with severe COVID-19: a retrospective, multicenter study.

In this retrospective study, patients with severe COVID-19 requiring oxygen therapy who received tocilizumab between 15/Mar/2020 to 30/Apr/2020 were included. Total, 28 patients were included (19 male), with a mean age of 60.71 +/- 12.39 years. The mean time from symptom onset to the first tocilizumab dose was 10.53 +/- 5.67 days. Adult patients (aged >=18 years) with COVID-19 who met the following criteria: cough, dyspnoea, or fever (> 38 degree Celsius); positive result of a polymerase chain reaction (PCR) test for SARS-CoV-2 from a pharyngeal swab; typical lung changes on chest x-ray (ground glass opacities) or chest computerized tomography (CT; cobblestone road sign, atoll sign); need for continuous oxygen therapy; oxygen saturation <=94% at any time after admission; and serum IL-6 concentration above



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17737377

the upper limit of normal (ULN) were included in the study. Fourteen (50%) patients had hypertension, six (21%) had diabetes, two (7%) had asthma, and two (7%) had chronic obstructive pulmonary disease. There were single instances of the following diseases: heart failure, stroke, chronic kidney disease, rheumatoid arthritis, chronic lymphocytic leukaemia, schizophrenia, depression, and factor V Leiden mutation. The tocilizumab was injected intravenously at a maximum single dose of 800 mg, and if there was no clinical improvement, the dose could be repeated after at least 8 hours for COVID-19 (unlabeled indication as off label use). Most patients (86%) received two tocilizumab doses. The mean time from symptom onset to the first tocilizumab dose was 10.53 +/- 5.67 days. Twenty-four patients (86%) received a second dose (9-92 hours after the first dose). The doses ranged from 3.8 mg/kg to 12 mg/kg (first dose, 6.36 +/- 1.95 mg/kg; second dose, 6.39 +/- 2.1 mg/kg). Within a week of the first dose, the clinical status improved in 25 (89%) patients, did not change in one (4%), and worsened in two (7%; both patients died). Sixteen patients (57%) no longer needed oxygen therapy within a week ($p < 0.001$). Oxygen saturation significantly improved the day after the first tocilizumab dose ($p = 0.001$). The serum concentrations of C-reactive protein, procalcitonin, and fibrinogen decreased significantly after tocilizumab treatment ($p \leq 0.001$). The author stated that the treatment with tocilizumab appeared safe with no adverse events attributable to tocilizumab. Patients with at least two chronic diseases have little chance of improvement in the clinical condition within 24 hours of the administration of tocilizumab and they have a greater risk of death. Not determinable which patient had which laboratory values in the current version of the report. The highest baseline IL-6 concentration of 1,041 pg/mL was noticed in a patient who later died, who also demonstrated extremely high IL-6 levels (19,770 pg/mL) seven days after tocilizumab administration. However, the baseline IL-6 concentration observed in the second patient who died was only 64 pg/mL.

This case concerns an 67 year old male patient.

The patient's concurrent conditions included hypertension, diabetes and chronic kidney disease. Medical history, past drugs and concomitant medications were not reported. No risk factors were available.

On an unspecified date, in 2020, the patient was diagnosed with COVID-19 infection. The diagnosis was made by polymerase chain reaction (PCR) test for SARS-CoV-2 from a pharyngeal swab. Later, he started therapy with intravenous (IV) tocilizumab 8 mg/kg (maximum of 800 mg) (lot number and frequency not reported) for COVID-19 infection (Off label use, intentional use of drug for unlabeled indication). He was also treated with chloroquine, lopinavir/ritonavir and low weight heparin. On the 3rd day after tocilizumab administration, he died (cause unknown) in intensive care unit. It was reported that in bone marrow aspiration biopsy (waited for trepanobiopsy results) hemofagocytosis, it seemed that he had MAS-like (sHLH). A huge IL-6 outbreak after tocilizumab would already indicate the huge activity of macrophages, which was reflected in the publications. It was not reported if an autopsy was performed or not.

At the time of death, there was insufficient information regarding therapy ongoing status of tocilizumab.

The reporter did not provide the causal relationship of tocilizumab with death.

The company considered death as unrelated to tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17737377

Further information has been requested.

Tomasiewicz K, Piekarska A, Stempkowska-Rejek J, Serafinska S, Gawkowska A, Parczewski M, Niscigorska-Olsen J, Lapinski T, Zarebska-Michaluk D, Kowalska J, Horban A and Flisiak R.

Tocilizumab for patients with severe COVID-19: a retrospective, multi-centre study.

The Lancet Infectious Diseases 2020: 1-14.

Additional information was received on 21/Jul/2020. Following information was added to the case: Source of the case was updated to literature-non-interventional study. Reporter details updated. Patient demographics updated (age). Patient's concurrent conditions added. Study details added. Therapy details added. Event description updated. New literature reference added.

This case is cross referenced with AER 2599261, 2592769 and 2602176 (same literature article).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Chronic kidney disease			
Diabetes mellitus			
Hypertension			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
SARS-CoV-2 test					N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17737377

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	CHLOROQUINE							
2	LOPINAVIR/RITONAVIR							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text: Tomaszewicz K, Piekarska A, Stempkowska-Rejek J, Serafinska S, Gawkowska A, Parczewski M, Niscigorska-Olsen J, Lapinski T, Zarebska-Michaluk D, Kowalska J, Horban A and Flisiak R. Tocilizumab for patients with severe COVID-19: a retrospective, multi-centre study.. The Lancet Infectious Diseases 2020;:1-14.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17742574

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: DEU
Event Date: Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 21-May-2020
Mfr Rcvd Date: 19-May-2020
Mfr Control #: DE-ROCHE-2590898
Application #: 125276

Patient Information:

Age:
Sex: Male
Weight: 85 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		680 MG/	Intravenous (not otherwise specified)	18/Apr/2020 once	Off label use		18-Apr-2020
2	ROACTEMRA					Multiple organ dysfunction syndrome		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		Unk	NA	UNKNOWN				
2	ROACTEMRA		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1)	ReC
Intentional product use issue	NA
Lactic acidosis	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17742574

Event/Problem Narrative:

AER 2590898 is a spontaneous case, received on 24/Apr/2020 from a physician (critical care medicine) in Germany and concerns an elderly male patient who developed lactic acidosis while being treated with tocilizumab (Roactemra) intentionally for an unapproved indication as off label use.

The patient's concurrent conditions included arterial hypertension and diabetes mellitus type 2. Concomitant medications included norepinephrine and epinephrine (Adrenaline). No medical history and past drugs were reported.

(b) (6) the patient had a Covid 19 infection, which was confirmed by pathological changes observed in a computer tomography or X ray of the thoracic region and a positive Covid 19 test. On (b) (6) IL 6 levels were 335 pg/L. On (b) (6) at midday IL 6 levels were 4331 pg/L and 7612 pg/L in the evening. He was treated in an intensive care unit, he required oxygen therapy, mechanical ventilation and was treated with norepinephrin and received continuous veno venous hemodialysis with cytosorb. On the same day, he started therapy with intravenous (IV) tocilizumab (lot number: unknown; dosing regimen not reported) at 680 mg once intentionally for an unapproved indication Covid 19 induced cytokine storm with IL-6 levels of over 400 pg/L and associated multiple organ failure as off label use. The pyhsician reported that by the time tocilizumab was administered and he was already in a critical condition and was receiving adrenalin via syringe pump (Perfusor). On an unspecified date in (b) (6) after the tocilizumab administration he survived for another (b) (6) without adrenalin and then died due to a severe lactic acidosis caused by the multiple organ failure. The physician noted that a positive clinical effect of tocilizumab had been observable, but an earlier administration would be more beneficial. It was reported that, his family did not agree to an autopsy, therefore no autopsy report would be available.

The physician did not report the causality between lactic acidosis and tocilizumab, but as a consequence of the Covid-19 associated multiple organ failure.

No further information was provided.

Additional information was received on 19/May/2020. The following information was added to the case: Event description (It was reported that, his family did not agree to an autopsy, therefore no autopsy report would be available) was updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension			
Type 2 diabetes mellitus			



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17742574

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Interleukin level	4331	pg/L			N
Interleukin level	335	pg/L			N
Interleukin level	7612	pg/L			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ADRENALINE [EPINEPHRINE]							
2	NOREPINEPHRINE				COVID-19			

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17744530

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 22-Apr-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 05-May-2020 Mfr Rcvd Date: 28-Apr-2020 Mfr Control #: IT-ROCHE-2593471 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB			Intravenous (not otherwise specified)	8 mg/kg (up to a maximum of 800mg per dose), with an interval of 12 hours, last dose on 22/Apr/2020	COVID-19 pneumonia			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC

Respiratory failure NA

Event/Problem Narrative:

AER 2593471 is a clinical study case, received on 28/Apr/2020 from a physician in Italy. It concerns a patient of unknown demographics (patient number: (b) (6)) who died due to respiratory failure whilst enrolled in (b) (6) (b) (6)

Concurrent conditions included hypertension. Concomitant medications included dexamethasone, enoxaparin, idrossiclorochina. No medical history or past drugs were reported.

On an unspecified date, (b) (6) (b) (6) . On an unknown date, the patient was hospitalized for fever and dyspnea. During the hospitalization patient's clinical and radiological conditions were getting progressively worse. On 22/Apr/2020, patient developed respiratory failure. (b) (6) (b) (6) . On the same day, the patient had a persistent low saturation despite oxygen therapy patient did not have any indication to intubation. (u) (6) the patient died due to respiratory failure (severity grade:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17744530

5). Patient's death was from progressive respiratory failure related to interstitial pneumonia in patient with SARS COV 2 infection. It was not reported whether an autopsy was performed or not.

At the time of death therapy with tocilizumab was not reported.

The physician assessed the respiratory failure as unlikely related to tocilizumab.

The company assessed the causality of respiratory failure as unrelated to tocilizumab considering that the event is more related with underlying disease of COVID-19 pneumonia and its complications rather than tocilizumab therapy.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	DEXAMETHASONE							
2	ENOXAPARIN							



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17744530

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17749423

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ROM Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 06-May-2020 Mfr Rcvd Date: 01-Apr-2020 Mfr Control #:RO-ROCHE-2578540 Application #: 125276

Patient Information:

Age: 46 YR Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		400 MG/QD	Intravenous (not otherwise specified)	No	Severe acute respiratory syndrome	31-Mar-2020	
2	ROACTEMRA					COVID-19		
3	ROACTEMRA					Acute respiratory failure		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN,Unkn own				
2	ROACTEMRA		NA	NA	UNKNOWN,Unkn own				
3	ROACTEMRA		NA	NA	UNKNOWN,Unkn own				

Event Information:

Preferred Term (MedDRA Ⓐ Version: 23.1) ReC

Death NA

Off label use NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17749423

Event/Problem Narrative:

AER 2578540 is a spontaneous case, received on 01/Apr/2020 from a pharmacist (pharmacy) in Romania. It concerns a 46 year old patient (gender unspecified) who off label use, whilst being treated with tocilizumab (Roactemra).

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On an (b) (6) the patient started therapy with intravenous tocilizumab 400 mg once a day (lot number not reported) for acute respiratory insufficiency or severe acute respiratory syndrome-COV-2 infection. (b) (6)

(b) (6) On unknown date, after tocilizumab administration the patient died. The cause of death was not provided. It was not reported if an autopsy was performed or not.

At the time of death, it was not reported if therapy with tocilizumab was ongoing or not.

The reporter did not report the causality of patient died with tocilizumab

No further information was provided.

Additional information received on 21/Apr/2020, following information was added to the case: Event (patient died) was added and event description was updated accordingly

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17749423

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17754876

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: BEL Event Date: 29-Apr-2020 Outcomes: DE,OT, Application Type: BLA
 FDA Rcvd Date: 27-May-2020 Mfr Rcvd Date: 20-May-2020 Mfr Control #: BE-SA-2020SA115641 Application #: 761037

Patient Information:

Age: 83 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	KEVZARA		400 MG/	Intravenous (not otherwise specified)	400 mg	COVID-19 pneumonia	29-Apr-2020	30-Apr-2020
2	HYDROXYCHLOROQUIN E SULFATE		1 DF/Q12H	Oral	1 DF, BID	Drug use for unapproved indication	28-Apr-2020	29-Apr-2020
3	HYDROXYCHLOROQUIN E SULFATE		2 DF/Q12H	Oral	2 DF, BID	COVID-19 pneumonia	27-Apr-2020	27-Apr-2020
4	KEVZARA					Interleukin-6 increased		
5	PLAQUENIL		1 DF/Q12H	Oral	1 DF, BID	Drug use for unapproved indication	28-Apr-2020	28-Apr-2020
6	PLAQUENIL		1 DF/Q12H	Oral	1 DF, BID		29-Apr-2020	01-May-2020
7	PLAQUENIL		2 DF/Q12H	Oral	2 DF, BID	Coronavirus pneumonia	27-Apr-2020	27-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	KEVZARA		Unk	NA				SANOFI	
2	HYDROXYCHLOROQUIN E SULFATE	2112 MINUTES	Unk	NA				SANOFI	
3	HYDROXYCHLOROQUIN E SULFATE	2112 MINUTES	Unk	NA				SANOFI	
4	KEVZARA		Unk	NA				SANOFI	
5	PLAQUENIL	2299 MINUTES	Unk	NA				SANOFI	
6	PLAQUENIL	2299 MINUTES	Unk	NA				SANOFI	



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17754876

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)	Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
7 PLAQUENIL	2299 MINUTES	Unk	NA				SANOFI	

Event Information:

Preferred Term (MedDRA Ⓜ Version: 23.1)	ReC
Condition aggravated	NA
Off label use	NA
Product use issue	NA
Respiratory failure	NA
Wrong technique in product usage process	NA

Event/Problem Narrative:

Based on additional information received on 02-May-2020, case has become serious due to addition of serious event death, with seriousness criteria as fatal.

Initial information from Belgium was received on 29-Apr-2020 regarding an unsolicited valid serious case received from a physician.

This case involves a 83 years old male patient who experienced aggravation of pulmonary failure, and who took sarilumab (Kevzara) at a dose of 400 mg, while he was treated with sarilumab delivered with the use of sarilumab autoinjector, hydroxychloroquine sulfate and hydroxychloroquine sulfate [Plaquenil]. It was reported that there was an urgent situation request for the treatment of a COVID-19 patient with sarilumab, hydroxychloroquine sulfate [Plaquenil], hydroxychloroquine sulfate and that the patient started taking sarilumab 200mg/1.14 ml injection at a dose of 400 mg subcutaneously in 100 ml of 0.9% Nacl.

The patient's past medical history included hospitalisation with severe pulmonary dysfunction and IL-6 high, urinary plains, Inappetance, confusion, Asthenia, spo2 at 88% gradually decreasing to 70-75%, Agitation, 2 hospitalisation, Multistentent ischemic heart disease (OM1, proximal and average IVA, distal Cx, average Cx), Left ischemic stroke with sequelae of phasic disorders and trouble in walking, Leukoencephalopathy, cortico-subcortical atrophy, Benign prostate enlargement with urinary retention, Sigmoid diverticulosis, Renal cyst, Bilateral inguinal hernia cured by laparoscopy, thyroid nodule, L3 disc herniation treatment, Meniscectomy of the right knee, Dupuytren's disease, bilateral cataract operation, hypoxia and high C-reactive protein (high CRP).

The patient's past medical treatment(s) and family history were not provided.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17754876

At the time of the event, the patient had ongoing Type 2 diabetes, Retinopathy, Peripheral polyneuropathy (vertigo in particular), arteriopathy, high blood pressure, Spondylolisthesis degenerative L3 L4 with CLE, Beginning cognitive disorders with MMSE 25/30 in 2006 with periventricular leukoencephalopathy and pollen allergy.

Concomitant medications included azithromycin for COVID-19 pneumonia; cefuroxime; clopidogrel (Clopidogrel Sandoz) as anticoagulant; propranolol hydrochloride (Inderal) and perindopril both taken for hypertension arterial (HTA); morphine hydrochloride mixed with sodium chloride for sedation; paracetamol (Dafalgan Forte) for pain, fever and inflammation; paracetamol B Braun for pyrexia; enoxaparin sodium (Clexane) delivered via enoxaparin pre-filled syringe for anticoagulation; simvastatine for hyperlipidaemia; pantoprazole sodium sesquihydrate (Pantomed) as an antacid; insulin glargine (Basaglar) for diabetes; insulin aspart (Novorapid) for diabetes; haloperidol (Haldol) for agitation; midazolam hydrochloride in sodium chloride (midazolam B Braun) for insomnia; mirtazapine (Remergon) for depression; tamsulosin for prostate hypertrophy; ciprofloxacin hydrochloride (Ciproxin) for urinary plains; duloxetine hydrochloride (Cymbalta); perindopril erbumine (Coversyl); acetylsalicylic acid (Asaflow); tramadol hydrochloride (Contramal); sildenafil citrate (Sildenafil Sandoz); simvastatin (Zocor); mirtazapine; insulin glargine (Lantus), Aquapak Respiflich, and perfusions: glucose/NaCl (sodium chloride/ potassium phosphate, glucose/KCl (potassium chloride), glucose/NaCl/KCl, NaCl/potassium phosphate.

Smear test - On 24-Apr-2020: [positive for Severe SARS-CoV2 pneumonia in MRS by RT-PCR]; on (b) (6) [positive]. Computerised tomogram - On (b) (6) : [Mediastin : Calcified atheromatosis of the thoracic aorta and coronary arteries. No mediastinal lymphadenopathy; some sequential calcified nodes.No pleuro-pericardial effusion.Tracheobronchial calcifications. Lung parenchyma: Multitude of vast areas of opacities in frosted glass with crazy paving of diffuse topography predominantly peripheral, and innumerable small confluent condensations in the two lower lobes. Bi-apical fibroretractile sequences.]

On (b) (6) at 09:41, the patient started taking hydroxychloroquine sulfate (Plaquenil) 200 mg capsule at a dose of 2 DF twice daily orally (lot details: unknown) for a severe SARS-Cov2 pneumonia and product use in unapproved indication.

On (b) (6) at 12:48, the patient started taking hydroxychloroquine sulfate 200 mg capsule at a dose of 2 DF twice daily orally (lot details: unknown) for a severe SARS-Cov2 pneumonia and Product use in unapproved indication.

Blood culture - On (b) (6) : [negative]

Computerised tomogram thorax - On (b) (6) : [High CoVid19 suspicion level: Multitude of vast areas of large frosted glass opacities with crazy paving of diffuse topography predominantly peripheral, and innumerable small confluent condensations in the two lower lobes. Bi-apical fibroretractile sequelae 70% of pulmonary parenchyma affected. Unfavorable evolution. Il6 measured at 866-high on an unknown date]

Oxygen saturation - On (b) (6) 75 %

On (b) (6) Gasometry : under NRBM FiO2 100% : 7.55 / 36/60 HCO3 32 - SaO2 92% - lactates 2.4, Saturation under FiO2 : 98 % under FiO2 100 % unknown date: Lungs: Crepitating major bibasal at the bases.

On (b) (6) hydroxychloroquine sulfate (Plaquenil) dosage was changed to 1 DF BID.

On (b) (6) 0 at 10:00 hydroxychloroquine sulfate dosage was changed to 1 DF BID.

Consent was made under normal emergency procedure. They believed that the risk for non-treatment was higher than the risk of treatment



FDA - Adverse Event Reporting System (FAERS)

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with sarilumab. The risks and benefits have been extensively discussed with the patient (and his/her family), he/she signed an informed consent and agreed to start treatment with sarilumab. They have notified the Ethics Committee of our hospital of this urgent request. On (b) (6) the patient started taking sarilumab 200mg/1.14 ml injection at a dose of 400 mg subcutaneously in 100 ml of 0.9% NaCl (Unapproved dose administered; wrong technique in drug usage process, latency: same day from sarilumab, 2 days from the other co suspect drugs; lot details: unknown) delivered via sarilumab autoinjector for a severe SARS-Cov2 pneumonia and as anti IL6. On (b) (6) hydroxychloroquine sulfate (Plaquenil) dosage was changed to 1 DF twice daily. There was an urgent situation request for the treatment of a COVID-19 patient with sarilumab, hydroxychloroquine sulfate (Plaquenil), hydroxychloroquine sulfate (off label use; onset date and latency: unknown)

The patient had aggravation of pulmonary failure on an unknown date (latency: unknown). Life expectancy was of more than 48 Hours. The patient died of it and COVID-19 pneumonia on (b) (6) and the death was not related to sarilumab. No autopsy was performed.

Action taken: unknown for aggravation of pulmonary failure and not applicable for the rest.

It was not reported if the patient received a corrective treatment.

Outcome: fatal for aggravation of pulmonary failure and not applicable for the rest.

Seriousness criteria: death of the patient and medically significant for aggravation of pulmonary failure.

Additional information received on 02-May-2020 from Physician:
New serious event death added. Text amended accordingly.

Additional information was received on 20-May-2020 by the physician: medical history, concurrent conditions were added. Concomitant medications and labs were updated. The event-aggravation of pulmonary failure, unapproved dose administered and wrong technique in drug usage process.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Pollen allergy	01-Jul-1936		YES
Hernia repair	1987	1987	NO
Meniscus removal	2000	2000	NO



FDA - Adverse Event Reporting System (FAERS)

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Dupuytren's contracture	2002	2002	NO
Atrophy	2006		UNKNOWN
Laparoscopy	2006	2006	NO
Leukoencephalopathy	2006		UNKNOWN
Cataract operation	Jan-2017	Jan-2017	NO
Pollakiuria	21-Apr-2020		UNKNOWN
Appetite lost	22-Apr-2020		UNKNOWN
Asthenia	22-Apr-2020		UNKNOWN
Confusion	22-Apr-2020		UNKNOWN
Hospitalization	(b) (6)		UNKNOWN
Agitated			
Arteriopathy			YES
Bilateral inguinal hernia			
Blood pressure high			YES
C-reactive protein increased			
Cognitive disorders			YES
Enlarged prostate (benign)			
Hospitalization			
Hypoxemia			
Ischemic heart disease			
Ischemic stroke			
Oxygen saturation decreased			
Polyneuropathy			YES
Pulmonary disorder			



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Renal cyst	
Retinopathy	YES
Sigmoid diverticulosis	
Spondylolisthesis	YES
Thyroid nodule	
Type II diabetes mellitus	YES
Urinary retention	
Vertigo	YES
Walking difficulty	

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
CT scan					Y
Oxygen saturation	75	%			N
Blood culture					Y
Interleukin-6	866	UNK			Y
Smear test					Y
Thorax CAT					Y
Smear test					Y

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ASAFLOW	1 DF/	Oral	1 DF				
2	AZITHROMYCIN	250 MG/QD	Oral	250 mg, QD	COVID-19 pneumonia	26-Apr-2020	01-May-2020	3 DAY
3	BASAGLAR	Q12H	Subcutaneous	18 U, BID		29-Apr-2020	30-Apr-2020	5 DAY



FDA - Adverse Event Reporting System (FAERS)

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	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
4	BASAGLAR	QD	Subcutaneous	22 U, QD	Diabetes	26-Apr-2020	28-Apr-2020	5 DAY
5	CEFUROXIME	1 DF/Q8H		1 DF, TID		26-Apr-2020	29-Apr-2020	5 DAY
6	CIPROXIN [CIPROFLOXACIN HYDROCHLORIDE]	2 DF/QD		2 DF, QD	Pollakiuria			
7	CLEXANE	60 MG/Q12H	Subcutaneous	60 mg, BID	Anticoagulant therapy	26-Apr-2020		5 DAY
8	CLOPIDOGREL SANDOZ [CLOPIDOGREL]	75 MG/		75 mg	Anticoagulant therapy			
9	CONTRAMAL	1 DF/	Oral	1 DF				
10	COVERSYL [PERINDOPRIL ERBUMINE]	1 DF/	Oral	1 DF				
11	CYMBALTA	1 DF/	Oral	1 DF				
12	DAFALGAN FORTE	Q6H	Oral	UNK UNK, Q6H	Pain	26-Apr-2020		5 DAY
13	DAFALGAN FORTE				Fever			5 DAY
14	DAFALGAN FORTE				Inflammation			5 DAY
15	HALDOL [HALOPERIDOL]	5 GTT/QD	Oral	5 Gtt drops, QD	Agitation	27-Apr-2020		4 DAY
16	INDERAL	40 MG/QD		40 mg, QD	Hypertension arterial	27-Apr-2020		4 DAY
17	LANTUS	22 IU/		22 iU				
18	MIDAZOLAM B BRAUN	5 MG/	Intravenous bolus	5 mg	Insomnia	30-Apr-2020	30-Apr-2020	1 DAY
19	MIRTAZAPINE	15 MG/		15 mg				
20	MORPHINE HYDROCHLORIDE	2 MG/Q4H	Intravenous bolus	2 mg, Q4H	Sedation	29-Apr-2020		2 DAY
21	NOVORAPID		Subcutaneous	UNK	Diabetes	26-Apr-2020		5 DAY
22	PANTOMED [PANTOPRAZOLE]	1 DF/QD	Oral	1 DF, QD	Antacid therapy	26-Apr-2020		5 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17754876

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
23 SODIUM SESQUIHYDRATE] PANTOMED [PANTOPRAZOLE SODIUM SESQUIHYDRATE]	1 DF/Q12H	Intravenous bolus	1 DF, BID		28-Apr-2020		5 DAY
24 PARACETAMOL B BRAUN	3 DF/	Intravenous drip	3 DF	Fever	28-Apr-2020		3 DAY
25 PERINDOPRIL	4 MG/QD		4 mg, QD	Hypertension arterial	27-Apr-2020	29-Apr-2020	4 DAY
26 REMERGON	1 DF/QD	Oral	1 DF, QD	Depression	26-Apr-2020	28-Apr-2020	5 DAY
27 SILDENAFIL SANDOZ	.5 DF/	Oral	0.5 DF				
28 SIMVASTATINE	1 DF/	Oral	1 DF	Hyperlipidemia	26-Apr-2020	28-Apr-2020	5 DAY
29 SODIUM CHLORIDE				Interleukin-6 increased			2 DAY
30 SODIUM CHLORIDE		Subcutaneous	UNK	COVID-19 pneumonia	29-Apr-2020	30-Apr-2020	2 DAY
31 SODIUM CHLORIDE		Intravenous bolus	UNK	Insomnia	30-Apr-2020	30-Apr-2020	1 DAY
32 SODIUM CHLORIDE	2 MG/Q4H	Intravenous bolus	2 mg, Q4H	Sedation	29-Apr-2020		2 DAY
33 TAMSULOSIN	1 DF/QD	Oral	1 DF, QD	Prostatic hypertrophy	26-Apr-2020		5 DAY
34 ZOCOR	1 DF/	Oral	1 DF				

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17759164

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: POL
Event Date: 17-Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 08-May-2020
Mfr Rcvd Date: 30-Apr-2020
Mfr Control #: PL-ROCHE-2593641
Application #: 125276

Patient Information:

Age: 72 YR
Sex: Male
Weight: 110 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		800 MG/	Intravenous (not otherwise specified)	frequency: 1x	COVID-19	17-Apr-2020	17-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	0 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2593641 is a spontaneous case, received on 30/Apr/2020 from a physician (anesthesiology) in Poland. It concerns a 72 year old male patient who died due to co morbidities (captured as death), who made use of tocilizumab in covid-19 (intentional use for unapproved indication) and off-label use whilst being treated with tocilizumab (Roactemra).

The patient's concurrent conditions included lymphocytic leukemia, ischemic heart disease, arterial hypertension, hyperlipidemia, obesity, heart arrhythmia, STEM (//2010), NYHA II/III, condition after hip replacement, PEEP positive and expiratory pressure. Concomitant medications included norepinephrine (Noradrenaline), dobutamine (Dobutamine). No medical history and past drugs reported.

He was on supplemental oxygen therapy (0,4 to 0,9), treated in ICU (b) (6) to (b) (6). On (b) (6), the patient started therapy with intravenous tocilizumab (lot number: not reported) 800 mg, frequency: 1x for covid-19 (unapproved indication, off label use). On



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17759164

(b) (6), the patient developed use of tocilizumab in covid-19 (intentional use for unapproved indication). He died on (b) (6) It was reported that he was died because of comorbidities and general condition, not because of tocilizumab. But, the comorbidities were not specified. It was unknown if an autopsy was performed or not.

At the time of death, therapy with tocilizumab was withdrawn.

The physician assessed the death as unrelated to tocilizumab.

No further information was provided.

Relevant Medical History:

STEM (//2010), NYHA II/III, condition after hip replacement, PEEP positive and expiratory pressure

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Arrhythmia			
Hyperlipidaemia			
Hypertension			
Lymphocytic leukaemia			
Myocardial ischaemia			
Obesity			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17759164

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	DOBUTAMINE							
2	NORADRENALINE [NOREPINEPHRINE]							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17759274

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 01-May-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 18-May-2020 Mfr Rcvd Date: 08-May-2020 Mfr Control #: US-ROCHE-2595334 Application #: 125276

Patient Information:

Age: 75 YR Sex: Male Weight: 53.5 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	BLINDED TOCILIZUMAB			Unknown		COVID-19	23-Apr-2020	23-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	BLINDED TOCILIZUMAB	8 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC
 COVID-19 NA
 Respiratory failure NA

Event/Problem Narrative:

AER 2595334 is a clinical study case, received on 02/May/2020 from a physician in the USA. It concerns a 75 year old male patient (patient number: (b) (6)) who developed respiratory failure, covid-19 and died whilst enrolled in (b) (6) (b) (6)

The patient's concurrent conditions included congestive heart failure, diabetes mellitus type II, Parkinson's disease and coronary kidney disease. No medical history, past drugs and concomitant medications were reported

On an unspecified date, the patient was found on the ground at the nursing home he lived in. He had no head strike however had altered mental status. On (b) (6) he was hospitalized and had respiratory failure. It was stated that, infectious disease work up was negative. Laboratory values revealed elevated CK, sodium and inflammatory markers. Increased inflammatory markers were concerning for COVID. Chest x ray revealed multifocal pneumonia consistent with COVID. (b) (6)

(b) (6) He was not intubated. On (b) (6) he was



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17759274

given comfort measures only for his respiratory status. On (b) (6) at 06:24 PM, he died due to respiratory failure and covid-19. It was not reported if an autopsy was performed or not.

The physician assessed the respiratory failure and covid-19 as not related to tocilizumab.

No further information was provided.

Additional information was received on 08/May/2020. The following information was added to the case : Protocol number: (b) (6) update the source to Clinical trial from spontaneous.

Relevant Medical History:

Coronary Kidney Disease

Disease/Surgical Procedure

Cardiac failure congestive

Parkinson's disease

Type 2 diabetes mellitus

Start Date

End Date

Continuing?

Medical History Product(s)

Start Date

End Date

Indications

Events

Relevant Laboratory Data:

Test Name

Result

Unit

Normal Low Range

Normal High Range

Info Avail

Concomitant Products:

Product Name

Dose/
Frequency

Route

Dosage Text

Indications(s)

Start Date

End Date

Interval 1st
Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17759274

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17761274

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 28-Mar-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 08-May-2020 Mfr Rcvd Date: 28-Apr-2020 Mfr Control #: IT-ROCHE-2593642 Application #: 125276

Patient Information:

Age: 61 YR Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		8 MG/KG/	Intravenous (not otherwise specified)	most recent dose: 25/Mar/2020	COVID-19 pneumonia			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC

Respiratory failure NA

Event/Problem Narrative:

AER 2593642 is a clinical study case, received on 28/Apr/2020 from a physician in Italy and concerns a 61 year old patient of unspecified gender (patient number: (b) (6)) who died of respiratory failure whilst enrolled in (b) (6) (b) (6)

No medical history, past drug, concurrent condition or concomitant medication were reported.

On an unknown date, (b) (6) (b) (6)

(b) (6) On 26/Mar/2020, the patient started treatment with piperacillin sodium;tazobactam sodium (Piperacillina/Tazobactam), 4.5 g (total: 4 doses). On (b) (6) the patient developed respiratory failure and died of it (severity: grade 5). It was not reported if an autopsy was performed or not.

The physician assessed the fatal respiratory failure as unlikely related (related) to tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17761274

The company assessed the fatal respiratory failure as unrelated to tocilizumab and rather related with underlying disease Covid-19 pneumonia.

No further information was performed.

Relevant Medical History:

None

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17761274

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17761778

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 18-Apr-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 08-May-2020 Mfr Rcvd Date: 05-May-2020 Mfr Control #: IT-ROCHE-2596994 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		8 MG/KG/Q12H	Unknown	last administration of tocilizumab: 11/Apr/2020 Tocilizumab 8 mg/kg (up to a maximum of 800mg per do	COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC

Respiratory failure NA

Event/Problem Narrative:

AER 2596994 is a clinical study case, received on 05/May/2020 from a physician in Italy. It concerns a patient of unknown demographics (patient number: (b) (6)) who died due to respiratory failure whilst enrolled in (b) (6) (b) (6)

The patient's concurrent conditions included GVHD. No past history, past drugs and concomitant medications were reported.

On an unknown date, (b) (6) (b) (6)

(u) (b) . On (b) (6) the patient died due to respiratory failure (severity: grade 5). It was not reported if an autopsy was performed or not.

The physician assessed the causality of fatal respiratory failure as related with tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17761778

The company assessed the causality of fatal respiratory failure as not related with tocilizumab but related to the underlying disease. Tocilizumab is a recombinant humanized monoclonal antibody of the immunoglobulin IgG1 subclass which acts on interleukin 6 receptors. No therapy details, past history, past drugs and concomitant medications, clinical course investigations and patient details were reported. The causality will be reassessed as per updated information is received.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Graft versus host disease			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17761778

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17763817

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ITA
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 15-May-2020
Mfr Rcvd Date: 08-May-2020
Mfr Control #: IT-ROCHE-2569193
Application #: 125276

Patient Information:

Age: 60 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA			Intravenous (not otherwise specified)	8 mg/kg	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
COVID-19	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2569193 is a spontaneous case, received on 13/Mar/2020 from a physician (rheumatology) in Italy. It concerns 60 year old male patient who had covid-19 infection when treated with tocilizumab (Roactemra) as an intentional drug used for unlabeled indication (off label use for COVID-19).

Past medical history included multiple myeloma and chronic kidney disease. No past drugs, concurrent condition and concomitant medications were reported.

In his medical history, four years before this admission, he received a diagnosis of multiple myeloma (MM) complicated by acute kidney injury (AKI). MM was successfully treated with VTD chemotherapy and subsequent autologous stem cell transplantation. He had been on complete remission since that time, receiving monthly administration of bortezomib as maintenance therapy. Despite complete hematological response,



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17763817

he did not fully recover kidney function, ending with CKD stage 4-5. He was presented to the emergency department after five days of unremitting high fever (T > 39 degree C), dry cough, progressive dyspnea, and diarrhea as prodromal symptom severe interstitial involvement. He was put on dialysis. He started therapy with intravenous tocilizumab infusion, solution of 8 mg/kg (lot number: unknown; dose and frequency not reported) for COVID-19 infection as an intentional drug used for unlabeled indication (off label use). He was afebrile and in respiratory distress. On an unknown date Chest radiograph was performed which showed bilateral basal and sub-pleural ground-glass opacities with no pleural effusion. Laboratory tests showed leukopenia with lymphocytopenia, low CD4 and CD8 cell count, significantly low platelet count, increased C-reactive protein (CRP) and lactate dehydrogenase (LDH), hyperfibrinogenemia, and AKI requiring dialysis. His therapy includes oxygen support, lopinavir/ritonavir (400/100mg x 2/day), hydroxychloroquine (200 mg x 2/day), and empirical antibiotic therapy. After three days progressive dyspnea and high unremitting fever persisted. On an unknown date, lab test were performed which showed remarkably high hyperferritinemia (4768 ng/ml) and IL-6 (300 pg/ml), with progressive lymphocytopenia. The blood and urine cultures was found to be negative on third day after admission. After 24 hrs of Tocilizumab, he became afebrile, with stabilization of respiratory exchanges. After 48 hours later, his lymphocyte and platelet count were increasing, while CRP, LDH and ferritin were decreasing. As adjunctive supporting measure, RRT was started. Four days after the first administration, a second dose of Tocilizumab (8 mg/kg IV) was used due to worsening of respiratory distress and laboratory data. Oxygen support was upgraded to continuous positive airway pressure (CPAP) ventilation. Respiratory exchanges drastically was improved and, after 48h, laboratory test showed again increased lymphocyte and platelet count, reduced CRP, LDH and ferritin levels. Three days later again, He went again in respiratory distress. Considering his medical history, a decision was made not to proceed to mechanical ventilation and a third dose of Tocilizumab (8 mg/kg IV) was administered as last rescue therapy. Despite the severe condition, he remained clinically stable for the following week. Finally, he developed sudden onset of severe hypoxemia and hypocapnia, and abdominal pain, with drastic increase in levels of LDH, lactate, liver enzymes and leukocytosis, suggestive for disseminated clotting with pulmonary embolism, hepatic and intestinal ischemia. A CT scan to confirm the diagnosis was not performed in light of his prognosis. On an unknown date, he had covid-19 infection and he died due to covid-19 infection. It was unknown whether the autopsy was performed or not.

At the time of this report, it was not reported if therapy with tocilizumab was altered or not in response to the covid-19 infection.

The physician did not report a causality between covid-19 infection and tocilizumab.

No further information was reported.

Additional information was received on 27/Apr/2020 and the following information was added to the case: Patient's information added and event description updated.

Additional information was received on 08/May/2020 and the following information was added to the case: Query reply confirmed that, patient died due to covid-19 infection, for that reason death had not considered as an event (so, event term amended as covid-19 infection with fatal outcome).



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17763817

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Chronic kidney disease			
Plasma cell myeloma			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Chest X-ray					N
Culture urine					N
Laboratory test					N
Blood culture					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17763825

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ITA **Event Date:** **Outcomes:** DE, **Application Type:** NDA

FDA Rcvd Date: 10-May-2020 **Mfr Rcvd Date:** 04-May-2020 **Mfr Control #:** IT-ROCHE-2598295 **Application #:** 050722

Patient Information:

Age: 63 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	MYCOPHENOLATE MOFETIL			Unknown		Prophylaxis against transplant rejection		
2	TOCILIZUMAB					Acute respiratory distress syndrome		
3	TOCILIZUMAB		8 MG/KG/	Intravenous (not otherwise specified)		COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	MYCOPHENOLATE MOFETIL		NA	NA	UNKNOWN				
2	TOCILIZUMAB		NA	NA	UNKNOWN				
3	TOCILIZUMAB		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Ⓜ Version: 23.1)	ReC
Acute respiratory distress syndrome	NA
COVID-19	NA
COVID-19 pneumonia	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17763825

Event/Problem Narrative:

AER 2598295 is a literature-non-interventional study case, received on 04/May/2020 from a health care professional in Italy and concerns a 63-year-old male patient (patient number: 12) who died due to COVID 19 infection, COVID 19 pneumonia and acute respiratory distress syndrome while being treated with mycophenolate mofetil (MMF) and calcineurin inhibitor (CNI) and later he was intentionally treated with tocilizumab for unlabeled indication (off label use) while enrolled in a single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia.

All the patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection admitted in the nephrology unit of hospital who had underwent kidney transplantation were included. In brief, all admitted patients were on baseline immunosuppression therapy (MMF, CNI, mammalian target of rapamycin inhibitor (mTOR) and Low-dose glucocorticoid (Prednisone 5 mg/d or methylprednisolone 4 mg/d) and later they all had immunosuppression withdrawn and were commenced on methylprednisolone 16 mg/d or equivalent dose of prednisone. Antiviral therapy with lopinavir/ritonavir plus hydroxychloroquine (dose adjusted for kidney function) was considered in all patients if not contraindicated. Antiviral therapy (duration: 5-20 days to be determined based on clinical progression, Lopinavir/ ritonavir 200/50 mg 2 tabs x2/day Or Darunavir 800 mg 1 tab/day + ritonavir 100 mg 1 tab/day Or Darunavir/cobicistat 800/150 mg 1 tab/day. Hydroxychloroquine was given in following doses: 200 mg x2/day if GFR >30 ml/min, 200 mg/day if GFR >15 ml/min and <30 ml/min, 200 mg every other day if GFR <15 ml/min. In case of shortage of lopinavir/ritonavir, darunavir and ritonavir were employed. Patients experiencing clinical deterioration after at least 7 days from symptoms onset or no temperature for > 72 hours but with escalating oxygen requirements or progression of the chest radiography and no signs of bacterial infection were considered for dexamethasone (20 mg/d for 5 days, then 10 mg/d for 5 days). Patients were considered for tocilizumab for at least 3 of the following criteria: the patient has dyspnoea or STACCATO SPEECH (inability to count rapidly to 20 after taking a deep breath) at rest or after minimum activity (sitting down on bed, standing up, speaking, swallowing, coughing), Respiratory rate > 22/min Or PaO₂ <65mmHg or SpO₂<90%, Significant worsening of chest x-ray (increased compactness and extension of infiltrate) And if the high viral load phase can be considered to be overcome (e.g. no fever for >72h and/or at least 7 days from symptoms onset), Ongoing superimposed bacterial infection can be ruled out clinically (patients at this stage of the disease usually present elevated CRP; a negative procalcitonine may be helpful in ruling out bacterial infection), Worsening of respiratory exchanges and/or significant worsening of chest imaging. Absence of the following exclusion criteria should be there for Tocilizumab infusion: AST/ALT 5 times higher than normal, Neutrophils below 500 cells/mm³, PLT below 50,000 cells/mm³, documented sepsis due to pathogens other than COVID-19, Presence of comorbidities associated with unfavorable outcome based on clinical judgement, Complicated diverticulitis or bowel perforation, Ongoing skin infection (e.g. antibiotic-induced uncontrolled dermatitis), On-going anti-rejection immunosuppressive therapy. The dose was up to 2 tocilizumab infusions at intervals of 12 to 24 hours (8 mg/kg of body weight, maximum dose per infusion 800 mg). In case of tocilizumab administration, broad spectrum antibiotics were employed and antiviral therapy maintained. Oxygen requirements were categorized as follow: no oxygen needs; low oxygen requirement, from nasal cannula up to Venturi mask with FiO₂ of 0.5, high oxygen requirement, including Venturi mask with FiO₂ of 0.6, reservoir mask with oxygen at 15 l/min, and high-flow nasal ventilation; non-invasive ventilation; and mechanical ventilation. Considering the well-documented effects of lopinavir/ritonavir and hydroxychloroquine on increasing the cardiac QTc interval, electrocardiograms were performed every 2 to 3 days. In case of prolongation compared with baseline, dose reduction was performed. Due to the small sample size, only descriptive statistics were performed, results were expressed as count (percentage) for categorical variables and median and IQR for continuous variables. In this report, they describe the progress of all patients with SARS-CoV2 pneumonia who had undergone kidney transplantation admitted up to 24/Mar/2020. These patients had a median inpatient



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17763825

stay of 7 days (interquartile range [IQR], 4-15). Briefly, all patients presented with fever; however, only 1 of the 20 complained of dyspnea; 50% of the patients who had undergone transplantation had radiographic changes of bilateral infiltrates on admission, while the remaining 50% showed unilateral changes or no infiltrates; 7 did not require supplemental oxygen at admission. All patients had their usual transplant immunosuppression withdrawn and were started on methylprednisolone 16 mg or equivalent dose of prednisone, and 19 of the 20 received antiviral therapy and hydroxychloroquine as per their institute protocol. As antiviral therapy was known to interfere with calcineurin inhibitor metabolism, in 4 patients, tacrolimus levels were monitored after these therapeutic changes were instituted. The median trough values before antiviral therapy were 7.05 ng/ml (IQR, 5.5-8.6): 1 patient had the level rechecked after 3 days with no change compared with baseline; 1 patient had the level rechecked 4 and 5 days after admission (-17% and -18% compared with baseline); 1 was rechecked 6 days after admission (-12% compared with baseline); and 1 was rechecked 8 days after admission (-21% compared with baseline). The median times from symptom onset and admission to these therapeutic changes were, respectively, 5 days (IQR, 3-8.25) for antiviral therapy and 0 days (IQR, 0-0) for hydroxychloroquine. During the follow-up, 1 patient had hydroxychloroquine withdrawn due to toxicity (nausea, vomiting); among the treated patients no prolongation of the cardiac QTc interval compared with baseline or cardiac arrhythmias were observed. Antibiotics were administered to 11 of the 20 patients (55%): cephalosporins in 64%; beta-lactams in 36%; fluoroquinolones in 25%; carbapenems in 10%; and glycopeptides in 5%. During hospitalization, chest radiographs were repeated in 15 patients and radiological findings worsened in 13 of those 15 (87%). In the 13 individuals with worsening radiological findings, 11 (85%) required an escalation of the oxygen supplemental therapy, including 1 patient switched from regular breathing to low oxygen requirement, 3 from regular breathing to high oxygen requirement, 3 from low to high oxygen requirement, 2 from high oxygen requirement to non-invasive ventilation, and 2 from high oxygen requirement to mechanical ventilation. Additional anti-inflammatory therapy with dexamethasone or tocilizumab, respectively, was given to 11 (55%) and 6 of the 20 patients (30%); in these patients, respectively, 4 (36%) and 2 (33%) subsequently died. Among these 6 patients, 3 (50%) experienced a reduction of the oxygen requirements and 2 (33%) showed amelioration of the radiological findings. In terms of kidney function, the medium creatinine level at admission was +17% (IQR, 12%-26%; range, 0%-143%) compared with baseline, and the highest creatinine level observed during the follow-up was +33% (IQR, 13%-59%; range, 0%-157%) compared with baseline; 6 of 20 patients developed acute kidney injury and 1 of those 6 required hemodialysis. During follow-up of the 20 patients, 4 (20%) required intensive care and 3 of these individuals subsequently died. Overall, 5 patients died after a median of 11 days from admission (IQR, 11-14 days) and 15 days (IQR, 15-19 days) from symptom onset; of these 5 patients, 4 died from complications of the respiratory failure secondary to SARS-CoV2 infection and 1 died of probable bacterial sepsis (fever, rise of C-reactive protein, and procalcitonin) despite a satisfactory recovery from SARS-CoV2 pneumonia-induced respiratory failure, need for intensive care unit care, and treatment with dexamethasone and tocilizumab. Three patients were discharged, after 7 days in 1 case and after 16 in the 2 remaining cases; at discharge, creatinine levels compared with baseline were 3.6 versus 2.1, 2.3 versus 2.5, and 2.1 versus 1.5 mg/dl. In terms of immunosuppressive therapy, 2 patients were discharged receiving methylprednisolone 16 mg/d and 1 with methylprednisolone 12 mg/d.

This case concerns patient number: 12.

The patient's concomitant conditions included hypertension, while concomitant medication and past drugs were not reported. No risk factors were available.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17763825

In Aug/2004, the patient underwent kidney transplantation (medical history). His baseline immunosuppression therapy included mycophenolate mofetil (lot number and dosage regimen not reported) and calcineurin inhibitor (CNI) (therapy details not reported). On an unspecified date, he was diagnosed with COVID 19 infection and admitted in the nephrology unit of the hospital for COVID 19 infection with COVID 19 pneumonia and investigated with routine investigations and Chest X-ray. His baseline creatinine was 203 mmol/l and eGFR was 29 ml/min per 1.73 m2. His immunosuppression was withdrawn and he was commenced on methylprednisolone 16 mg/day or equivalent dose of prednisone. Antiviral therapy with lopinavir/ritonavir 200/50 mg 2 tabs x 2/day plus hydroxychloroquine was started at a recommended dose as per the eGFR. However, he developed acute respiratory distress syndrome and was on non-invasive ventilation. Later, he was started with additional anti-inflammatory therapy of intravenous tocilizumab infusion 8 mg/kg (lot number, dose and frequency not reported, Off label use, intentional use of drug for unlabeled indication) and dexamethasone (20 mg/d for 5 days, then 10 mg/d for 5 days) for COVID 19 infection and ARDS. On an unspecified date, he died due to COVID 19 infection, COVID 19 pneumonia and acute respiratory distress syndrome. It was not reported whether autopsy was performed or not.

At the time of death, there was insufficient information regarding the therapy ongoing status of tocilizumab.

The author stated that immunosuppression (mycophenolate mofetil, calcineurin inhibitor and low-dose steroids) and chronic kidney disease may represent additional risk factors for COVID 19 infection and its complications (COVID 19 pneumonia and acute respiratory distress syndrome).

Additional information has been requested.

Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, Maffei C, Possenti S, Zambetti N, Moscato M, Venturini M, Affatato S, Gaggiotti M, Bossini N and Scolari F.

A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia.

Kidney International, 2020: 1-6. DOI: 10.1016/j.kint.2020.04.002.

This case is cross referenced with AER: 2594877 (Base case, same literature article).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Renal transplant	(b) (6)		
Hypertension			



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FOIA Case Report Information

Case ID: 17763825

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Coronavirus test					N
Blood creatinine	203	µmol/L			N
Glomerular filtration rate	29	ml/min/1.73 sq meter			N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding Outsourcing Facility?:

Literature Text:

Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, Maffei C, Possenti S, Zambetti N, Moscato M, Venturini M, Affatato S, Gaggiotti M, Bossini N and Scolari F A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. Kidney International 2020 Apr 09;;1-6.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17763830

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ITA
Event Date:
Outcomes: DE,HO,
Application Type: NDA
FDA Rcvd Date: 10-May-2020
Mfr Rcvd Date: 04-May-2020
Mfr Control #: IT-ROCHE-2598288
Application #: 050722

Patient Information:

Age: 57 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	MYCOPHENOLATE MOFETIL			Unknown		Prophylaxis against transplant rejection		
2	TOCILIZUMAB					Acute respiratory distress syndrome		
3	TOCILIZUMAB		8 MG/KG/	Intravenous (not otherwise specified)		COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	MYCOPHENOLATE MOFETIL		Unk	NA	UNKNOWN				
2	TOCILIZUMAB		Unk	NA	UNKNOWN				
3	TOCILIZUMAB		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Ⓜ Version: 23.1)	ReC
Acute respiratory distress syndrome	NA
Bacterial sepsis	NA
COVID-19	NA
COVID-19 pneumonia	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17763830

Event/Problem Narrative:

AER 2598288 is a literature-non-interventional study case, received on 04/May/2020 from a health care professional in Italy and concerns a 57-year-old male patient (patient number: 4) who developed COVID 19 infection, COVID 19 pneumonia, acute respiratory distress syndrome (ARDS) while being treated with mycophenolate mofetil (MMF), calcineurin inhibitor (CNI) and low-dose steroids and later he was intentionally treated with tocilizumab for unlabeled indication (off label use) and died due to bacterial sepsis while enrolled in a single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia.

All the patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) infection admitted in the nephrology unit of hospital who had underwent kidney transplantation were included. In brief, all admitted patients were on baseline immunosuppression therapy (MMF, CNI, mammalian target of rapamycin inhibitor (mTOR) and Low-dose glucocorticoid (Prednisone 5 mg/d or methylprednisolone 4 mg/d) and later they all had immunosuppression withdrawn and were commenced on methylprednisolone 16 mg/d or equivalent dose of prednisone. Antiviral therapy with lopinavir/ritonavir plus hydroxychloroquine (dose adjusted for kidney function) was considered in all patients if not contraindicated. Antiviral therapy (duration: 5-20 days to be determined based on clinical progression, Lopinavir/ ritonavir 200/50 mg 2 tabs x2/day Or Darunavir 800 mg 1 tab/day + ritonavir 100 mg 1 tab/day Or Darunavir/cobicistat 800/150 mg 1 tab/day. Hydroxychloroquinine was given in following doses: 200 mg x2/day if GFR >30 ml/min, 200 mg/day if GFR >15 ml/min and <30 ml/min, 200 mg every other day if GFR <15 ml/min. In case of shortage of lopinavir/ritonavir, darunavir and ritonavir were employed. Patients experiencing clinical deterioration after at least 7 days from symptoms onset or no temperature for > 72 hours but with escalating oxygen requirements or progression of the chest radiography and no signs of bacterial infection were considered for dexamethasone (20 mg/d for 5 days, then 10 mg/d for 5 days). Patients were considered for tocilizumab for at least 3 of the following criteria: the patient has dyspnoea or STACCATO SPEECH (inability to count rapidly to 20 after taking a deep breath) at rest or after minimum activity (sitting down on bed, standing up, speaking, swallowing, coughing), Respiratory rate > 22/min Or PaO₂ <65mmHg or SpO₂<90%, Significant worsening of chest x-ray (increased compactness and extension of infiltrate) And if the high viral load phase can be considered to be overcome (e.g. no fever for >72h and/or at least 7 days from symptoms onset), Ongoing superimposed bacterial infection can be ruled out clinically (patients at this stage of the disease usually present elevated CRP; a negative procalcitonine may be helpful in ruling out bacterial infection), Worsening of respiratory exchanges and/or significant worsening of chest imaging. Absence of the following exclusion criteria should be there for Tocilizumab infusion: AST/ALT 5 times higher than normal, Neutrophils below 500 cells/mm³, PLT below 50,000 cells/mm³, documented sepsis due to pathogens other than COVID-19, Presence of comorbidities associated with unfavorable outcome based on clinical judgement, Complicated diverticulitis or bowel perforation, Ongoing skin infection (e.g. antibiotic-induced uncontrolled dermatitis), On-going anti-rejection immunosuppressive therapy. The dose was up to 2 tocilizumab infusions at intervals of 12 to 24 hours (8 mg/kg of body weight, maximum dose per infusion 800 mg). In case of tocilizumab administration, broad spectrum antibiotics were employed and antiviral therapy maintained. Oxygen requirements were categorized as follow: no oxygen needs; low oxygen requirement, from nasal cannula up to Venturi mask with FiO₂ of 0.5, high oxygen requirement, including Venturi mask with FiO₂ of 0.6, reservoir mask with oxygen at 15 l/min, and high-flow nasal ventilation; non-invasive ventilation; and mechanical ventilation. Considering the well-documented effects of lopinavir/ritonavir and hydroxychloroquine on increasing the cardiac QTc interval, electrocardiograms were performed every 2 to 3 days. In case of prolongation compared with baseline, dose reduction was performed. Due to the small sample size, only descriptive statistics were performed, results were expressed as count (percentage) for categorical variables and median and IQR for continuous variables. In this report, they describe the progress of all patients with SARS-CoV2 pneumonia who had undergone kidney transplantation admitted up to 24/Mar/2020. These patients had a median inpatient



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17763830

stay of 7 days (interquartile range [IQR], 4-15). Briefly, all patients presented with fever; however, only 1 of the 20 complained of dyspnea; 50% of the patients who had undergone transplantation had radiographic changes of bilateral infiltrates on admission, while the remaining 50% showed unilateral changes or no infiltrates; 7 did not require supplemental oxygen at admission. All patients had their usual transplant immunosuppression withdrawn and were started on methylprednisolone 16 mg or equivalent dose of prednisone, and 19 of the 20 received antiviral therapy and hydroxychloroquine as per their institute protocol. As antiviral therapy was known to interfere with calcineurin inhibitor metabolism, in 4 patients, tacrolimus levels were monitored after these therapeutic changes were instituted. The median trough values before antiviral therapy were 7.05 ng/ml (IQR, 5.5-8.6): 1 patient had the level rechecked after 3 days with no change compared with baseline; 1 patient had the level rechecked 4 and 5 days after admission (-17% and -18% compared with baseline); 1 was rechecked 6 days after admission (-12% compared with baseline); and 1 was rechecked 8 days after admission (-21% compared with baseline). The median times from symptom onset and admission to these therapeutic changes were, respectively, 5 days (IQR, 3-8.25) for antiviral therapy and 0 days (IQR, 0-0) for hydroxychloroquine. During the follow-up, 1 patient had hydroxychloroquine withdrawn due to toxicity (nausea, vomiting); among the treated patients no prolongation of the cardiac QTc interval compared with baseline or cardiac arrhythmias were observed. Antibiotics were administered to 11 of the 20 patients (55%): cephalosporins in 64%; beta-lactams in 36%; fluoroquinolones in 25%; carbapenems in 10%; and glycopeptides in 5%. During hospitalization, chest radiographs were repeated in 15 patients and radiological findings worsened in 13 of those 15 (87%). In the 13 individuals with worsening radiological findings, 11 (85%) required an escalation of the oxygen supplemental therapy, including 1 patient switched from regular breathing to low oxygen requirement, 3 from regular breathing to high oxygen requirement, 3 from low to high oxygen requirement, 2 from high oxygen requirement to non-invasive ventilation, and 2 from high oxygen requirement to mechanical ventilation. Additional anti-inflammatory therapy with dexamethasone or tocilizumab, respectively, was given to 11 (55%) and 6 of the 20 patients (30%); in these patients, respectively, 4 (36%) and 2 (33%) subsequently died. Among these 6 patients, 3 (50%) experienced a reduction of the oxygen requirements and 2 (33%) showed amelioration of the radiological findings. In terms of kidney function, the medium creatinine level at admission was +17% (IQR, 12%-26%; range, 0%-143%) compared with baseline, and the highest creatinine level observed during the follow-up was +33% (IQR, 13%-59%; range, 0%-157%) compared with baseline; 6 of 20 patients developed acute kidney injury and 1 of those 6 required hemodialysis. During follow-up of the 20 patients, 4 (20%) required intensive care and 3 of these individuals subsequently died. Overall, 5 patients died after a median of 11 days from admission (IQR, 11-14 days) and 15 days (IQR, 15-19 days) from symptom onset; of these 5 patients, 4 died from complications of the respiratory failure secondary to SARS-CoV2 infection and 1 died of probable bacterial sepsis (fever, rise of C-reactive protein, and procalcitonin) despite a satisfactory recovery from SARS-CoV2 pneumonia-induced respiratory failure, need for intensive care unit care, and treatment with dexamethasone and tocilizumab. Three patients were discharged, after 7 days in 1 case and after 16 in the 2 remaining cases; at discharge, creatinine levels compared with baseline were 3.6 versus 2.1, 2.3 versus 2.5, and 2.1 versus 1.5 mg/dl. In terms of immunosuppressive therapy, 2 patients were discharged receiving methylprednisolone 16 mg/d and 1 with methylprednisolone 12 mg/d.

This case concerns patient number: 4.

The patient's concomitant conditions included HCV infection while past drugs and concurrent medication were not reported. No risk factors were available.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17763830

In Aug/2018, the patient underwent kidney transplantation (medical history). His baseline immunosuppression therapy included mycophenolate mofetil (lot number and dosage regimen not reported), calcineurin inhibitor (CNI) and low-dose steroids (therapy details not reported). On an unspecified date, he was diagnosed with COVID 19 infection and admitted in the nephrology unit of the hospital for COVID 19 infection with COVID 19 pneumonia and investigated with routine investigations and Chest X-ray. His baseline creatinine was 141 mmol/l and eGFR was 47 ml/min per 1.73 m². His immunosuppression was withdrawn and he was commenced on methylprednisolone 16 mg/day or equivalent dose of prednisone. Antiviral therapy with lopinavir/ritonavir 200/50 mg 2 tabs x 2/day plus hydroxychloroquine was started at a recommended dose as per the eGFR. However, he developed acute respiratory distress syndrome and was shifted to intensive care unit. Later, he was started with additional anti-inflammatory therapy of intravenous tocilizumab infusion 8 mg/kg (lot number, dose and frequency not reported, Off label use, intentional use of drug for unlabeled indication) and dexamethasone (20 mg/d for 5 days, then 10 mg/d for 5 days) for COVID 19 infection and ARDS. On an unspecified date, despite a satisfactory recovery from SARS-CoV2 pneumonia-induced respiratory failure, he died due to bacterial sepsis (fever, rise of C-reactive protein, and procalcitonin). It was not reported whether autopsy was performed or not.

At the time of death, there was insufficient information regarding the therapy ongoing status of tocilizumab.

The author stated that immunosuppression (mycophenolate mofetil, calcineurin inhibitor and low-dose steroids) and chronic kidney disease may represent additional risk factors for COVID 19 infection and its complications (COVID 19 pneumonia, acute kidney injury and acute respiratory distress syndrome).

The company has assessed causality between fatal event of bacterial sepsis and mycophenolate mofetil and tocilizumab as possible since a temporal correlation cannot be ruled out at this time but the patient's immunocompromised state and other immunosuppressive agents make the patients susceptible to infections regardless if they are taking mycophenolate mofetil or not.

The company has assessed causality of the events COVID 19 infection, COVID 19 pneumonia and acute respiratory distress syndrome as unrelated with mycophenolate mofetil and tocilizumab and rather related with immunosuppressive status due to chronic kidney disease and use of immunosuppressive drugs calcineurin inhibitor and steroids.

Additional information has been requested.

Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, Maffei C, Possenti S, Zambetti N, Moscato M, Venturini M, Affatato S, Gaggiotti M, Bossini N and Scolari F.

A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia.

Kidney International, 2020: 1-6. DOI: 10.1016/j.kint.2020.04.002.

This case is cross referenced with AER: 2594877 (base case, same literature article).



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17763830

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Renal transplant	(b) (6)		

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood creatinine	282	µmol/L			N
Coronavirus test					N
Glomerular filtration rate	16	ml/min/1.73 sq meter			N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No Sender Organization: ROCHE 503B Compounding Outsourcing Facility?:

Literature Text: Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A, Maffei C, Possenti S, Zambetti N, Moscato M, Venturini M, Affatato S, Gaggiotti M, Bossini N and Scolari F A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. Kidney International 2020 Apr 09;:1-6.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17764633

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: BRA Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 11-May-2020 Mfr Rcvd Date: 04-May-2020 Mfr Control #: BR-ROCHE-2596756 Application #: 125276

Patient Information:

Age: Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		680 MG/	Unknown	2 doses of 680 mg	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	ASKED BUT UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2596756 is a spontaneous case, received on 04/May/2020 from a physician (neurology) in Brazil. It concerns a male patient (age not reported) who died and had intentional use of tocilizumab (Actemra) for unlabeled indication.

Patient's medical history, past drug, concurrent condition and concomitant medications was not reported.

On an unknown date, the patient started therapy with tocilizumab (lot number: asked but unknown) (route not reported) 680 mg, 2 doses for COVID-19 (off-label use for unlabeled indication), after the use, he had a radiological improvement but later he died (Unknown cause of death). The patient died on an unknown date. It was unknown if an autopsy was performed or not.

At the time of death, therapy with tocilizumab was not reported.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17764633

The physician did not report a causality of unknown cause of death with tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17764633

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17769300

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 29-Mar-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 12-May-2020 Mfr Rcvd Date: 30-Apr-2020 Mfr Control #: IT-ROCHE-2594798 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		8 MG/KG/	Intravenous (not otherwise specified)		COVID-19 pneumonia	26-Mar-2020	
2	TOCILIZUMAB		8 MG/KG/	Intravenous (not otherwise specified)	On 27/Mar/2020, the patient received tocilizumab		27-Mar-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN,UNK NOWN				
2	TOCILIZUMAB		NA	NA	UNKNOWN,UNK NOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1) ReC
Respiratory failure NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17769300

Event/Problem Narrative:

AER 2594798 is a clinical study case, received on 30/Apr/2020 from a physician in Italy. It concerns a patient of unknown demographics (patient number: (b) (6)) who developed respiratory failure and died due to the progression of the disease whilst enrolled in (b) (6) (b) (6)

Patient's concurrent conditions included serious respiratory insufficiency, COVID-19. Concomitant medications included morphine (Morfina), midazolam (Midazolam), enoxaparin sodium (Enoxaparina).No past drugs and medical conditions were reported.

On (b) (6) the patient was hospitalized due to the SARS-CoV2 in sufficiency respiratory.The patient required CPAP on (b) (6) (b) (6) (b) (6) (b) (6) . The patient was already in serious condition before administration. On (b) (6) the patient developed respiratory failure (severity: grade 5).The condition was progressively got worst until the death.The patient died on (b) (6) It was not reported if an autopsy was performed or not.

The physician assessed the causality of the event respiratory failure as related to tocilizumab.

The company assessed the causality of the event respiratory failure as not related to tocilizumab and related to underlying COVID-19 pneumonia. Acute respiratory distress syndrome and respiratory failure with fatal outcome are known to occur due to COVID-19 pneumonia. Respiratory failure is not a known pattern of response with tocilizumab.

No further information was reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
COVID-19				
Respiratory failure				
Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17769300

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Viral test					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ENOXAPARINA							
2	MIDAZOLAM							
3	MORFINA [MORPHINE]							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17770111

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 06-Apr-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 12-May-2020 Mfr Rcvd Date: 05-May-2020 Mfr Control #: IT-ROCHE-2597337 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB			Unknown	On 23/Mar/2020, the patient received most recent dose of tocilizumab prior to serious adverse event.	COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC
 Respiratory failure NA

Event/Problem Narrative:

AER 2597337 is a clinical study case, received on 05/May/2020 from a physician in Italy. It concerns a patient of unknown demographics (patient number: (b) (6)) who had respiratory failure whilst enrolled in (b) (6) (b) (6)

No medical history, past drugs, concurrent conditions or concomitant medications were reported.

On an unknown date, (b) (6) (b) (6) On (b) (6) , the patient had respiratory failure (severity: grade 5) due to which patient died on (b) (6) (b) (6) It was not reported if an autopsy was performed or not.

The physician assessed the respiratory failure as related to tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17770111

The company assessed the respiratory failure as not related to tocilizumab. As COVID-19 pneumonia damages the walls and linings of the air sacs in lungs, which causes the inflammatory response of cytokines, overwhelming the immune system response to the infection, which can lead to damage of organs, including lungs, heart, and kidneys, leading to severe pneumonia or acute respiratory distress syndrome (ARDS) and other complications leading to death. Respiratory failure is not a known pattern of response with tocilizumab.

No further information was reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17770111

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17773731

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ESP **Event Date:** 31-Mar-2020 **Outcomes:** DE, **Application Type:** ANDA

FDA Rcvd Date: 13-May-2020 **Mfr Rcvd Date:** 08-May-2020 **Mfr Control #:** ES-AUROBINDO-AUR-APL-2020-024369 **Application #:** 203294

Patient Information:

Age: 26 YR **Sex:** Female **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Azithromycin		500 MG/QD	Oral	500 milligram, Once a Day	COVID-19 pneumonia	23-Mar-2020	24-Mar-2020
2	Dexamethasone		20 MG/QD	Intravenous (not otherwise specified)	20 milligram, Once a Day	Product used for unknown indication	28-Mar-2020	01-Apr-2020
3	Dexketoprofen		25 MG/TID	Intravenous (not otherwise specified)	25 milligram, 3 Times a Day	Product used for unknown indication	27-Mar-2020	01-Apr-2020
4	Enoxaparin		40 MG/QD	Subcutaneous	40 milligram, Once a Day	Product used for unknown indication	27-Mar-2020	
5	Hydroxychloroquine		400 MG/QD	Oral	400 milligram, Once a Day	COVID-19 pneumonia	23-Mar-2020	01-Apr-2020
6	Tocilizumab		600 MG/	Intravenous (not otherwise specified)	600 milligram, total	Severe acute respiratory syndrome	29-Mar-2020	29-Mar-2020
7	Tocilizumab					COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Azithromycin	9 Day	NA	NA				AUROBINDO	
2	Dexamethasone	4 Day	NA	NA					
3	Dexketoprofen	5 Day	NA	NA					
4	Enoxaparin	5 Day	NA	NA					
5	Hydroxychloroquine	9 Day	NA	NA					



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17773731

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
6 Tocilizumab	3 Day	NA	NA					
7 Tocilizumab	3 Day	NA	NA					

Event Information:

Preferred Term (MedDRA ® Version: 23.1)

ReC

Coagulopathy

NA

Event/Problem Narrative:

Initial report received on 08-May-2020: This is a spontaneous report received from Eudravigilance Database Management System (EVDMS) with ADR reference number ES-AEMPS-628824, by physician.

This report concerned about a 26-year-adult female patient from Spain.

Medical history of the patient was not reported, procedures included C-section from (b) (6) to (b) (6) and historical drugs of the patient were not reported.

Concomitant medications were not reported.

On 23-Mar-2020, the patient received azithromycin of unknown strength and formulation at a dose of 500 milligram, once a day via oral route for COVID-19 pneumonia, hydroxychloroquine of unknown strength and formulation at a dose of 400 milligram, once a day via oral route for COVID-19 pneumonia, last dose of azithromycin was administered on 24-Mar-2020, on 27-Mar-2020 dexketoprofen of unknown strength and formulation at a dose of 25 milligram, 3 times a day via intravenous route for unknown indication, enoxaparin of unknown strength and formulation at a dose of 40 milligram, once a day via subcutaneous route for unknown indication, on 28-Mar-2020 dexamethasone of unknown strength and formulation at a dose of 20 milligram, once a day via intravenous route for unknown indication, on 29-Mar-2020 tocilizumab of unknown strength and formulation at a dose of 600 milligram, total via intravenous route for Severe acute respiratory syndrome and COVID-19 pneumonia, last dose of tocilizumab was administered on 29-Mar-2020, last dose of dexamethasone, enoxaparin, dexketoprofen, hydroxychloroquine was administered on 01-Apr-2020.

On 31-Mar-2020, the patient had coagulopathy and on (b) (6) the patient was died due to multiple organ failure, coagulopathy and COVID-19 pneumonia, It was unknown whether autopsy performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17773731

Laboratorial examinations and treatment medications were not reported.

The outcome of the event coagulopathy was fatal.

The case was assessed as serious (death) for the event coagulopathy.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Caesarean section	(b) (6)	(b) (6)	NO

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17773731

Reporter Source:

Study Report?: No

Sender Organization: AUROBINDO

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17773868

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 13-May-2020 Mfr Rcvd Date: 05-May-2020 Mfr Control #: IT-ROCHE-2596959 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB			Unknown	last administration date of tocilizumab was 25/Mar/2020	COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC

Multiple organ dysfunction syndrome NA

Event/Problem Narrative:

AER 2596959 is a clinical study case, received on 05/May/2020 from a physician in Italy. It concerns a patient of unknown demographics (patient number: (b) (6)) who had multi-organ failure whilst enrolled in (b) (6) (b) (6)

The patient's concurrent conditions included systemic hypertension, multiple agent septic shock, candida parapsilosis, staphylococcus and pseudomonas spp. No medical history, past drugs and concomitant medications were not reported.

On an unknown date, (b) (6) (b) (6) . On (b) (6) the patient died due to multi organ failure (severity: grade 5). The patient's white blood cell count was also increased . Test report for Dimer was 1265 ng/ml (range was 0-250). It was not reported if an autopsy was performed or not.

The physician reported the causality of multi-organ failure as related with tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17773868

The company assessed the causality of multi-organ failure as unrelated with tocilizumab. COVID-19 pneumonia damages the walls and linings of the air sacs in lungs, which causes the inflammatory response of cytokines, overwhelming the immune system response to the infection, which can lead to damage of organs, including lungs, heart, and kidneys, leading to death. Hypertension and infection by candida parapsilosis, staphylococcus and pseudomonas spp are confounding factors.

No further information was provided

Relevant Medical History:

multiple agent septic shock, CANDIDA PARAPSILOSIS, stafilococcus and psedomonas spp

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17773868

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17778290

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ESP **Event Date:** 26-Mar-2020 **Outcomes:** DE,HO, **Application Type:** NDA

FDA Rcvd Date: 13-May-2020 **Mfr Rcvd Date:** 08-May-2020 **Mfr Control #:** ES-PFIZER INC-2020185611 **Application #:** 050733

Patient Information:

Age: 70 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	AZITHROMYCIN		500 MG/	Intravenous (not otherwise specified)	500 mg, daily	COVID-19 pneumonia	26-Mar-2020	30-Mar-2020
2	HYDROXYCHLOROQUIN E		400 MG/QD	Oral	400 mg, 1x/day	COVID-19 pneumonia	26-Mar-2020	30-Mar-2020
3	TOCILIZUMAB					SARS		
4	TOCILIZUMAB					COVID-19		
5	TOCILIZUMAB		600 MG/	Intravenous (not otherwise specified)	600 mg, single	Coronavirus infection	27-Mar-2020	27-Mar-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	AZITHROMYCIN	6 Day	NA	NA				PFIZER	
2	HYDROXYCHLOROQUIN E	6 Day	NA	NA					
3	TOCILIZUMAB	5 Day	NA	NA					
4	TOCILIZUMAB	5 Day	NA	NA					
5	TOCILIZUMAB	5 Day	NA	NA					

Event Information:

Preferred Term (MedDRA Version: 23.1) **ReC**

Atrial flutter NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17778290

Bundle branch block right	NA
Hypertension	NA
Hypofibrinogenaemia	NA
Off label use	NA
Pneumonia escherichia	NA
Product use in unapproved indication	NA
Ventricular tachycardia	NA

Event/Problem Narrative:

This is a spontaneous report from a contactable physician downloaded from the European Medicines Agency (EMA) EudraVigilance-WEB (ES-AEMPS-624232).

A 70 year-old male patient started to receive azithromycin (MANUFACTURER UNKNOWN), intravenous from (b) (6) to (b) (6) at 500 mg daily for pneumonia COVID19, hydroxychloroquine (MANUFACTURER UNKNOWN), orally from (b) (6) to (b) (6) at 400 mg once a day for pneumonia COVID19 and tocilizumab (MANUFACTURER UNKNOWN), intravenous on (b) (6) at 600 mg single for coronavirus infection and severe acute respiratory syndrome (SARS) COVID19. The patient's medical history and concomitant medications were not reported. The patient experienced hypofibrinogenemia on (b) (6) pneumonia due to escherichia coli (E. coli) on (b) (6) arterial hypertension on (b) (6) atrial flutter and complete right bundle branch block on (b) (6) and episodes of ventricular tachycardia with cardiopulmonary resuscitation on (b) (6) which were all reported with the seriousness criteria of being fatal and hospitalization. On (b) (6) the patient received azithromycin for pneumonia COVID19. The action taken in response to the events for azithromycin and hydroxychloroquine was post-therapy and for tocilizumab was not applicable. The outcome of hypofibrinogenemia, pneumonia due to escherichia coli (E. coli), arterial hypertension, atrial flutter, complete right bundle branch block and episodes of ventricular tachycardia with cardiopulmonary resuscitation was fatal. The outcome of patient received azithromycin for pneumonia COVID19 was unknown. The patient died on an unspecified date. It was not reported if an autopsy was performed.

Pfizer is a marketing authorization holder of azithromycin in the country of incidence or the country where the product was purchased (if different). This may be a duplicate report if another marketing authorization holder of azithromycin has submitted the same report to the regulatory authorities.

No follow-up attempts are possible. No further information is expected.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17778290

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: PFIZER

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17778672

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: FRA
Event Date: 23-Apr-2020
Outcomes: DE,HO,
Application Type: BLA
FDA Rcvd Date: 13-May-2020
Mfr Rcvd Date: 08-May-2020
Mfr Control #: FR-ROCHE-2599053
Application #: 125276

Patient Information:

Age: 62 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		800 MG/	Intravenous (not otherwise specified)		COVID-19	15-Apr-2020	15-Apr-2020
2	TOCILIZUMAB		400 MG/	Intravenous (not otherwise specified)			17-Apr-2020	17-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN				
2	TOCILIZUMAB		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Pulmonary embolism	NA
Pulmonary necrosis	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17778672

Event/Problem Narrative:

AER 2599053 is a clinical study case, received on 08/May/2020 from a physician in France. It concerns a 63 year old male patient (patient number: (b) (6)) who experienced pulmonary necrosis, pulmonary embolism whilst enrolled in (b) (6)

The patient's concurrent conditions included hypertension arterial, type 2 diabetes mellitus, dyslipidemia. No medical history, past drugs and concomitant medications were reported.

(b) (6)
(b) (6) On 22/Apr/2020, bronchoalveolar lavage was performed and the results showed positive to E. cloacae and C. freundii. On 22/Apr/2020, CT scan was performed the results showed severe involvement and foci of bi-basal parenchymal necrosis. Right lower segmental pulmonary embolism. Moderate distension of the colic setting, without signs of suffering. On (b) (6) he experienced a bi-basal parenchymatous necrosis and a right lower lobar segment pulmonary embolism in the main necrosis area. Later, worsening of the hematosi. On the same day CT scan was performed the results showed bi-basal parenchymatous necrosis. Right lower lobar segment pulmonary embolism. He had developed pulmonary necrosis and pulmonary embolism. The patient was hospitalised. an unspecified anticoagulant was given as treatment medication. He was put in a prone position for pleural puncture. Later, C. freundi wild and KP BLSE found in the pleural drainage. On (b) (6) thorax scan showed a defavourable outcome of Covid-19 pneumopathy, complicated by a pulmonary embolism and a parenchymatous pulmonary abscess, drained. Conclusions included: drained aspect with residual cavity of right basal pyramid abscess, drain placed on lower part; increase of Covid-19 related lesions; right posterobasal segmental pulmonary embolism and small abscesses of left basal pyramid known and stable. On (b) (6) poor respiratory evolution on purulent pleuropneumopathy with necrosis with C. freundi, wild E. cloacae, flora found in bronchoalveolar lavage. On (b) (6) D14 of Percutaneous Endoscopic Colostomy was performed and results showed acute respiratory distress syndrome on Sars-Cov-2 complicated on D9 of septic shock on multi-germ purulent pleuropneumopathy with bi basal necrosis and increased respiratory failure, severe hemodynamic failure and renal failure. On (b) (6) refractory shock ocured leading to his death. It was unknown if an autopsy was performed or not. No procedures were performed nor was he discontinued from study.

The physician assessed the pulmonary necrosis and pulmonary embolism as related to tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Dyslipidaemia			
Hypertension			



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17778672

Type 2 diabetes mellitus

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Bronchoalveolar lavage					N
Computerised tomogram					N
Computerised tomogram					N
Chest scan					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17779081

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Event Date:** 11-Apr-2020 **Outcomes:** CA,DE,HO,LT,OT, **Application Type:** BLA

FDA Rcvd Date: 25-Jun-2020 **Mfr Rcvd Date:** 16-Jun-2020 **Mfr Control #:** US-SA-2020SA100372 **Application #:** 761037

Patient Information:

Age: **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	200 mg, single	COVID-19	07-Apr-2020	07-Apr-2020
2	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	200 mg, single		16-Apr-2020	16-Apr-2020
3	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	200 mg, single		10-Apr-2020	10-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	20730 MINUTES	NA	NA				SANOFI	
2	SARILUMAB	20730 MINUTES	NA	NA				SANOFI	
3	SARILUMAB	20730 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA Ⓜ Version: 23.1)	ReC
Acute kidney injury	NA
Alanine aminotransferase increased	NA
Aspartate aminotransferase increased	NA
COVID-19	NA
Deep vein thrombosis	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17779081

Hepatic failure	NA
Hypotension	NA
Hypotension	NA
Metabolic encephalopathy	NA
Pneumonia bacterial	NA
Renal failure	NA
Urinary tract infection	NA

Event/Problem Narrative:

Based on addition information received on 04-May-2020 and 05-May-2020 (processed together), the overall reporter causality is updated from not related to related.

Initial information received on 13-Apr-2020 regarding a solicited valid serious case received from (lp) regeneron-usa gsa-pcp under reference number 2020-31166 on 13-Apr-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6)
Patient ID (b) (6) Site: (b) (6) Country: United States.

Study title: (b) (6)
(b) (6)

A 47-year-old, male, Hispanic or Latino patient severe or critical COVID-19 was enrolled in study (b) (6)
(b) (6)
(u) (v)
(b) (6)
(b) (6). The patient experienced SAEs Hypotension on (b) (6)
(b) (6) Metabolic encephalopathy on (b) (6) DVT on (b) (6) Acute kidney injury on (b) (6) Hypotension on (b) (6)
(b) (6) Liver failure and Renal failure on (b) (6) and Death due to COVID-19 on (b) (6) and serious AESIs Bacterial pneumonia
on (b) (6) Urinary tract infection on (b) (6) and Elevated ALT and Elevated AS I on (b) (6) after receiving study drug.

Relevant medical history was included diabetes mellitus, hypertension and hypoxic respiratory failure.
No relevant concomitant medications were reported.

On 28-Mar-2020, the patient experienced earliest symptoms of pneumonia without rales/crackles on lung auscultation present. The highest body temperate measured orally, within 24 hours of baseline was 100.1 degreeF (Fahrenheit). The patient received treatment with



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supplemental oxygen by non-rebreather mask.

On 05-Apr-2020, X-ray showed faint, hazy, airspace disease, in the mid to lower lungs bilaterally which could represent Covid 19 infection.

On 06-Apr-2020, nasopharyngeal swab was positive on SARS-CoV-2 virus test.

On 07-Apr-2020, the following parameters were measured: spO2 94%; blood pressure 131/82 mmHg; pulse 70 beats per minute (bpm); respiratory rate 43 respirations per minute (rpm); temperature 98.8 degree F (Fahrenheit). The following laboratory results were reported: alanine aminotransferase (ALT) 30 U/L (lab range 1-45), aspartate aminotransferase (AST) 36 U/L (lab range 1-40) and potassium 4.6 mEq/L (lab range 3.5-5). Haematology test were performed: platelets 282 / nL (150-440), white blood cells (WBC) 11.70 /nL (Lab range 3.9-8.7) and neutrophils (absolute) 1.43/ nL (1.9-8.7).

On 08-Apr-2020 intubation was performed.

On 09-Apr-2020, results of the arterial blood gas analysis were the following: pH was 7.49, partial pressure CO2 (PaCO2) was 35.1 mmHg, partial pressure O2 (PaO2) was 107.9 mmHg, while the arterial oxygen saturation (SaO2) was 98.3%.

On (b) (6), (b) (6) days 9 hrs 30 min after the administration of study drug, the patient started experiencing hypotension (grade 3), his blood pressure was 95/57 mmHg and pulse 97 bpm. This event required hospitalization. On the same day, the patient started treatment with norepinephrine 1-30 mcg/min, i.v. (via continual infusion).

On (b) (6) the patient blood pressure was 97/63 mmHg and pulse 93 bpm. On the same day (b) (6) days 9 hrs 30 min after the administration of study drug, the patient was diagnosed with metabolic encephalopathy (grade 4). The event was assessed as medically significant. Outcome of the event was unknown.

On (b) (6) the patient blood pressure was 110/66 mmHg and pulse 95 bpm.

On (b) (6) the patient sputum culture test was with normal respiratory flora present. The patients lactate dehydrogenase LDH was 675 u/L (60-200), WBC count was 8.29 and neutrophils count was 6.57.

On (b) (6) the patient blood pressure was 90/58 mmHg and pulse 76 bpm.

On (b) (6) event respiratory failure was downgraded from SAE to non-serious non-AESI and inactivated. No rationale was provided.

On (b) (6) (b) (6) days 9 hrs 30 min after the administration of study drug, the patient was diagnosed with bacterial pneumonia (grade 3). This event was assessed to be adverse event of special interest and required hospitalization. Unspecified final culture showed many



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Pseudomonas aeruginosa and a moderate amount of Escherichia coli. WBC was 16.77 and neutrophils 13.37. The patient creatinine was 1 mg/dL (0.5 - 1). The patient received meropenem 1000 mg, every 8 hours, iv, as corrective treatment for adverse event pneumonia. Outcome of the event was unknown. On the same day, the patient experienced deep vein thrombosis (DVT; grade 4). This event corresponded to a congenital anomaly and was assessed to be medically significant. Lower extremity ultrasound was positive for acute DVT within 2 soleal veins of the left lower extremity. Platelets were 396.

On (b) (6) the patient creatinine was 1.5. The patient received continuous infusion of heparin at dose 970 units per hour, as corrective treatment for DVT.

On (b) (6) (b) (6) days 9 hrs 30 min after the administration of study drug, the patient was diagnosed with acute kidney injury (grade 3). This event required hospitalization. The patient was instructed to maintain renal diet, avoid nephrotoxins and to take renally dose medications. Outcome of the event was unknown. WBC was 28.44 and neutrophils count was 26.36, while creatinine was 1.7.

On (b) (6) blood pressure was 112/72 mmHg and the event hypotension was considered resolved.

On (b) (6) the patient creatinine was 1.7 and LDH was 607. WBC was 19.34 and neutrophils 17.5.

On (b) (6) (b) (6) days 9 hrs 30 min after the administration of study drug, the patient experienced urinary tract infection (grade 3). This event was assessed to be medically significant, adverse event of special interest and required hospitalization. Body temperature was 98.6 degree F, WBC were 20.69 and neutrophils were 16.59. Unspecified medication was given as a corrective treatment.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

On (b) (6) unspecified final culture result was reported. WBC and neutrophils further increased to 38.17 and 32.50, respectively.

On (b) (6) (b) (6) days 9 hrs 30 min after the administration of study drug, the patient again experienced hypotension (grade 4), reported blood pressure was 124/67 mmHg. This event was assessed to be life threatening. Information regarding corrective treatment was not provided.

On (b) (6) (b) (6) days 9 hrs 30 min after the administration of study drug, the patient experienced liver (grade 4) and renal failure (grade 4). Both the events were assessed to be life threatening. Chemistry and haematology results were as follows: calcium-7.5 mg/dL (8-10.5), sodium-133 mEq/L (135-145), potassium-6.9 mEq/L (3.5-5), bicarbonate-13.5 mEq/L (20-28), creatinine 3.6, LDH>1800, total bilirubin- 2.8, WBC- 53.74, neutrophils-45.35. Corrective treatment included supportive care. On the same day, (b) (6) days 9 hrs 30 min after the administration of study drug, the patient experienced elevated ALT (grade 4) and AST (grade 4), with levels of 497 and 3017, respectively. The event of elevated ALT was assessed to be medically significant, life threatening, adverse event of special interest and required hospitalization. The event of elevated AST was assessed to be medically significant and adverse event of special interest. Imaging to rule out



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(R/O) hepatic vein thrombosis and embolus was performed. Blood pressure decreased to 92/64 mmHg and temperature to 92.8 degF. information regarding corrective treatment for elevated ALT and elevated AST was not provided.

On (b) (6) ALT an AST further increased to 1021 and 5919, respectively. Creatinine phosphokinase was 9530 U/L (5-225). Other chemistry and haematology results did not improve significantly. The patient died on (b) (6) at 22:47, (b) (6) days 8 hrs 17 min after the administration of study drug) due to COVID-19 (grade 5). Information regarding corrective treatment was not provided. The patient died on (b) (6) (b) (6) The cause of death was reported as COVID-19. An autopsy was not performed.

At the time of reporting, the patient had not recovered from elevated ALT, Liver failure, Bacterial pneumonia, Acute kidney injury, Elevated AST and DVT.

Outcome for metabolic encephalopathy, Hypotension (Onset: (b) (6)), Renal failure and Urinary tract infection was Unknown.

Action taken with study drug in response to event Death due to COVID-19 was not applicable, and for all other events it was dose not changed.

Causality assessment is as follows:

For death due to COVID-19:

Investigator Causality = Not Related; Company Causality = Not related

Investigator causality rationale: Other suspect causes included COVID-19.

For elevated ALT:

Investigator Causality = Related; Company Causality = related

Investigator causality rationale: Adverse event of interest. Other suspect causes included possible hepatic vein thrombosis.

For hypotension (onset (b) (6)):

Investigator Causality = Not Related; Company Causality = Not related

Investigator causality rationale: Other suspect causes included COVID-19 infection, critical illness, sedation.

For hepatic failure:

Investigator Causality = Not Related; Company Causality = Not related

Investigator causality rationale: Other suspect causes included COVID-19 infection.

For renal failure:

Investigator Causality = Not Related; Company Causality = Not related

Investigator causality rationale: Other suspect causes included worsening of prior acute kidney injury.



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Company causality rationale: A 47-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia died due to COVID-19, (b) (6) days after receiving the last dose of the study drug. The patient also experienced increased ALT, hypotension, hepatic and renal failure after treatment with the study drug. Relevant medical history was included diabetes mellitus, hypertension and hypoxic respiratory failure. Patient's baseline ALT values were within reference ranges however, they've further increased following study drug administration. Based on a plausible temporal association between study drug administration and the reported event and known potential effect of study drug on functional liver enzymes, causality for the event of increased ALT is assessed as related to study drug. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation. The event is not related to any clinical trial procedure. Based on the information provided, underlying comorbidities in addition to severe or critical COVID-19 with pneumonia before initiation of the study drug are the most plausible causes for the development of hypotension, hepatic and renal failure and subsequent death in this patient. Therefore, the events are assessed as unrelated to the study drug or to any clinical trial procedure.

For Pneumonia bacterial:

Investigator Causality = Related; Company Causality = Not related

Investigator causality rationale: Adverse event of special interest. Other suspect causes were reported as sequelae of COVID-19/critical illness.

Company causality rationale: A 47-year-old, male, Hispanic or Latino patient with severe or critical COVID-19 infection and worsening pneumonia experienced Pneumonia bacterial 14 days after receiving the study drug. The event Pneumonia bacterial is assessed as not related to study drug or any clinical trial procedure. Bacterial infections are common in intubated and catheterized patients, especially in a setting of pre-existing worsening infection. This patient was already compromised by COVID-19 and pneumonia aggravated by underlying chronic conditions such as diabetes mellitus and hypertension.

For urinary tract infection:

Investigator Causality = Related; Company Causality = Not related

Investigator causality rationale: Adverse event of special interest. Other suspected causes included sequelae of COVID-19/critical illness/foley catheter.

Company causality rationale: A 47-year-old male patient enrolled in the trail, experiencing urinary tract infection after administration of the blinded study drug. Based on the information provided, patient's compromised state due to severe or critical COVID-19 with pneumonia, medical history of diabetes mellitus and use of Foley catheter provide most likely aetiology for the event of urinary tract infection. Therefore, this event is assessed as unrelated to the study drug or to any clinical trial procedure.

For Hypotension (onset (b) (6)):

Investigator Causality = Not related; Company Causality = Not related

Investigator causality rationale: Other suspect causes included COVID-19 infection.

Company causality rationale: A 47-year-old male patient enrolled in the trail, experiencing hypotension after administration of the blinded study drug. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug in addition to patients underlying diseases provides most plausible cause for the event of hypotension in this patient. Therefore, this event is also assessed as



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unrelated to the study drug or to any clinical trial procedure.

For Metabolic encephalopathy and acute kidney injury:

Investigator Causality = Not related; Company Causality = Not related

Investigator causality rationale: Other suspect causes included Covid-19 infection.

Company causality rationale: A 47-year-old, male, Hispanic or Latino patient with severe or critical COVID-19 infection and worsening pneumonia experienced Metabolic encephalopathy and Acute kidney injury after receiving the study drug. The events of Metabolic encephalopathy and Acute kidney injury are assessed as not related to study drug. The events are secondary to progression of COVID-19 infection and pneumonia further aggravated by comorbidities like diabetes mellitus and hypertension. The events Metabolic encephalopathy and Acute kidney injury are not related to any clinical trial procedure.

For elevated AST:

Investigator Causality = related; Company Causality = related

Investigator causality rationale: Adverse event of special interest. Other suspect causes included possible hepatic vein thrombosis.

Company causality rationale: A 47-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced increased AST, ^(b)₍₆₎ days after receiving the last dose of the study drug. Patient's baseline AST values were within reference ranges however, they've further increased following study drug administration. Based on a plausible temporal association between study drug administration and the reported event and known potential effect of study drug on functional liver enzymes, causality for the event of increased AST is assessed as related to study drug. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation. The event is not related to any clinical trial procedure.

For DVT:

Investigator Causality = Not related; Company Causality = Not related

Investigator causality rationale: Not applicable. Other suspected causes included COVID coagulopathy.

Company causality rationale: A 47-year-old male patient enrolled in the trial, experiencing deep vein thrombosis after administration of the blinded study drug. Based on the information provided, patient's compromised state due to severe or critical COVID-19 with pneumonia, medical history of diabetes mellitus and prolonged hospitalisation with use of ventilation provide most likely aetiology for the event of deep vein thrombosis. Therefore, this event is assessed as unrelated to the study drug or to any clinical trial procedure

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 20-Apr-2020

The Investigator provided the following updates: event Respiratory failure downgraded. Action taken, clinical and event course updated.

Follow up: 21-Apr-2020 and 27-Apr-2020 (processed together).

The Investigator provided the following updates: three events added, event course and concomitants updated.



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Follow up: 29-Apr-2020 and 30-Apr-2020 (processed together)

The Investigator provided the following updates: new events added (DVT and UTI), clinical course updated.

Follow up: 04-May-2020 and 05-May-2020 (processed together)

The Investigator provided the following updates: new events added, outcome and resolution date for Hypotension updated, clinical course and concomitant medication updated.

Follow up: 19-May-2020

The Investigator provided the following updates: outcome (for events: Elevated ALT, Liver failure, Bacterial pneumonia, Urinary tract infection, Hypotension (onset date (b) (6)), Acute kidney injury, DVT and Elevated AST) updated, blood culture results added.

Follow up: 29-May-2020

The Investigator provided the following updates: study drug dosing details updated.

Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up: 16-Jun-2020

Correction on 18-May-2020: The following was corrected based on internal review - seriousness criteria for events DVT and metabolic encephalopathy and outcome for the event liver failure.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Diabetes mellitus	2000		YES
Hypertension	2000		YES
Hypoxic respiratory failure	05-Apr-2020		YES

Medical History Product(s)	Start Date	End Date	Indications	Events



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Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Aspartate aminotransferase	3017	U/L	1	40	N
Aspartate aminotransferase	5919	U/L	1	40	N
Creatinine	1.5	mg/dL	0.5	1	N
Creatinine	1.7	mg/dL	0.5	1	N
Lactate dehydrogenase			60	200	Y
Diastolic blood pressure	57	mmHg			N
Diastolic blood pressure	72	mmHg			N
Systolic blood pressure	131	mmHg			N
Systolic blood pressure	92	mmHg			N
Body temperature	92.8	degF			Y
Neutrophil count	45.35	/nL	1.9	8.7	N
Partial pressure O2	107.9	mmHg			N
WBC count	19.34	/nL	3.9	8.7	N
WBC count	20.69	/nL	3.9	8.7	N
Creatinine	1.7	mg/dL	0.5	1	N
Diastolic blood pressure	82	mmHg			N
Diastolic blood pressure	64	mmHg			N
Sodium	133	meq/L	135	145	N
Neutrophil count	16.77	/nL	1.9	8.7	N
Oxygen saturation	94	%			N
WBC count	16.77	/nL	3.9	8.7	N
Alanine aminotransferase	30	U/L	1	45	N
Alanine aminotransferase	1021	U/L	1	45	N
Diastolic blood pressure	63	mmHg			N
Systolic blood pressure	90	mmHg			N
Body temperature	98.9	degF			Y
Heart rate	76	beats/min			N
Neutrophil count	26.36	/nL	1.9	8.7	N
Neutrophil count	16.59	/nL	1.9	8.7	N
Partial pressure CO2	35.1	mmHg			N
Platelet count	282	/nL	150	440	N
SARS-CoV-2 test					Y
Ultrasound examination					Y
Aspartate aminotransferase	36	U/L	1	40	N
Bicarbonate	13.5	meq/L	20	28	N
Calcium	7.5	mg/dL	8	10.5	N
Lactate dehydrogenase	675	U/L	60	200	N
Systolic blood pressure	110	mmHg			N
Heart rate	97	beats/min			N
Neutrophil count	13.37	/nL	1.9	8.7	N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Creatinine	1	mg/dL	0.5	1	N
Diastolic blood pressure	66	mmHg			N
Diastolic blood pressure	67	mmHg			N
Systolic blood pressure	124	mmHg			N
Heart rate	95	beats/min			N
Neutrophil count	1.43	/nL	1.9	8.7	N
Neutrophil count	32.50	/nL	1.9	8.7	N
Respiratory rate	43	breaths/min			N
WBC count	11.70	/nL	3.9	8.7	N
Blood bilirubin	2.8	mg/dL	0.2	1.2	N
Lactate dehydrogenase	607	U/L	60	200	N
Potassium	6.9	meq/dL	3.5	5	N
Diastolic blood pressure	58	mmHg			N
Systolic blood pressure	95	mmHg			N
Culture					Y
Lymphocyte count	1.43	UNK			Y
Arterial oxygen saturation	98.3	%			N
Platelet count	396	/nL	150	440	N
WBC count	16.77	/nL	3.9	8.7	N
CPK	9530	iU/L	5	225	N
Creatinine	3.6	mg/dL	0.5	1	N
Potassium	4.6	meq/dL	3.5	5	N
Body temperature	98.6	degF			Y
Culture					Y
Heart rate	70	beats/min			N
Neutrophil count	6.57	/nL	1.9	8.7	N
Neutrophil count	17.5	/nL	1.9	8.7	N
WBC count	38.17	/nL	3.9	8.7	N
WBC count	53.74	/nL	3.9	8.7	N
Alanine aminotransferase	497	U/L	1	45	N
Arterial blood pH	7.49	UNK			Y
Systolic blood pressure	97	mmHg			N
Systolic blood pressure	112	mmHg			N
Heart rate	93	beats/min			N
WBC count	8.29	/nL	3.9	8.7	N
WBC count	28.44	/nL	3.9	8.7	N
X-ray					Y



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Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/	Oral	650 mg, PRN		07-Apr-2020	23-Apr-2020	6 DAY
2	ACETAMINOPHEN	975 MG/1X	Oral	975 mg, 1X	Fever	05-Apr-2020	05-Apr-2020	6 DAY
3	AZITHROMYCIN	250 MG/	Oral	250 mg, PRN	COVID-19 pneumonia	07-Apr-2020	10-Apr-2020	4 DAY
4	AZITHROMYCIN	500 MG/QD	Oral	500 mg, qd		05-Apr-2020	06-Apr-2020	4 DAY
5	CEFPODOXIME	200 MG/Q12H	Oral	200 mg, bid	COVID-19 pneumonia	07-Apr-2020	08-Apr-2020	4 DAY
6	CEFTRIAZONE	500 MG/QD		500 mg, QD	COVID-19 pneumonia	05-Apr-2020	06-Apr-2020	6 DAY
7	CEFTRIAZONE	1000 MG/QD	Intravenous (not otherwise specified)	1000 mg, QD		08-Apr-2020	12-Apr-2020	6 DAY
8	CEFTRIAZONE	1000 MG/QD	Intravenous (not otherwise specified)	1000 mg, QD		05-Apr-2020	05-Apr-2020	6 DAY
9	FENTANYL [FENTANYL CITRATE]	100 UG/1X	Intravenous (not otherwise specified)	100 ug, single	Sedation	09-Apr-2020	09-Apr-2020	2 DAY
10	FENTANYL [FENTANYL CITRATE]		Intravenous (not otherwise specified)	25-250MCG/HR		09-Apr-2020		2 DAY
11	HYDROXYCHLOROQUIN E	400 MG/QD	Oral	400 mg, qd	COVID-19	07-Apr-2020	10-Apr-2020	4 DAY
12	METHYLPREDNISOLON E [METHYLPREDNISOLON E ACETATE]	80 MG/1X	Intravenous (not otherwise specified)	80 mg, single	Inflammation	19-Apr-2020	19-Apr-2020	
13	METHYLPREDNISOLON E [METHYLPREDNISOLON E ACETATE]			UNK				
14	METHYLPREDNISOLON E [METHYLPREDNISOLON E ACETATE]	40 MG/Q12H	Intravenous (not otherwise specified)	40 mg, BID		23-Apr-2020	27-Apr-2020	



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Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
15 VANCOMYCIN	1000 MG/Q12H	Intravenous (not otherwise specified)	1000 mg, bid		23-Apr-2020	23-Apr-2020	11 DAY
16 VANCOMYCIN	1000 MG/Q8H	Intravenous (not otherwise specified)	1000 mg, tid	COVID-19 pneumonia	22-Apr-2020	23-Apr-2020	11 DAY

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



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FOIA Case Report Information

Case ID: 17779155

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 25-Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 13-May-2020
Mfr Rcvd Date: 05-May-2020
Mfr Control #: US-ROCHE-2597432
Application #: 125276

Patient Information:

Age: 37 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		600 MG/QD	Intravenous (not otherwise specified)		COVID-19	25-Apr-2020	
2	ACTEMRA		600 MG/QD	Intravenous (not otherwise specified)			28-Apr-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		Unk	NA	UNKNOWN				
2	ACTEMRA		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Intentional product use issue	NA
Multiple organ dysfunction syndrome	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17779155

Event/Problem Narrative:

AER 2597432 is a spontaneous case, received on 05/May/2020 from a pharmacist in the USA. It concerns a 37 year old male patient who developed multi-organ system failure whilst intentionally being treated with tocilizumab (Actemra) for unlabeled indication (off label use).

Concurrent conditions included hypertension, sleep apnea, asthma, attention deficit hyperactivity disorder (ADHD), bipolar disorder, pneumonia, fever and acute respiratory failure. Concomitant medications included hydroxychloroquine. No medical history and past drugs were reported.

On ^{(b) (6)} he presented with shortness of breath (SOB), fever attributed to COVID-19. The pharmacist stated this was an inpatient but did not disclose the start date for Covid-19 or admission to the hospital. He was mentally challenged and was residing in nursing home. On ^{(b) (6)}, he was COVID positive and was diagnosed with COVID pneumonia, acute respiratory failure. Laboratory values revealed ferritin at 854, lactate dehydrogenase (LDH) at 515, C-reactive protein (CRP) at 11, lactate at 0.8 and d-dimer at 1010. He was on supplemental oxygen. He was administered hydroxychloroquin. Clinical status was worsening. On ^{(b) (6)}, the patient started therapy with intravenous (IV) tocilizumab (lot number: UNKNOWN) at 600 mg, every day for covid-19 (used for intentional use for unlabeled indication as off label use). On ^{(b) (6)} he received therapy with IV tocilizumab at 600 mg, every day. On ^{(b) (6)}, he had very high fever (41 degree C) and passed away. He had COVID-19 coagulopathy, COVID-19 with uncontrollable fever, COVID-19 infection and pneumonia. He passed away due to multi-organ system failure and COVID-19 with uncontrollable fever. It was not reported if an autopsy was performed or not.

At the time of death, it was unknown if therapy with tocilizumab was altered or not in response to the multi-organ system failure. The patient died on an unknown date.

The pharmacist assessed the multi-organ system failure as not related to tocilizumab

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute respiratory failure			
Asthma			
Attention deficit hyperactivity disorder			
Bipolar disorder			
Hypertension			



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FOIA Case Report Information

Case ID: 17779155

Pneumonia

Sleep apnoea syndrome

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Serum ferritin	854	not reported			N
C-reactive protein	11	not provided			N
Blood lactate dehydrogenase	515	not provided			N
Blood lactic acid	0.8	not provided			N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	HYDROXYCHLOROQUIN E							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17780019

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: NLD Event Date: 09-May-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 21-May-2020 Mfr Rcvd Date: 18-May-2020 Mfr Control #: NL-ROCHE-2599697 Application #: 125276

Patient Information:

Age: 85 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		520 MG/	Intravenous (not otherwise specified)		COVID-19	07-May-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	2 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC
 Respiratory failure NA

Event/Problem Narrative:

AER 2599697 is a clinical study case, received on 11/May/2020 from a physician in the Netherlands. It concerns an 85 year old male patient (patient number (b) (6) who died due to respiratory insufficiency whilst enrolled in (b) (6) (b) (6)

Concurrent conditions included dyspnoea, covid pneumonia, asthma, recurrent pneumonia, IgM deficiency, klebsiella pneumonia. No concomitant medications, medical history and past drugs were reported.

On an unknown date, (b) (6) (b) (6) On the same day, he received subcutaneous (SC) morphine 2.5mg, Sat was 92% at 11 L oxygen (O2). In night he had acute respiratory deterioration and morphine elevation. On 08/May/2020, picture persistent, so policy continued. On 09/May/2020, O2 Sat was 95% at 12 L, O2 was increased to 15L, morphine raised, making him look more restful and he had severe respiratory insufficiency. On (b) (6) strong tachy/dyspnoeic, sounds very full. Sat initially was 80-85% at the ear with 15L O2 via NRM but drops further to 70-75%. Over all lung fields especially expiratory wet rochi. In the night of 9 to 10 acutely more dyspnoea with sat 80% at 15L O2, cattle sounds fuller



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than before. Morphine bolus 2.5 mg was given, 20 mg furosemide (Lasix) intramuscular later 80 mg furosemide intravenous given. No improvement observed. Sat drops to 70%. He was peripherally colder and less approachable. Morphine elevation. On the same day at 06:00 am the morning, he died due to respiratory insufficiency. It was unknown if an autopsy was performed or not.

At the time of death, it was not reported if therapy with tocilizumab was ongoing or not.

The physician did not report the causality of respiratory insufficiency with tocilizumab but assessed related with disease under study.

The company assessed the causality of respiratory insufficiency as not related with tocilizumab as it is likely to be caused by COVID-19 infection, The underlying disease of COVID-19 pneumonia can weaken the local defenses in the respiratory tract and lead to severe lung damage causing respiratory insufficiency.

No further information was provided.

Additional information was received on 18/May/2020: Following information was added to the case: concurrent conditions, treatment medications and description.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Asthma				
Blood immunoglobulin M decreased				
COVID-19 pneumonia				
Dyspnoea				
Pneumonia				
Pneumonia klebsiella				
Medical History Product(s)	Start Date	End Date	Indications	Events



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Case ID: 17780019

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17780160

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: HUN Event Date: Outcomes: DE,OT, Application Type: BLA

FDA Rcvd Date: 25-May-2020 Mfr Rcvd Date: 22-May-2020 Mfr Control #:HU-ROCHE-2598804 Application #: 125276

Patient Information:

Age: Sex: Female Weight: 55 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		800 MG/	Intravenous (not otherwise specified)		COVID-19 pneumonia	25-Apr-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Off label use	NA
Product use in unapproved indication	NA

Event/Problem Narrative:

AER 2598804 is a spontaneous case, received on 08/May/2020 from a physician via company representative in Hungary. It concerns a 38 year old female patient who deceased NOS whilst being treated with tocilizumab (RoActemra) for unlabelled indication.

Concurrent conditions included severe obesity, chronic obstructive pulmonary disease, type 2 diabetes. No medical history, past drugs and concomitant medications were reported. Allergy, drug or alcohol use not known, reportedly took no medicines.

On 25/Apr/2020, the patient started therapy with intravenous (IV) tocilizumab (lot number: not reported) at 800 mg single use in 60-minute NaCl infusion for covid-19 infection (off label use). The covid-19 infection confirmed by a relative living in her household was in official quarantine due to COVID-19 infection. Her clinical condition (high fever of 40 degree centigrade, positional oxygenation disorder, etc.), imaging test results: (bilateral ground-glass opacification (GGO) affecting 75% of the lungs, detected by computed tomography (CT)).



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Laboratory test results (elevated ferritin level (1240 ng/mL, in addition to elevated C-reactive protein (CRP) level of 384 mg/mL. indicating non-bacterial infection, quasi-normal procalcitonin (PCT) of 0.23 ng/mL). The polymerase chain reaction (PCR) test of the lower respiratory tract sample ordered by the on-call physician at the time of admission was positive for SARS-Cov-2 virus. Her husband living in the same household was confirmed to be positive for SARS-Cov-2. Travel history was not listed (except that he came from (b) (6)). She had clinical symptoms of high fever, cough, dyspnoea, severe positional oxygenation disorder (which improved when she was put in the prone position). Repeated US examinations showed B-profile in both lungs. Reverse transcription polymerase chain reaction (rRTPCR) of lower respiratory tract sample was positive, whereas the rapid serology test targeted at IgM and IgG detection, performed at the time of admission, was negative. Following her admission, she had to be put in the prone position and invasive ventilation had to be administered (mean airway pressure >23 mmHg, Tlow <0.4 sec, FiO2 >100%). Despite the supportive therapy, on the seventh day of treatment, after repeated progression following a temporary improvement, her condition deteriorated to an extent where her circulatory system was also affected and pressor amines had to be administered. Her ferritin level started to increase, on the eight day of treatment her oxygenation was insufficient despite the use of 100% FiO2, and she died on the 12th day of treatment in 2020. The patient needed mechanical ventilation throughout the period of treatment. On an unknown date in 2020, she was critically ill and died within 24 hours. It was not reported if autopsy was performed or not.

The physician did not report a causality between deceased NOS and tocilizumab.

No further information was provided.

Additional information was received on 15/May/2020 and following information was added to the case: Suspect updated with trade name (RoActemra) and dosage details updated, event description updated for covid-19 infection details, concurrent conditions (severe obesity, chronic obstructive pulmonary disease, type 2 diabetes).

Additional information was received on 22/May/2020 and following information was added to the case: New primary reporter and patient details updated. Event description updated accordingly.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Chronic obstructive pulmonary disease			
Obesity			
Type 2 diabetes mellitus			



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Case ID: 17780160

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
C-reactive protein	384	mg/mL			N
Coronavirus test					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17780331

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: GBR Event Date: 05-May-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 19-May-2020 Mfr Rcvd Date: 13-May-2020 Mfr Control #: GB-ROCHE-2598473 Application #: 125276

Patient Information:

Age: 85 YR Sex: Female Weight: 69.8 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		200 MG/	Intravenous (not otherwise specified)		COVID-19 pneumonia	29-Apr-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	6 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) COVID-19 pneumonia ReC NA

Event/Problem Narrative:

AER 2598473 is a clinical study case, received on 08/May/2020 from a physician in the United Kingdom. It concerns a 85 year old female patient (patient number: (b) (6)) who died due to COVID-19 pneumonia progression whilst enrolled in (b) (6) (b) (6)

Concurrent conditions included CKD (chronic kidney disease) stage 3, lipodermatosclerosis, hemiplegia, osteoarthritis, hiatus hernia, breathlessness, pneumonia, indigestion, dry skin, allergies, cholesterol and hypertension. Concomitant medications included lansoprazole to reduce stomach acid, tramadol as analgesia, bendroflumethiazide, atorvastatin, loratadine, enoxaparin sodium, clopidogrel, Dermal Cream, macrogol 3350 potassium chloride, sodium bicarbonate, sodium chloride (Movicol), antacids, other combinations (Gaviscon), Amoxicillin/Potassium clavulanate as pneumonia prophylaxis, paracetamol to maintain temperature, morphine sulfate, salbutamol to maintain airway, ipratropium bromide to maintain airway, senna spp. (Senna) and oxygen. No medical history and past drugs were reported.

(b) (6) (b) (6) On 05/May/2020, she



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had COVID-19 pneumonia progression (initial severity: grade 3 and most extreme : grade 5). She had a chest X-ray which showed worsening of pneumonia related to Covid-19. No other relevant diagnostic tests were performed. No further treatment was offered and she commenced end of life care as per trust guidance. On (b) (6) she died due to COVID-19 pneumonia progression. It was unknown if an autopsy was performed or not.

The physician assessed the causality of fatal COVID-19 pneumonia progression as not related to blinded tocilizumab, while assessed it as related to disease under study.

The sponsor assessed the causality of fatal COVID-19 pneumonia progression as not related to blinded tocilizumab and more likely related to underlying COVID-19 infection and its complications, considering high levels of pro-inflammatory cytokines resulting from the viral illness, results in injury to multiple organs. Other confounding factors include the patient's advanced age (85 years) and concurrent conditions chronic kidney disease stage 3 and hypertension.

No further information was provided.

Additional information was received on 13/May/2020, following information was added to the case: New secondary reporter, onset date of the event (COVID-19 pneumonia progression) was updated to 05/May/2020 (previously reported as 06/May/2020), other suspected causality of the event, tocilizumab details (volume, date of most recent dose, time of administration, lot/batch number), reporter causality of the event (COVID-19 pneumonia progression) with suspect drug (tocilizumab) was updated to not related (previously not reported) and event description (She had chest X-ray which showed worsening of pneumonia related to Covid-19. No further treatment was offered and she commenced end of life care as per trust guidance.

This case no longer meets expedited reporting requirements because the causality of event "COVID-19 pneumonia progression" was updated as unrelated to study drug tocilizumab.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Blood cholesterol			
Chronic kidney disease			YES
Dry skin			
Dyspepsia			



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Dyspnoea	
Hemiplegia	YES
Hiatus hernia	YES
Hypersensitivity	
Hypertension	
Osteoarthritis	YES
Pneumonia	
Post thrombotic syndrome	YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
X-ray					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ATORVASTATIN	20 MG/QD	Unknown		Blood cholesterol			
2	BENDROFLUMETHIAZID E	2.5 MG/QD	Unknown		Hypertension			
3	CLOPIDOGREL	75 MG/QD	Unknown					
4	ENOXAPARIN SODIUM	40 MG/QD	Unknown			27-Apr-2020		8 DAY
5	IPRATROPIUM BROMIDE		Unknown	500 inhalation		26-Apr-2020		9 DAY
6	LANSOPRAZOLE	15 MG/QD	Unknown					
7	LORATADINE	10 MG/QD	Unknown		Hypersensitivity			



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	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
8	MORPHINE SULPHATE	2.5 MG/	Unknown		Dyspnoea	26-Apr-2020		9 DAY
9	MOVICOL [MACROGOL 3350;POTASSIUM CHLORIDE;SODIUM BICARBONATE;SODIUM CH	BID	Unknown	other		26-Apr-2020		9 DAY
10	OXYGEN		Unknown	2 inhalation		26-Apr-2020		9 DAY
11	PARACETAMOL	1 G/QID	Unknown			26-Apr-2020		9 DAY
12	SALBUTAMOL	5 MG/	Unknown			26-Apr-2020		9 DAY
13	SENNA [SENNA SPP.]	7.5 MG/QD	Unknown			26-Apr-2020		9 DAY
14	TRAMADOL	50 MG/	Unknown		Analgesic therapy			

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17785405

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 27-Apr-2020 Outcomes: DE,HO,OT, Application Type: BLA
 FDA Rcvd Date: 27-Oct-2020 Mfr Rcvd Date: 14-Oct-2020 Mfr Control #:US-SA-2020SA119798 Application #: 761037

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	REGN mAb1 400 mg, 1X	COVID-19	23-Apr-2020	23-Apr-2020
2	SARILUMAB			Intravenous (not otherwise specified)	REGN88 or placebo 200 mg or 400 mg, single dose or multiple doses for 1 hour		24-Apr-2020	24-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	53419 MINUTES	NA	NA				SANOFI	
2	SARILUMAB	53419 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Acute respiratory distress syndrome	NA
Transaminases increased	NA



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Case ID: 17785405

Event/Problem Narrative:

Based on additional information received on 14-Oct-2020, the company causality for event elevated alanine aminotransferase (ALT)/ aspartate aminotransferase (AST) which was previously assessed as related was updated to not related. Consequently, the case was downgraded from suspected unexpected serious adverse reaction (SUSAR) to non-SUSAR.

Initial information received on 29-Apr-2020, 30-Apr-2020, 01-May-2020 and 06-May-2020 (processed together) regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference number 2020-34949 on 29-Apr-2020, 30-Apr-2020, 01-May-2020 and 06-May-2020 (processed together) and transmitted to Sanofi, in the scope of company sponsored study (b) (6)

Patient ID: (b) (6) Site (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

Acute respiratory distress syndrome (ARDS) due to COVID-19 [Acute respiratory distress syndrome]: Death; Onset date: (b) (6)
Severity: Grade 5; Outcome: Fatal; Event resolved on: (b) (6)

Elevated ALT/AST [Transaminases increased] (initially reported Elevated ALT [Alanine aminotransferase increased]: Hospitalization, Medically significant; serious adverse event of special interest (AESI) (ALT or AST increase); Onset date: (b) (6) Severity: Grade 4; Outcome: Recovered/Resolved; Event resolved on: (b) (6)

On 06-Oct-2020, the event Elevated ALT was upgraded from serious non-AESI to serious AESI since it was confirmed that event meet AESI criteria-ALT or AST increase.

On 05-Oct-2020, the event Elevated AST was downgraded from non-serious AESI to non-serious non-AESI, as it was confirmed that event Elevated AST did not meet AESI criteria.

On (b) (6) the event acute kidney injury (AKI) was downgraded from serious non-AESI to non-serious non-AESI, since it was found to be same as the event elevated ALT.

A 75-year-old, Hispanic, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6)

The patient experienced above-referenced serious AESI on (b) (6) and serious adverse event (SAE) on (b) (6) after receiving study drug.



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Relevant medical history included atrial fibrillation, chronic kidney disease, pre-diabetes and hyperlipidemia.

Relevant concomitant medications included amiodarone, doxycycline, methylprednisolone and piperacillin/tazobactam.

On (b) (6) the patient had earliest onset of symptoms of pneumonia (fever/feverishness, cough, dyspnoea/short of breath), with rales/crackles on lung auscultation present at baseline. Patient's highest temperature recorded within 24 hours prior to study drug dosing was 98.4 degrees Fahrenheit (degree F). The patient received vasopressors, renal replacement therapies, and invasive mechanical ventilation, which required treatment in intensive care unit. Chest X-ray showed bilateral airspace opacities suspicious for multifocal pneumonia.

On (b) (6), oxygen saturation (SpO₂) was 100%, blood pressure was 106/67 mmHg, pulse rate 83 beats per minute (bpm), respiratory rate 25 respirations per minute (rpm), temperature 36.1 degrees Celsius (degree C), alanine aminotransferase (ALT) was 16 U/L (9-50), aspartate aminotransferase (AST) was 19 U/L (10-37), total bilirubin 0.2 mg/dl (0.2-1.3), white blood cells (WBC) count was 14.03 x10³ /mcl (3.12-8.44), neutrophils (absolute) count was 12.45 (units and reference range not reported), and platelets count was 177x10³/mcl (156-325).

On (b) (6) at 04:33 (b) (6) days 18 hours 10 minutes after first administration of study drug, the patient experienced Elevated ALT/AST. ALT increased to 1046, AST increased to 1328, and WBC count increased to 31.79. Blood pressure decreased to 88/69 mmHg, pulse increased to 94 bpm and respiratory rate increased to 39 rpm. Corrective treatment consisted of electrolyte repletion and continuous renal replacement therapies. The participant was no longer eligible to receive weekly follow-up study drug dosing.

On (b) (6), ALT and AST further increased to 1938 and 3060, respectively and neutrophils increased to 26.51.

On (b) (6), ALT and AST values decreased to 1561 and 1604, respectively.

On (b) (6) AST was 679, while ALT was 1002, WBC count was 22.25 and platelets decreased to 40.

On (b) (6) event Elevated ALT/AST was deemed resolved. ALT decreased to 123 and AST to 75. In the following days, both continued to decrease.

On (b) (6) ALT was at 35 and AST at 41.

On (b) (6) ALT was at 45 and AST at 50.

On (b) (6) at 12:42, (b) (6) days 2 hours after first administration of study drug, the patient suffered an acute respiratory distress syndrome and passed away. No additional information was provided. The patient died as a result of acute respiratory distress syndrome due to COVID-19. It was not reported whether an autopsy was performed.



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Action taken with study drug in response to the events was not applicable.

On (b) (6) treatment assignment blind was broken for regulatory reporting purposes

Causality assessment is as follows: (b) (6)

Acute respiratory distress syndrome: Severity = Grade 5; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 75-year-old, male patient enrolled in the trial experienced acute respiratory distress syndrome which ended fatally (b) (6) days after receiving the last dose of the study drug. The reported event is most likely secondary to COVID-19 progression further aggravated by prolonged hospitalization in ICU with mechanical ventilation and patient's advanced age. Therefore, the event is assessed as not related to study drug or to any clinical trial procedure.

Transaminases increased: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Patient in critical care. Acute kidney injury (AKI) related to critical clinical status. AKI occurred as a result of COVID-19 infection, respiratory failure and shock. Elevated AST/ALT as a result of AKI. Other suspected cause was reported as critical illness.

Company causality rationale: A 75-year-old male patient with COVID-19 enrolled in the trial experienced elevated ALT/AST (b) (6) days after receiving (b) (6) dose of study drug. Although baseline AST and ALT were normal and sarilumab is known for potential transient effect on functional liver enzymes, substantial increase in ALT and AST, along with progression of underlying COVID-19 disease and subsequent acute kidney injury further aggravated by patient's age and comorbidities provide plausible explanation for the event and therefore, causality for the event is assessed as not related to study drug or any clinical trial procedure.

Causality assessment for initially reported event term Elevated ALT: Alanine aminotransferase increased: Severity = Grade 4; Investigator Causality = Not Related;

Company Causality = Related Investigator causality rationale: Patient in critical care. Acute kidney injury (AKI) related to critical clinical status. AKI occurred as a result of COVID-19 infection, respiratory failure and shock. Elevated AST/ALT as a result of AKI. Other suspected cause was reported as critical illness.

Company causality rationale: A 75-year-old male patient enrolled in the trial, experienced acute kidney injury and ALT increase after administration of the blinded study drug. Based on a plausible temporal association between study drug administration and the reported elevation of ALT and known potential effect of study drug on functional liver enzymes, causality for the event elevated ALT is assessed as related to study drug and not related to any clinical trial procedure. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation. Patient's underlying severe or critical COVID-19 with pneumonia before initiation of the study drug confounds causality for the events.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.



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Follow up: 28-May-2020 and 29-May-2020 (processed together) The Investigator provided the following updates: dosing details, outcomes, corrective treatment and Investigator causality rationale for the event Elevated ALT updated, event acute kidney injury (AKI) downgraded from serious non-AESI to non-serious non-AESI

Follow up: 05-Jun-2020 The investigator provided the following updates: fatal event of Acute respiratory distress syndrome (ARDS) due to COVID-19 with death details added, outcome of the events Elevated ALT, AST and clinical course updated.

Correction on 30-Jul-2020 The following was corrected based on internal review AESI category.

Follow up: 05-Oct-2020 and 06-Oct-2020 (processed together) The investigator provided the following updates: event Elevated AST downgraded from non-serious AESI to non-serious non-AESI and Elevated ALT upgraded to serious AESI.

Follow up: 14-Oct-2020 The investigator provided the following updates: event term updated from Elevated ALT to Elevated ALT/AST and relevant medical history updated.

Expectedness Assessment per current IB (version 14): Acute respiratory distress syndrome (ARDS) due to COVID-19: unexpected
Elevated ALT/AST: unexpected Expectedness

Assessment for initially reported event term Elevated ALT: Expectedness Assessment per current IB (version 14): Elevated ALT: unexpected

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Chronic kidney disease	2020		YES
Hyperlipidemia	2020		YES
Hypertension	2020		YES
Pre-diabetes	2020		YES
Pulmonary granulomatosis	2020		YES
Atrial fibrillation	(b) (6)		YES



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Case ID: 17785405

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	16	U/L	9	50	N
Alanine aminotransferase	1002	U/L	9	50	N
Alanine aminotransferase	123	U/L	9	50	N
Pulse rate	94	beats/min			N
Neutrophil count	26.51	UNK			Y
Respiratory rate	25	breaths/min			N
Respiratory rate	39	breaths/min			N
Aspartate aminotransferase	19	U/L	10	37	N
Aspartate aminotransferase	3060	U/L	10	37	N
Aspartate aminotransferase	679	U/L	10	37	N
Aspartate aminotransferase	50	U/L	10	37	N
Body temperature	36.1	Cel			N
WBC	31.79	10 ⁹ /uL	3.12	8.44	N
Alanine aminotransferase	1561	U/L	9	50	N
Alanine aminotransferase	45	U/L	9	50	N
Aspartate aminotransferase	1604	U/L	10	37	N
Aspartate aminotransferase	41	U/L	10	37	N
Blood pressure	88/69	mmHg			N
Neutrophil count	12.45	UNK			Y
Blood bilirubin total	0.2	mg/dL	0.2	1.3	N
Pulse rate	83	beats/min			N
Platelet count	177	10 ³ /uL	156	325	N
WBC	22.25	10 ⁹ /uL	3.12	8.44	N
X-ray					Y
Alanine aminotransferase	1046	U/L	9	50	N
Alanine aminotransferase	35	U/L	9	50	N
Aspartate aminotransferase	1328	U/L	10	37	N
Body temperature	98.4	degF			Y
Oxygen saturation	100	%			N
Alanine aminotransferase	1938	U/L	9	50	N
Aspartate aminotransferase	75	U/L	10	37	N
Blood pressure	106/67	mmHg			N
Platelet count	40	10 ³ /uL	156	325	N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
WBC	14.03	10 ⁹ /uL	3.12	8.44	N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	AMIODARONE		Intravenous (not otherwise specified)	150 mg bolus then 1mg/min titrated to 0.5 mg/min, CONT	Cardiac arrhythmia	22-Apr-2020	23-Apr-2020	7473 MIN
2	DOXYCYCLINE	100 MG/Q12H	Other	100 mg, BID orogastric	Ant biotic therapy	21-Apr-2020	23-Apr-2020	8913 MIN
3	METHYLPREDNISOLON E	40 MG/Q12H	Intravenous (not otherwise specified)	40 mg, BID	COVID-19	18-Apr-2020	22-Apr-2020	13233 MIN
4	NOREPINEPHRINE		Intravenous (not otherwise specified)	1-40 mg/min, continuous infusion	Vasopressive therapy	20-Apr-2020	30-May-2020	10353 MIN
5	PHENYLEPHRINE		Intravenous (not otherwise specified)	10-400 mcg/min, continuous infusion	Vasopressive therapy	19-Apr-2020	20-Apr-2020	11793 MIN
6	PIPERACILLIN TAZOBACTAM PA	4.5 MG/Q8H	Intravenous (not otherwise specified)	4.5 mg, q8h	Ant biotic therapy	17-Apr-2020	23-Apr-2020	14673 MIN
7	VANCOMYCIN	1250 MG/QD	Intravenous (not otherwise specified)	1250 mg, QD	Ant biotic therapy	17-Apr-2020	21-Apr-2020	14673 MIN
8	VASOPRESSIN		Intravenous (not otherwise specified)	2.4 U/hour, continuous infusion	Pituitary insufficiency	20-Apr-2020	30-May-2020	10353 MIN

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17785409

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Event Date:** 07-Apr-2020 **Outcomes:** DE,DS,HO,LT, **Application Type:** BLA

FDA Rcvd Date: 02-Sep-2020 **Mfr Rcvd Date:** 26-Aug-2020 **Mfr Control #:** US-SA-2020SA104835 **Application #:** 761037

Patient Information:

Age: **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	400 mg, single	COVID-19	07-Apr-2020	07-Apr-2020
2	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	400 mg, single, 1X		20-Apr-2020	20-Apr-2020
3	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	400 mg, single, 1X		13-Apr-2020	13-Apr-2020
4	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	400 mg, 1X		26-Apr-2020	26-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	26590 MINUTES	NA	NA				SANOFI	
2	SARILUMAB	26590 MINUTES	NA	NA				SANOFI	
3	SARILUMAB	26590 MINUTES	NA	NA				SANOFI	
4	SARILUMAB	26590 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA Version: 23.1)	ReC
Bacteraemia	NA
COVID-19	NA



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Deep vein thrombosis	NA
Gastrointestinal haemorrhage	NA
Hypotension	NA
Septic shock	NA

Event/Problem Narrative:

Upon internal review with CSD 27-Apr-2020, the case initially assessed as non-SUSAR was upgraded to SUSAR case as event of bacteremia was added. Also, the overall company causality initially assessed as not reportable was updated to reportable, reporter causality initially assessed as not related was updated to related.

Initial information received on 13-Apr-2020 regarding a solicited valid serious case received from (lp) regeneron-usa gsa-pcp under reference 2020-31182 on 12-Jun-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6)
Patient ID: (b) (6) Site (b) (6) Country: United States

Study title: (b) (6)

(b) (6)

A 68-year-old, female patient of unreported ethnicity with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6)

(b) (6)

(b) (6)

The patient experienced Bacteremia [Bacteraemia]: Life threatening, Hospitalization; Serious AESI (clinically significant invasive bacterial or fungal infections) (Severity: Grade 3) serious AESI on (b) (6) and Death related to Covid-19 [Covid-19]; Death (Severity: Grade 5) on (b) (6) Septic shock [Septic shock], (Life threatening, Disability, Severity: Grade 4) on (b) (6) Hypotension [Hypotension]: Hospitalization, (Severity: Grade 3) on (b) (6) Bilateral lower extremity deep vein thrombosis [Deep vein thrombosis]: Life threatening, Hospitalization (Severity: Grade 4) on (b) (6) and Gastrointestinal bleed [Gastrointestinal haemorrhage]: Hospitalization (Severity: Grade 3) on (b) (6) after receiving study drug.

Relevant medical history included hypertension, hyperlipidaemia, acute respiratory distress syndrome.

No relevant concomitant medications were reported.



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On 21-Mar-2020, the patient started experiencing earliest symptoms of pneumonia. Highest temperature recorded within 24 hours prior to dosing was 98.3 degrees Fahrenheit (F).

On (b) (6) the patient was admitted to hospital. Electrocardiogram (ECG) results showed sinus tachycardia, chest X-ray showed bilateral diffuse infiltrates and SARS-CoV-2 test was positive.

On (b) (6) (b) (6) after the administration of study drug, patient's temperature was 98.2 F, oxygen saturation (SpO₂) was 100%, blood pressure was 147/87 mmHg, pulse 116 beats per minute (bpm), respiratory rate 20 respirations per minute (rpm), rales and crackles were present upon auscultation at baseline. Patient's blood chemistry results were: alanine aminotransferase (ALT) 125 U/L (1-45), aspartate aminotransferase (AST) 146 U/L (1-40), total bilirubin 0.5 mg/dl (0.1-1.2), and haematology results were: red blood cell count (RBC) 4.21x10¹²/L (4.1- 5.3), platelets 255/nL (150-440), white blood cells (WBC) 15.82/nl (3.5-11), neutrophils (absolute) 14.56/nl (1.7-9). The patient was using supplemental oxygen by non-rebreather mask. On the same day, intubation was performed.

On (b) (6) WBC was 8.48 and neutrophils 7.37.

On (b) (6) (b) (6) days 11 hrs 10 min after the administration of study drug, the patient experienced bacteremia and septic shock. Echocardiogram st was performed but results were not reported. Central line was inserted for disease under study. White blood cells were at 13.36, neutrophils 11.06. The patient started treatment with Zosyn (piperacillin / tazobactam) at a dose of 4.5g, every 6 hours, IV, until (b) (6) (b) (6) and vancomycin at a dose of 1000mg, every 12 hours, IV, until (b) (6) for bacteremia. Norepinephrine at a dose of 8 mg until (b) (6) was started for hypotension and 1000 ml of 0.9% sodium chloride, both via continuous infusion, was started for septic shock, until (b) (6) Blood pressure was 104/74.

On (b) (6) (b) (6) days 11 hours 10 min after the administration of study drug, the patient was diagnosed with hypotension. Blood pressure was 98/62, pulse was 64 and respiratory rate was 24. On the same day, echocardiogram was performed for septic shock.

On (b) (6) vancomycin was given at a dose of 250mg.

On (b) (6) platelets were at 262, WBC 14.54, neutrophils 12.28 and blood pressure 164/100.

On (b) (6) (b) (6) days 11 hours 10 min after the administration of study drug, the patient experienced bilateral lower extremity deep vein thrombosis in right popliteal and left tibial veins, confirmed via ultrasound. Platelets were at 204. Heparin at a dose of 25000 units/250ml via continuous infusion and Cathflo (alteplase) at a dose of 2mg, twice, via intracatheter, were given on for the event.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.



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On (b) (6) WBC decreased to 8.31, neutrophils (absolute) to 6.15 and platelets to 137. Vena cava filter was inserted as a corrective treatment for the event deep vein thrombosis. On the same day, (b) (6) days 11 hours 10 min after the administration of study drug, the patient was diagnosed with gastrointestinal haemorrhage and treatment for anticoagulants was withheld. RBC count was 2.47 and blood pressure 125/64. On (b) (6) platelets were at 177, WBC 17.11 and neutrophils (absolute) 15.14. On the same day endotracheal tube was exchanged.

On (b) (6) (b) (6) days 11 hours after the administration of study drug, the patient experienced bacteraemia. Patient's cultures were positive with staphylococcus epidermidis and preliminary coagulase negative staphylococci. Possible contamination was noted. Platelets count was 140, RBC 2.49, WBC 8.82 and neutrophil 7.24.

On (b) (6) the patient was scheduled for esophagogastroduodenoscopy. Platelets 136, WBC 8.42, neutrophils 6.16 and RBC 2.72.

On (b) (6) blood pressure was 95/60.

On (b) (6) platelets count was 133, RBC 2.73, WBC 8.52 and neutrophils were 8.12. Blood pressure was 103/65. On the same day, the patient recovered from gastrointestinal bleed.

On (b) (6) the events hypotension and bacteremia were considered resolved. Blood pressure was 121/71, platelets 162, WBC count 10.99 and neutrophils 9.05.

On (b) (6) SpO2 was 97, pulse 109/64, pulse 78, and respiratory rate 36.

On (b) (6) SpO2 was 94, blood pressure 96/60, pulse 64, respiratory rate 16 and at 16:37 h, the patient died due to COVID-19. Autopsy was not performed.

Action taken with study drug in response to the events was dose not changed, while action taken with study drug in response to the event death due to COVID-19 was not applicable.

At the time of death, patient had not recovered from septic shock and Bilateral lower extremity deep vein thrombosis.

Causality assessment is as follows:

Covid-19: Investigator Causality = Not Related; Company Causality = Not Related Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 68-year-old female patient enrolled in the trail died due to COVID 19 infection, after administration of the blinded study drug. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug in addition to risk factors such as hypertension, hyperlipidemia, acute respiratory distress syndrome in this elderly patient is the cause for the



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reported event. Therefore, the event is assessed as unrelated to the study drug or to any clinical trial procedure.

Septic shock: Investigator Causality = Not Related; Company Causality = Not Related Investigator causality rationale: No alternative explanation was provided. Other suspected causes included COVID-19, infection and sedation.

Deep vein thrombosis: Investigator Causality = Not Related; Company Causality = Not Related Investigator causality rationale: No alternative explanation was provided. Other suspected causes included COVID-19 coagulopathy.

Hypotension: Investigator Causality = Not Related; Company Causality = Not Related Investigator causality rationale: No alternative explanation was provided. Other suspected causes included Covid-19 infection.
Company causality rationale: A 68-year-old female patient enrolled in the trial experienced septic shock, hypotension and lower extremity deep vein thrombosis after administration of the blinded study drug. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug in addition to risk factors such as hypertension, hyperlipidemia, acute respiratory distress syndrome in this elderly patient are the most plausible cause for the reported events. Covid19 is associated with increased risk of thromboembolic events. Hypotension is secondary to shock observed in critical and advanced Covid19. Therefore, all events are assessed as unrelated to the study drug or to any clinical trial procedure.

Bacteraemia: Investigator Causality = Related; Company Causality =Not Related Investigator causality rationale: AE of special interest. Other suspected causes include sequelae of COVID- 19/critical illness/invasive lines
Company causality rationale: A 68-year-old,female patient with severe or critical COVID-19 infection and worsening pneumonia experienced bacteremia, (b) (6) days after start of treatment and (b) (6) days after receiving last of the multiple doses of the study drug. The patient's culture bottles were positive one with staphylococcus epidermidis, one preliminary coagulase-negative staphylococci. The event of bacteremia is assessed as not related to study drug or any clinical trial procedure. Although, Sarilumab is associated with increased risk of infections, there are other contributory factors. Staphylococcus epidermidis infections are common in intubated and catheterized patient's, especially in a setting of pre-existing worsening infection where the patient had already been compromised such as patient's COVID-19 pneumonia and concurrent septic shock. Possibility of contamination of samples is also present. Previous company causality assessment for event of Bacteraemia was related with following rationale: A 68-year-old,female patient with severe or critical COVID- 19 infection and worsening pneumonia experienced bacteremia, (b) (6) days after start of treatment and (b) (6) day after receiving last of the multiple doses of the study drug. The patient's culture bottles were positive one with staphylococcus epidermidis, one preliminary coagulase-negative staphylococci. The event of bacteremia is assessed as possibly related to study drug and unrelated to any clinical trial procedure. Sarilumab is associated with increased risk of infections. However, there are other contributory factors. Staphylococcus epidermidis infections are common in intubated and catheterized patient's, especially in a setting of pre-existing worsening infection where the patient had already been compromised such as patient's COVID-19 pneumonia. Possibility of contamination of samples is also present.



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Gastrointestinal haemorrhage: Investigator Causality = Not Related; Company Causality = Not Related Investigator causality rationale: Other suspected causes include anticoagulation for DVTS.

Company causality rationale: A 68-year-old female patient enrolled in the trial experienced gastrointestinal haemorrhage after administration of the blinded study drug. The patient experienced deep vein thrombosis three days prior to gastrointestinal bleed and was receiving treatment with anticoagulants, which were withdrawn with onset of gastrointestinal bleed. Platelets count was reported as 137. Considering patient's underlying COVID-19 infection and pneumonia, concurrent conditions and anticoagulant treatment, which provide likely aetiology, causality is assessed as not related to study drug or any clinical trial procedure.

Causality assessment for the previously reported event is as follows:

Shock: Investigator Causality = Not Related; Company Causality = Not Related Investigator causality rationale: No alternative explanation was provided. Other suspected causes included COVID-19, infection and sedation.

Company causality rationale: A 68-year-old female patient enrolled in the trial experienced shock, hypotension and lower extremity deep vein thrombosis after administration of the blinded study drug. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug in addition to risk factors such as hypertension, hyperlipidemia, acute respiratory distress syndrome in this elderly patient are the most plausible cause for the reported events. Covid19 is associated with increased risk of thromboembolic events. Hypotension is secondary to shock observed in critical and advanced Covid19. Therefore, all events are assessed as unrelated to the study drug or to any clinical trial procedure.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 17-Apr-2020, 19-Apr-2020 and 20-Apr-2020 (processed together) The Investigator provided the following updates: new events added and relevant updates made.

Follow up: 27-Apr-2020, 29-Apr-2020 and 30-Apr-2020 (process together) The Investigator provided the following updates: event Bacteremia (12-Apr-2020) downgraded; action taken, study drug dosing, event outcome, stop date, seriousness criteria, investigator causality rationale and concomitant medications updated; new events added, and relevant updates made.

Follow up: 05-May-2020 and 09-May-2020 The Investigator provided the following updates: new event death related to Covid-19 added. Concomitant medications, relevant test, medical history, clinical course, outcome and resolution date for event gastrointestinal bleed updated.

Follow up: 12-May-2020 and 17-May-2020 (processed together) The Investigator provided the following updates: event outcome and clinical course updated. Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up: 19-May-2020 The Investigator provided the following updates: outcome and resolution date for events updated, clinical course updated.



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Follow up: 12-Jun-2020 and 16-Jun-2020 (processed together) The Investigator provided the following updates: protocol amendment added. Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow-up: 26-Aug-2020 and 27-Aug-2020 (processed together) The Investigator provided the following updates: event of Shock updated to Septic shock, clinical course, relevant labs and concomitant medications updated.

Expectedness Assessment per current IB (version 16): Death related to Covid-19: unexpected Septic shock: unexpected Bilateral lower extremity deep vein thrombosis: unexpected Bacteremia: unexpected Hypotension: unexpected Gastrointestinal bleed: unexpected
Expectedness Assessment per current IB (version 16) for the previously reported event: Shock: unexpected

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute respiratory distress syndrome	(b) (6)		YES
Gout			
Hyperlipidemia			
Hypertension			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Pulse rate	116	beats/min			N
Absolute neutrophil count	14.56	10 ⁹ /L	1.7	9	N
White blood cells	8.52	10 ⁹ /L	3.5	11	N
White blood cells	10.99	10 ⁹ /L	3.5	11	N
Aspartate aminotransferase	146	U/L	1	40	N
Systolic blood pressure	98	mmHg			N
Systolic blood pressure	109	mmHg			N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Absolute neutrophil count	6.15	10 ⁹ /L	1.7	9	N
SARS-CoV-2 test					N
White blood cells	13.36	10 ⁹ /L	3.5	11	N
White blood cells	14.54	10 ⁹ /L	3.5	11	N
Diastolic blood pressure	60	mmHg			N
Systolic blood pressure	103	mmHg			N
Systolic blood pressure	96	mmHg			N
Pulse rate	64	beats/min			N
Absolute neutrophil count	7.37	10 ⁹ /L	1.7	9	N
Absolute neutrophil count	11.06	10 ⁹ /L	1.7	9	N
Absolute neutrophil count	6.16	10 ⁹ /L	1.7	9	N
Platelet count	255	10 ⁹ /L	150	440	N
Platelet count	137	10 ⁹ /L	150	440	N
Platelet count	140	10 ⁹ /L	150	440	N
Red blood cell count	2.49	10 ¹² /L	4.1	5.3	N
Respiratory rate	20	breaths/min			N
Respiratory rate	24	breaths/min			N
Respiratory rate	36	breaths/min			N
White blood cells	8.31	10 ⁹ /L	3.5	11	N
Alanine aminotransferase	125	U/L	1	45	N
Bilirubin total	0.5	mg/dL	0.1	1.2	N
Pulse rate	64	beats/min			N
Pulse rate	78	beats/min			N
Absolute neutrophil count	12.28	10 ⁹ /L	1.7	9	N
Red blood cell count	2.73	10 ¹² /L	4.1	5.3	N
Respiratory rate	16	breaths/min			N
Diastolic blood pressure	65	mmHg			N
Diastolic blood pressure	64	mmHg			N
Systolic blood pressure	95	mmHg			N
ECG					Y
Oxygen saturation	100	%			N
White blood cells	8.48	10 ⁹ /L	3.5	11	N
White blood cells	8.82	10 ⁹ /L	3.5	11	N
Diastolic blood pressure	62	mmHg			N
Diastolic blood pressure	100	mmHg			N
Systolic blood pressure	147	mmHg			N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Systolic blood pressure	104	mmHg			N
Systolic blood pressure	125	mmHg			N
Chest X-ray					Y
Culture					Y
Absolute neutrophil count	8.12	10 ⁹ /L	1.7	9	N
Oxygen saturation	94	%			N
Platelet count	262	10 ⁹ /L	150	440	N
Platelet count	204	10 ⁹ /L	150	440	N
Red blood cell count	4.21	10 ¹² /L	4.1	5.3	N
Ultrasound scan					Y
White blood cells	15.82	10 ⁹ /L	3.5	11	N
Diastolic blood pressure	64	mmHg			N
Systolic blood pressure	121	mmHg			N
Absolute neutrophil count	7.24	10 ⁹ /L	1.7	9	N
Absolute neutrophil count	9.05	10 ⁹ /L	1.7	9	N
Oxygen saturation	97	%			N
Platelet count	136	10 ⁹ /L	150	440	N
Platelet count	133	10 ⁹ /L	150	440	N
White blood cells	8.42	10 ⁹ /L	3.5	11	N
Diastolic blood pressure	87	mmHg			N
Diastolic blood pressure	74	mmHg			N
Diastolic blood pressure	71	mmHg			N
Diastolic blood pressure	60	mmHg			N
Systolic blood pressure	164	mmHg			N
Body temperature	98.3	degF			Y
Body temperature	98.2	degF			Y
Platelet count	162	10 ⁹ /L	150	440	N
Red blood cell count	2.47	10 ¹² /L	4.1	5.3	N
Red blood cell count	2.72	10 ¹² /L	4.1	5.3	N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	AZITHROMYCIN	250 MG/QD	Intravenous (not otherwise specified)	250 mg, qd		09-Apr-2020	10-Apr-2020	8 DAY
2	AZITHROMYCIN	500 MG/QD	Intravenous (not otherwise specified)	500 mg, qd	COVID-19	04-Apr-2020	04-Apr-2020	8 DAY



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	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
3	CEFTRIAXONE	1000 MG/QD	Intravenous (not otherwise specified)	1000 mg, qd	COVID-19	04-Apr-2020	06-Apr-2020	8 DAY
4	FENTANYL	1000 MG/	Intravenous (not otherwise specified)	1000 mg, continuous infusion	Sedation	07-Apr-2020	08-May-2020	19 DAY
5	HYDROCORTISONE SODIUM SUCCINATE	100 MG/Q8H	Intravenous (not otherwise specified)	100 mg, tid	Respiratory failure	14-Apr-2020	15-Apr-2020	12 DAY
6	HYDROCORTISONE SODIUM SUCCINATE				COVID-19			12 DAY
7	HYDROXYCHLOROQUIN E	400 MG/QD	Oral	400 mg, qd	COVID-19	04-Apr-2020	09-Apr-2020	8 DAY
8	VANCOMYCIN	1250 MG/Q12H	Intravenous (not otherwise specified)	1250 mg, bid	COVID-19	14-Apr-2020	15-Apr-2020	12 DAY
9	VANCOMYCIN	1500 MG/Q12H	Intravenous (not otherwise specified)	1500 mg, BID	Pneumonia	16-Apr-2020	21-Apr-2020	12 DAY
10	ZOSYN	4.5 G/QD	Intravenous (not otherwise specified)	4.5 g, QD	COVID-19	20-Apr-2020	22-Apr-2020	6 DAY

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



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FOIA Case Report Information

Case ID: 17787108

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 30-Apr-2020
Outcomes: DE,LT,OT,
Application Type: BLA
FDA Rcvd Date: 27-Oct-2020
Mfr Rcvd Date: 16-Oct-2020
Mfr Control #: US-SA-2020SA116382
Application #: 761037

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	mAb1 400 mg, 1X	COVID-19	23-Apr-2020	23-Apr-2020
2	SARILUMAB		1X	Intravenous (not otherwise specified)	REGN88 or placebo, 200 mg or 400 mg intravenously (IV) single or multiple dose for 1 hour		24-Apr-2020	24-Apr-2020
3	SARILUMAB		1X	Intravenous (not otherwise specified)	REGN88 or placebo, 200 mg or 400 mg intravenously (IV) single or multiple dose for 1 hour UNK		01-May-2020	01-May-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	11984 MINUTES	NA	NA				SANOFI	
2	SARILUMAB	11984 MINUTES	NA	NA				SANOFI	
3	SARILUMAB	11984 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Atrial fibrillation	NA
Gastrointestinal haemorrhage	NA
Hypocalcaemia	NA
Hyponatraemia	NA
Hypotension	NA



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Hypoxia	NA
Lactic acidosis	NA
Liver function test increased	NA
Pneumonia bacterial	NA
Renal failure	NA
Septic shock	NA

Event/Problem Narrative:

Based on the information received on 04-May-2020, this case has been upgraded to suspected unexpected serious adverse reaction (SUSAR) from non-SUSAR due to addition of related serious unlisted event Elevated liver function studies.

Initial information received on 01-May-2020 regarding a solicited valid serious unlisted event received from (LP) REGENERON-USA GSA-PCP under reference 2020-35279 and transmitted to Sanofi on 04-May-2020, in the scope of company sponsored study (b) (6)

Center ID: (b) (6) Patient ID: (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

Septic shock [Septic shock]: Death; Onset date: (b) (6); Severity: Grade 5; Outcome: Fatal; Event resolved on: (b) (6)

Hypoxia [Hypoxia]: Life threatening; Onset date: (b) (6); Severity: Grade 2; Outcome: Recovered / Resolved; Event resolved on: (b) (6)

Lactic acidosis [Lactic acidosis]: Life-threatening; Onset date: (b) (6); Severity: Grade 4; Outcome: Not Recovered / Not Resolved; Event resolved on: Ongoing

Hypotension [Hypotension]: Medically Significant; Onset date: (b) (6); Severity: Grade 3; Outcome: Not Recovered / Not Resolved; Event resolved on: Ongoing

Atrial fibrillation [Atrial fibrillation]: Medically Significant; Onset date: (b) (6); Severity: Grade 3; Outcome: Recovered/resolved; Event resolved on: (b) (6)

GL bleed [Gastrointestinal haemorrhage]: Medically Significant; Onset date: (b) (6); Severity: Grade 3; Outcome: Not Recovered / Not Resolved; Event resolved on: Ongoing



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Renal failure [Renal failure]: Medically Significant; Onset date: (b) (6) Severity: Grade 3; Outcome: Not Recovered / Not Resolved; Event resolved on: Ongoing

Hyponatremia [Hyponatraemia]: Medically Significant; Onset date: (b) (6) Severity: Grade 3; Outcome: Not Recovered / Not Resolved; Event resolved on: Ongoing

Hypocalcemia [Hypocalcaemia]: Medically Significant; Onset date: (b) (6) Severity: Grade 3; Outcome: Not Recovered / Not Resolved; Event resolved on: Ongoing

Elevated liver function studies [Liver function test increased]: Medically Significant; Serious adverse event of special interest (AESI) (alanine aminotransferase (ALT) or aspartate aminotransferase (AST) increase); Onset date: (b) (6) Severity: Grade 3; Outcome: Not Recovered / Not Resolved; Event resolved on: Ongoing

Bacterial pneumonia [Pneumonia bacterial]: Non-serious AESI (Clinically significant or invasive bacterial or fungal infections; Onset date: (b) (6) Severity: Grade 3; Outcome: Not Recovered / Not Resolved; Event resolved on: Ongoing

An 81-year-old, male patient of unknown ethnicity with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6)

The patient experienced above-referenced non-serious AESI on (b) (6) serious adverse events (SAEs) on (b) (6), (b) (6) (b) (6) and serious AESI on (b) (6) after receiving study drug.

Patient's relevant medical history included hypertension, systemic inflammatory response syndrome (SIRS) / sepsis, mixed disorder of acid-base balance, hypoxic respiratory failure and severe acute respiratory distress syndrome.

Concomitant medications reported included azithromycin, linezolid and zosyn (piperacillin sodium, tazobactam sodium).

On (b) (6) patient experienced earliest symptoms of pneumonia without rales/crackles on lung auscultation present at baseline. The highest temperature that was recorded within 24 hours prior to dosing was 102.8 degrees Fahrenheit (F), measured rectally. On the same day, the patient was admitted to intensive care unit (ICU) and received treatment with supplemental oxygen by high-flow nasal cannula, mechanical ventilation and vasopressors.

On (b) (6), the following parameters were measured and included: SpO2 100%; blood pressure 104/50 mmHg; pulse 64 beats per



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minute (bpm); respiratory rate 18 respirations per minute (rpm); temperature 97.5 F measured axillary, and the patient was unresponsive. The following laboratory parameters were measured and included: alkaline phosphatase (ALP) 64 U/L (40-129), ALT 24 U/L (4-51), AST 22 U/L (5-46), calcium 7.2 mg/dl (8.5-10.5), sodium 144 mmol/L (135-145), potassium 4.6 mmol/L (3.5-5), chloride 112 mmol/L (98-110), carbon dioxide (bicarbonate) 19 mmol/L (24-32), creatinine 1.77 mg/dl (0.6-1.2), total bilirubin 0.2mg/dL (0.1-1.5) and glucose 245 mg/dl (70-100). The following haematological tests were performed and included: haemoglobin 10.4 g/dl (12.6-16.7), haematocrit 31.3% (36.9-48.5), white blood cells (WBC) 16.35x10E3/mcL (4.4-10.5), neutrophils (absolute) 15.19x10E3/mcL (1.5-7.5), and platelets 222x10E3/mcL (139-361).

On (b) (6) chest X-ray showed extensive infiltrate on the right with interval improvement. Patchy infiltrate at left base which may be worse. Patient's lactate dehydrogenase (LDH) value was 492 U/L (60-200).

On (b) (6) another chest X-ray showed bilateral infiltrates most pronounced within the right upper lobe and left lower lobe. No pleural effusions.

On the following days SpO2, blood pressure, pulse, respiratory rate and temperature did not vary significantly from the initial readings.

On (b) (6) WBC and neutrophils were 8.48 and 6.16, respectively.

On (b) (6) at 20:57, i.e. 7 days 4 hrs 41 min after the first study drug administration, sputum culture was collected which showed that the patient developed bacterial pneumonia infection. WBC and neutrophils were 9.45 and 7.07.

On (b) (6) vitals were SpO2 95, blood pressure 154/65, pulse 69, respiratory rate 18, and temperature 100.4. Laboratory parameters: glucose 156 and white blood cells 23.88. On the same day at 02:07, i.e. 10 days 9 hrs 51 min after the first study drug administration, liver enzymes increased: ALT was 166, and AST was 154. Potassium was 3.6, bicarbonate 28 and creatinine 1.69. WBC increased to 23.88 and neutrophils 15.76. On the same day at 03:32, i.e. (b) (6) days 11 hrs 16 min after the first study drug administration, the patient experienced life-threatening hypoxia. Event was resolved on the same day at 08:55. No corrective treatment was given for the event. The patient received a dose of investigational product (IP) for bacterial pneumonia.

On (b) (6), i.e. (b) (6) days 7 hrs after the first study drug administration, patient's O2 was low, requiring increasing fraction of inspired oxygen (FiO2). SpO2 was 100 and blood pressure 115/47. Calcium was 7.5, sodium 131, potassium 3.8, chloride 87, bicarbonate 29, LDH 418 and creatinine 1.72. WBC count was 20.83 and neutrophils 18.61. At 16:30, patient's blood pressure decreased to 75/35, with mean arterial pressure (MAP) 33 and he started receiving a continuous infusion of Levophed (norepinephrine bitartrate), at a dose of 3 mcg/kg/min as a corrective treatment. On the same day, the patient experienced new onset of atrial fibrillation and received bolus of 150 mg of amiodarone, intravenously, as a corrective treatment for the event. Patient's haemoglobin was 11.2 and haematocrit 30.5. On the same day, the patient experienced septic shock, for which no corrective treatment was used, and sputum culture was positive for unspecified bacterial



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pneumonia infection. As corrective treatment for bacterial pneumonia, patient received 200 mg of minocycline once and started treatment with 100 mg twice daily, both intravenously, until (b) (6)

By (b) (6), i.e. (b) (6) days 9 hrs after the first study drug administration, the patient started requiring 100% FiO2. At 01:49, patient's creatinine level was 3, with decreased urine output. At the same time, critical lactic acid level of 4.0 was measured. At 12:17, creatinine test was repeated, and the result was 3.5. Nephrology was consulted, and continuous renal replacement therapy (CRRT) was started at 21:00. Patient's blood pressure was 92/56. Calcium was 6.5, potassium 4.1, chloride 79 and bicarbonate 25. ALP was 71, ALT 80 and AST 45. On the same day, he started receiving continuous infusions of vasopressin, at a dose of 0.03 units per minute, for hypotension, and amiodarone, at a dose of 16.67 ml/hr, for atrial fibrillation. The patient converted to normal sinus rhythm (NSR) later that day. On the same day, active oral and rectal bleeding was noted, and heparin drip was stopped. Patient's haemoglobin was 8.9 and haematocrit 26.9, which later decreased to 8.5 and 26, respectfully. At 20:18, hyponatremia was noted, with the sodium level 122. No corrective treatment was applied for the event. IP was held if result has been received before dose due date.

On (b) (6) at 00:00, patient's blood pressure was 77/61. The patient was oliguric. At 00:17, i.e. 10 days 8 hrs 1 min after the first study drug administration, critical calcium level of 6.0 was measured. No corrective treatment was applied for the event. At 00:39, CRRT had to be stopped due to hypotension. Studies results were noted - ALP was 97, ALT increased to 656, AST - 1176 and LDH to 1722. No corrective treatment was applied for the event. On the same day, Patient's lactic acid level was 13.6, WBC 25.64, neutrophils 19.74. At 04:18, patient's CO2 was 9. The patient became critically ill with blood pressure 85/45 with MAP of 57, measured at 07:00, and started receiving a continuous infusion of Neosynephrine (phenylephrine hydrochloride), at a dose of 9 mcg/kg/min, as well as epinephrine, at unspecified dose for hypotension. By 08:01, CO2 decreased to 7. The patient had central line placed and started receiving sodium bicarbonate, at a dose of 50 mEq as needed, intravenously, as a corrective treatment for acidosis. Patient's creatinine further increased to 3.83. At 15:15, the patient died. The cause of death was due to septic shock. Autopsy was not performed.

Action taken with study drug in response to the event Hypoxia and Bacterial pneumonia was dose not changed. Action taken with study drug in response to the events Hypotension, Atrial fibrillation, Lactic acidosis, Renal failure, Hyponatremia, Hypocalcemia, Elevated liver function studies, GL bleed and Septic shock was not applicable.

Causality assessment is as follows:

(b) (6)

Septic shock: Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Not applicable.

Company causality rationale: An 81-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced



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fatal septic shock following study drug initiation. The event is assessed as not related to the study drug or any clinical trial procedure since progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and underlying hypertension, systemic inflammatory response syndrome (SIRS) / sepsis and mixed disorder of acid-base balance provide alternative etiology.

Hypoxia: Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: No other suspect causes provided.

Company causality rationale: An 81-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced hypoxia one week following study drug initiation. The event is assessed as not related to the study drug or any clinical trial procedure since progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and underlying hypertension, systemic inflammatory response syndrome (SIRS) / sepsis and mixed disorder of acid-base balance provide alternative etiology.

Lactic acidosis: Investigator Causality = Not Related; Company Causality = Not Related

Hypotension: Investigator Causality = Not Related; Company Causality = Not Related

Atrial fibrillation: Investigator Causality = Not Related; Company Causality = Not Related

Gastrointestinal haemorrhage: Investigator Causality = Not Related; Company Causality = Not Related

Renal failure: Investigator Causality = Not Related; Company Causality = Not Related

Hyponatraemia: Investigator Causality = Not Related; Company Causality = Not Related

Hypocalcaemia: Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Not applicable.

Company causality rationale: An 81-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced lactic acidosis, hypotension, atrial fibrillation, gastrointestinal haemorrhage, renal failure, hyponatremia and hypocalcemia following study drug initiation. The events are assessed as not related to the study drug or any clinical trial procedure since progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and underlying hypertension, systemic inflammatory response syndrome (SIRS) / sepsis and mixed disorder of acid-base balance provide alternative etiology.

Liver function test increased: Investigator Causality = Related; Company Causality = Related



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Investigator causality rationale: Related - known complication of drug.

Company causality rationale: An 81-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced elevated liver function studies after receipt of study drug. Based on a plausible temporal association between study drug administration and the reported event, and considering known potential effect of study drug on the functional liver enzymes, causality for the event of elevated liver function studies is assessed as related to study drug and not related to any clinical trial procedure. Progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and underlying hypertension, systemic inflammatory response syndrome (SIRS) / sepsis and mixed disorder of acid-base balance confound causality.

Pneumonia bacterial: Investigator Causality = Related; Company Causality = Related

Investigator causality rationale: No alternative explanation provided.

Company causality rationale: An 81-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced bacterial pneumonia^(b) days after second dose and ^(b) days after initiating study drug. Although a drop in WBC and neutrophil count was noted after study drug introduction the values remained in reference range window. Based on a plausible temporal association between study drug administration and the reported event and a known fact that higher rate of bacterial infections was observed in patients treated with sarilumab, causality for the event bacterial pneumonia is assessed as related to study drug. The event is not related to any clinical trial procedure. Patient's underlying progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and underlying hypertension, systemic inflammatory response syndrome (SIRS) / sepsis, hypoxic respiratory failure and severe acute respiratory distress syndrome confound causality.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 04-May-2020

The Investigator provided the following updates: events added (Hypotension, Atrial fibrillation, Lactic acidosis, Renal failure, Hyponatremia, Hypocalcemia, Elevated liver function studies, GL bleed and Septic shock).

Follow-up: 16-Oct-2020

The investigator provided the following updates: added new event (Bacterial pneumonia), study drug administration, medical history, concomitant medications, clinical course and relevant labs updated.

Expectedness Assessment per current IB (version 14):



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Septic shock: unexpected

Hypoxia: unexpected

Lactic acidosis: unexpected

Hypotension: unexpected

Atrial fibrillation: unexpected

GL bleed: unexpected

Renal failure: unexpected

Hyponatremia: unexpected

Hypocalcemia: unexpected

Elevated liver function studies: unexpected

Bacterial pneumonia: unexpected

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acid-base balance disorder	(b) (6)		YES
Acute respiratory distress syndrome	(b) (6)		YES
Fever	(b) (6)		YES
Hypoxic respiratory failure	(b) (6)		YES
Lymphopenia	(b) (6)		YES
Pneumonia	(b) (6)		YES



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SIRS	(b) (6)	YES
Sepsis	(b) (6)	YES
Hypertension		

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Calcium	6.5	mg/dL	8.5	10.5	N
Potassium	3.6	mmol/L	3.5	5	N
Body temperature	97.5	degF			Y
Hematocrit	36.7	%	36.9	48.5	N
Hemoglobin	11.6	g/dL	12.6	16.7	N
Hemoglobin	8.5	g/dL	12.6	16.7	N
Heart rate	69	beats/min			N
Neutrophil count	18.61	10*3/uL	1.5	7.5	N
Oxygen saturation	100	%			N
Respiratory rate	18	breaths/min			N
White blood cell count	20.83	10*3/uL	4.4	10.5	N
White blood cell count	25.64	10*3/uL	4.4	10.5	N
Alanine aminotransferase	656	iU/L	4	51	N
Alkaline phosphatase	71	U/L	40	129	N
Chloride	87	mmol/L	98	110	N
CO2	19	mmol/L	24	32	N
Hematocrit	26	%	36.9	48.5	N
Neutrophil count	15.19	10*3/uL	1.5	7.5	N
Neutrophil count	7.07	10*3/uL	1.5	7.5	N
Oxygen saturation	95	%			N
Alanine aminotransferase	80	iU/L	4	51	N
Aspartate aminotransferase	22	iU/L	5	46	N
Bilirubin	0.2	mg/dL	0.1	1.5	N
Calcium	6.0	mg/dL	8.5	10.5	N
Creatinine	1.69	mg/dL	0.6	1.2	N
Lactic acid	4.0	UNK			Y
CO2	28	mmol/L	24	32	N
Heart rate	64	beats/min			N
White blood cell count	16.35	10*3/uL	4.4	10.5	N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Creatinine	1.77	mg/dL	0.6	1.2	N
Lactate dehydrogenase	418	U/L	60	200	N
Lactic acid	13.6	UNK			Y
Blood pressure measurement	104/50	mmHg			N
Blood pressure measurement	75/35	mmHg			N
Blood pressure measurement	77/61	mmHg			N
Hemoglobin	11.2	g/dL	12.6	16.7	N
Mean arterial pressure	33	UNK			Y
Neutrophil count	15.76	10 ³ /uL	1.5	7.5	N
Platelet count	222	10 ³ /uL	139	361	N
Alanine aminotransferase	166	iU/L	4	51	N
Aspartate aminotransferase	154	iU/L	5	46	N
Aspartate aminotransferase	45	iU/L	5	46	N
Alkaline phosphatase	97	U/L	40	129	N
Creatinine	3.5	mg/dL	0.6	1.2	N
Potassium	4.6	mmol/L	3.5	5	N
Potassium	4.1	mmol/L	3.5	5	N
Blood pressure measurement	154/65	mmHg			N
Blood pressure measurement	92/56	mmHg			N
Blood pressure measurement	85/45	mmHg			N
Sodium	144	mmol/L	135	145	N
Sodium	122	mmol/L	135	145	N
Oxygen saturation	100	%			N
White blood cell count	9.45	10 ³ /uL	4.4	10.5	N
Alanine aminotransferase	24	iU/L	4	51	N
Chloride	112	mmol/L	98	110	N
Creatinine	1.72	mg/dL	0.6	1.2	N
Creatinine	2.73	mg/dL	0.6	1.2	N
Glucose	245	mg/dL	70	100	N
Lactate dehydrogenase	1722	U/L	60	200	N
Chest X-ray					Y
Neutrophil count	6.16	10 ³ /uL	1.5	7.5	N
White blood cell count	8.48	10 ³ /uL	4.4	10.5	N
White blood cell count	23.88	10 ³ /uL	4.4	10.5	N
Alkaline phosphatase	64	U/L	40	129	N
Calcium	7.2	mg/dL	8.5	10.5	N
Calcium	7.5	mg/dL	8.5	10.5	N
Creatinine	3.83	mg/dL	0.6	1.2	N
Lactate dehydrogenase	492	U/L	60	200	N
Sodium	131	mmol/L	135	145	N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
CO2	29	mmol/L	24	32	N
Chest X-ray					Y
Hematocrit	30.5	%	36.9	48.5	N
Neutrophil count	19.74	10 ³ /uL	1.5	7.5	N
Aspartate aminotransferase	1176	iU/L	5	46	N
Chloride	79	mmol/L	98	110	N
Potassium	3.8	mmol/L	3.5	5	N
Blood pressure measurement	115/47	mmHg			N
Body temperature	102.8	degF			Y
Body temperature	100.4	degF			Y
CO2	25	mmol/L	24	32	N
CO2	7	UNK			Y
CO2	9	UNK			Y
Hematocrit	26.9	%	36.9	48.5	N
Hemoglobin	8.9	g/dL	12.6	16.7	N
Respiratory rate	18	breaths/min			N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/	Oral	650 mg, PRN	Fever	23-Apr-2020	04-May-2020	15967 MIN
2	AZITHROMYCIN	150 MG/QD	Oral	150 mg, QD	COVID-19	22-Apr-2020	25-Apr-2020	17407 MIN
3	CEFTRIAXONE	2 G/QD	Intravenous (not otherwise specified)	2 g, QD	Pneumonia	21-Apr-2020	25-Apr-2020	18847 MIN
4	DECADRON [DEXAMETHASONE]	10 MG/Q12H	Intravenous (not otherwise specified)	10 mg, BID	Respiratory failure	23-Apr-2020	26-Apr-2020	15967 MIN
5	HEPARIN		Intravenous (not otherwise specified)	8 U/KG	Venous thromboembolism prophylaxis	22-Apr-2020	03-May-2020	17407 MIN
6	HYDROXYCHLOROQUIN E	200 MG/Q12H		200 mg, BID	COVID-19	23-Apr-2020	04-May-2020	15967 MIN
7	LINEZOLID	600 MG/Q12H	Intravenous (not otherwise specified)	600 mg, Q12H	Ant biotic therapy	30-Apr-2020	04-May-2020	5887 MIN



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	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
8	PLASMA	1 IU/	Intravenous (not otherwise specified)	1 iU, TOTAL	COVID-19	23-Apr-2020	23-Apr-2020	15967 MIN
9	ZOSYN	3.375 G/Q8H	Intravenous (not otherwise specified)	3.375 g, TID	Ant biotic therapy	01-May-2020	04-May-2020	4447 MIN

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17787203

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 01-Apr-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 14-May-2020 Mfr Rcvd Date: 05-May-2020 Mfr Control #: IT-ROCHE-2596469 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB			Intravenous (not otherwise specified)	last dose on 18/mar/2020	COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC

Multiple organ dysfunction syndrome NA

Event/Problem Narrative:

AER 2596469 is a clinical study case, received on 05/May/2020 from a physician in Italy. It concerns a patient of unknown demographics (patient number: (b) (6)) who died from multi organ failure whilst enrolled in (b) (6) (b) (6)

The patient's medical history, past drugs, concurrent conditions or concomitant medications was not reported.

On an unknown date, the patient started therapy with intravenous (iV) tocilizumab (lot number: not reported). On 18/Mar/2020, the patient received last dose of tocilizumab. On (b) (6) the patient developed multi organ failure candidemia and on (b) (6) the patient died from multi organ failure (severity: grade 5). It was not reported if therapy with tocilizumab was altered or not in response to the multi organ failure. An autopsy was not performed.

The physician assessed the multi organ failure as unlikely to tocilizumab.



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The company assessed the causality of multi organ failure as not related to blinded tocilizumab. The inflammatory response of cytokines overwhelms immune system response to the infection, which can lead to damage of organs, including lungs, heart, and kidneys. Contributory factor includes the underlying condition of COVID-19. There is no information of patient's medical history, past drugs, concurrent conditions or concomitant medications. The causality will be reassessed on receiving updated information.

No further information was provided.

The following information originally received on 05/May/2020 was corrected using the latest received date of previous version 05/May/2020: Reporter's causality was corrected from unrelated to related for multi organ failure with tocilizumab.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17787203

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17787343

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: CUB
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 14-May-2020
Mfr Rcvd Date: 25-Apr-2020
Mfr Control #: CU-ROCHE-2591433
Application #: 125472

Patient Information:

Age:
Sex: Female
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		162 MG/	Subcutaneous	3 syringes of Actemra SC (486 mg) in intravenous infusion	COVID-19 pneumonia		
2	ACTEMRA					COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				
2	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Ⓜ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17787343

Event/Problem Narrative:

AER 2591433 is a spontaneous case, received on 25/Apr/2020 from a consumer in Cuba. It concerns a female patient (age not reported) who died due to unknown cause while intentionally being treated with tocilizumab (Actemra) for unlabeled indication and unapproved route (off label use).

No medical history, past drugs or concurrent conditions, concomitant medications were reported.

On an unknown date, the patient started therapy with subcutaneous tocilizumab (lot number: unknown), 162 mg (frequency not reported) for pneumonia due to COVID-19 and COVID-19 severe Respiratory Distress (off label use). She was administered 3 syringes of subcutaneous tocilizumab 162 mg as intravenous infusion (off label use) according to the shared recommendations for patients with this condition. Later, she died due to unknown cause. Autopsy details were not reported.

No further information was provided.

Additional information was received on 06/May/2020 and following information was added to the case: event (unknown cause of death, drug intentionally used for unapproved route), country updated to Cuba.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17787343

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17788916

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: CHE
Event Date: Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 15-May-2020
Mfr Rcvd Date: 07-May-2020
Mfr Control #: CH-ROCHE-2597361
Application #: 125276

Patient Information:

Age: 73 YR
Sex: Female
Weight: 74 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ACTEMRA		600 MG/QD	Intravenous (not otherwise specified)		COVID-19 pneumonia			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Haemodynamic instability	NA
Off label use	NA
Product use in unapproved indication	NA

Event/Problem Narrative:

AER 2597361 is a spontaneous case, received on 07/May/2020 from a physician (internal medicine) in Switzerland. It concerns a 73 year old female patient who was treated with tocilizumab (Actemra) for unapproved indication (off label use) and died due to hemodynamic insufficiency.

The patient's medical history included arterial hypotension. No past drugs, concomitant medications or concurrent condition were reported.

On 11/Apr/2020, the patient started therapy with intravenous tocilizumab (lot number not reported) 600 mg per day for COVID-19 pneumonia (drug use for unapproved indication, off label use). Under treatment with tocilizumab inflammation signs decreased but her clinical condition did not improve. She was treated ^(b)₍₆₎ further days with ventilation support but died due hemodynamic insufficiency and it was not reported if an autopsy was performed or not.



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FOIA Case Report Information

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At the time of this death, therapy status with tocilizumab was not reported.

The physician did not report a causality between fatal hemodynamic insufficiency and tocilizumab.

No further information was provided.

Swiss specific medical assessment

Company assessed fatal hemodynamic insufficiency as unlabeled based on the current CDS of tocilizumab (Actemra). Tocilizumab is a recombinant humanized anti-human interleukin-6 (IL-6R) receptor monoclonal antibody of the immunoglobulin (Ig) IgG1 subclass. Inhibition of IL-6R may cause IL-6 to be free in the periphery where it can bind alternative targets that in combination with other inflammatory mediators and macrophages results in off-target effects leading to inflammation in various organs. A 73 year old female patient was treated with tocilizumab for COVID 19 as off label use and later died due to hemodynamic insufficiency. At present, the exact nature of an event, clinical course, investigations are not provided. An event is not expected with a similar class of drugs. Thus based on the temporal relation, mechanism of action, safety profile and drug class effect; the company assessed fatal hemodynamic insufficiency is unlikely due to tocilizumab but may be more likely due to underlying COVID 19 medical history hypotension and advanced age of the patient. There was 1 case found for PT Haemodynamic instability with tocilizumab use with no literature cases in safety database. No additional risk minimization activities are warranted following the review of this single report.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypotension			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17788916

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17789436

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** BEL **Event Date:** 24-Apr-2020 **Outcomes:** DE,OT, **Application Type:** BLA
FDA Rcvd Date: 15-May-2020 **Mfr Rcvd Date:** 22-Apr-2020 **Mfr Control #:** BE-SA-2020SA110587 **Application #:** 761037

Patient Information:

Age: 62 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	KEVZARA		400 MG/	Intravenous (not otherwise specified)	400 mg	Bilateral pneumonia	24-Apr-2020	
2	KEVZARA					Drug use for unapproved indication		
3	KEVZARA					COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	KEVZARA		Unk	NA				SANOFI	
2	KEVZARA		Unk	NA				SANOFI	
3	KEVZARA		Unk	NA				SANOFI	

Event Information:

Preferred Term (MedDRA ® Version: 23.1) **ReC**
Off label use NA
Respiratory failure NA



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FOIA Case Report Information

Case ID: 17789436

Event/Problem Narrative:

Based on the information received on 08-May-2020, the case updated from non-serious to serious case due to the fatal event respiratory failure.

Initial information received on 22-Apr-2020 regarding an unsolicited valid serious case from Belgium received from a physician.

This case involves a 62 years old male patient was having off label use with sarilumab (Kevzara) (Kevzara (IV) for patient suffering from suffering of a severe COVID 19 bilateral pneumonia and life threatening respiratory conditions) and died of respiratory failure secondary to SARS-COV2 (severe acute respiratory syndrome coronavirus 2).

The patient's past medical history included kidney transplant on (b) (6) with Renal function was correct and stable. The regiment of immunosuppressors had been adapted considering the need of an adequate T cell immune response against the viral replication.

The patient's past medical treatment(s), and family history were not provided.

At the time of the event, the patient had ongoing Bilateral pneumonitis-SARS at COVID - 19 since (b) (6) Acute respiratory distress syndrome with severe hypoxemia. The patient was currently with a breathing support consisting of a continuous positive airway pressure with high fraction of inspired oxygen (FiO2 60%), Hypertension, Type 2 diabetes mellitus, Diabetic neuropathy.

Concomitant medications included hydroxychloroquine sulfate (Plaquenil).

It was also reported that physician believed that the risk for non-treatment was higher than the risk of treatment with sarilumab. The risks and benefits had been extensively discussed with the patient (and his family), he signed an informed consent and agreed to start treatment with sarilumab. The patient could not be included in the COV-AID study (anti-IL1 /anti-IL-6 monoclonal antibodies) because of his previous kidney transplantation. The reporter believed that this condition did not contraindicate the use of sarilumab for controlling the COVID 19-associated cytokine storm.

The patient could not be said to have improved. On the contrary, the situation had worsened. The situation was critical and he had reached the threshold of maximum respiratory assistance. Intubated in intensive care with 100% oxygen. Any further damage would be fatal. But the reporter still had hope.

On (b) (6) the patient started treatment with sarilumab 400 mg via IV route (strength, formulation, frequency, batch number unknown) for severe COVID 19 bilateral pneumonia and life- threatening respiratory conditions via sarilumab autoinjector (off label use, latency same day).

Information on the batch number was not obtained despite contact attempts with the reporter.

On (b) (6) the patient died of respiratory failure secondary to SARS-COV2 (respiratory failure) (onset and latency unknown). Autopsy was not done. The cause of death was reported as Respiratory failure secondary to SARS-COV2.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17789436

Relevant laboratory test results included:

Computerised Tomogram Scan for chest - On (b) (6) Opacities in diffuse and bilateral lesions compatible with a COVID 19 infection with a condensation of the anterior segment of the right upper lobe.

Polymerase chain reaction test - On (b) (6) COVID smear with positive; on (b) (6) COVID smear with positive LBA performed on the (b) (6) no argument for a bacterial co-infection. No embolic complications.

Action taken: Unknown for respiratory failure and not applicable for off label use.

Outcome: Not Applicable for off label use and fatal for respiratory failure.

Seriousness: Fatal for respiratory failure

Additional information was received on 08-May-2020 from physician: New event respiratory failure added. Text was amended accordingly.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Kidney transplant	(b) (6)		UNKNOWN
Bilateral pneumonia	(b) (6)		YES
Corona virus infection	(b) (6)		YES
SARS	(b) (6)		YES
Acute respiratory distress syndrome			YES
Diabetic neuropathy			YES
Hypertension			YES
Hypoxemia			YES
Respiratory disorder			
Type 2 diabetes mellitus			YES



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FOIA Case Report Information

Case ID: 17789436

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Chest CT					Y
PCR					Y
Blood test					Y
PCR					Y

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	PLAQUENIL [HYDROXYCHLOROQUI NE SULFATE]			UNK				

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17791424

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 27-Apr-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 15-May-2020 Mfr Rcvd Date: 14-May-2020 Mfr Control #: IT-ROCHE-2601591 Application #: 125276

Patient Information:

Age: 39 YR Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		800 MG/BID	Intravenous (not otherwise specified)	Most recent dose of tocilizumab 24/Apr/2020	COVID-19 pneumonia	23-Apr-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	4 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC

Embolism NA

Event/Problem Narrative:

AER 2601591 is a clinical study case, received on 14/May/2020 from a physician in Italy. It concerns a 39 year adult patient (gender unspecified) (patient number: (b) (6)) who died due to life threatening thromboembolic event whilst enrolled in (b) (6)

Concurrent conditions included obesity, obstructive sleep apnea syndrome and mild mental retardation. Concomitant medications included piperacillin;tazobactam, linezolid, methylprednisolone, hydroxychloroquine, clonidine, lansoprazole, darunavir/ritonavir and n acetylcysteine. No medical history and past drugs were reported.

(b) (6)

(u) (b) . Respiratory conditions stabilized and continuous positive airway pressure (C-Pap) was suspended for some intervals during daytime. However, on (b) (6) the patient hemodynamic and respiratory conditions suddenly worsened with development of shock (life threatening thromboembolic event (initial 4 and most extreme severity: grade 5). The patient was urgently transferred to intensive care unit (ICU), where deep venous thrombosis and acute pulmonary embolism were diagnosed.



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Case ID: 17791424

The patient was undergoing treatment with fondaparinux (Fondaparinux) 10 mg per day. On ^{(b) (6)} of stay in the ICU and died due to life threatening thromboembolic event. It was not reported if an autopsy was performed or not.

The physician assessed the life threatening thromboembolic event as (unlikely) related to tocilizumab.

The company assessed the causality of the thromboembolic event as unrelated to tocilizumab and rather related with underlying disease COVID-19 pneumonia. Also event is not expected based on, pathophysiology of the event, known drug response pattern and reference safety labeling documents of the suspect drug. Dechallenge and rechallenge is not possible. Causality will be reassessed after receiving further more detail information. Concurrent conditions included obesity, obstructive sleep apnea syndrome and mild mental retardation may be the contributing factor. Past medical and drug history was not reported.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Intellectual disability			
Obesity			
Sleep apnoea syndrome			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17791424

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	CLONIDINE							
2	HYDROXYCHLOROQUIN E							
3	LANSOPRAZOLE							
4	LINEZOLID							
5	METHYLPREDNISOLON E							
6	PIPERACILLINE / TAZOBACTAM							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17792471

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 03-May-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 30-Jun-2020
Mfr Rcvd Date: 20-Jun-2020
Mfr Control #: US-SA-2020SA126167
Application #: 761037

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB			Intravenous (not otherwise specified)	REGN88 or placebo 200 mg or 400 mg, single or multiple doses	COVID-19	10-Apr-2020	10-Apr-2020
2	SARILUMAB			Intravenous (not otherwise specified)	REGN88 or placebo 200 mg or 400 mg, single or multiple doses		21-Apr-2020	21-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	63680 MINUTES	NA	NA				SANOFI	
2	SARILUMAB	63680 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Aspartate aminotransferase increased	NA
Hypoxia	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17792471

Event/Problem Narrative:

Based on additional information received on 20-Jun-2020, the overall company causality was updated from reportable to not reportable and this case was downgraded from SUSAR to non-SUSAR.

Initial information received on 11-May-2020 (significant) and 12-May-2020 (processed together) regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference number 2020-37086 on 11-May-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6)

Patient ID: (b) (6) Site: (b) (6) Country: United States.

Study title: (b) (6)
(b) (6)

A 57-year-old, female patient of unreported ethnicity with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)
(b) (6)
(b) (6) The patient experienced elevated
AST ([Aspartate aminotransferase increased]: Non-serious AESI (ALT or AST increase); Onset date: (b) (6); Severity: Grade 2;
Outcome: Not Recovered/Not resolved; Event resolved on: Ongoing) and SAE, Hypoxia (initially reported as Asystole [Cardiac arrest]):
Death; Onset date: (b) (6) Severity: Grade 5; Outcome: Fatal; Event resolved on: (b) (6), after receiving study drug.

No relevant medical history was reported.

Relevant concomitant medications included azithromycin, ceftriaxone and hydroxychloroquine.

On 01-Apr-2020 the patient experienced earliest symptoms of pneumonia without rales/crackles on lung auscultation present. On 06-Apr-2020 chest X-ray revealed ARDS (acute respiratory disease syndrome) pattern that could be due to viral pneumonia. The highest temperature that was recorded within 24 hours prior to dosing was 101.7Å F (Fahrenheit), measured axillary.

On (b) (6), the patient was admitted to hospital and treated with supplemental oxygen by non-rebreather mask. On the same day, the following parameters were measured: oxygen saturation (SpO2) 89%; blood pressure 137/86 mmHg; pulse 103 beats per minute (bpm); respiratory rate 19 respirations per minute (rpm); temperature 101.6Å F (Fahrenheit), measured axillary, and the patient was alert. On the same day, the following laboratory tests were measured: alanine aminotransferase (ALT) 73 U/L (reference range: 0-41), aspartate aminotransferase (AST) 104 U/L (reference range: 0-40), total bilirubin 0.28 mg/dl (reference range: 0-1.2), platelets 187x10E3/mcL (reference range: 150-450), white blood cells 3.88x10E3/mcL (reference range: 4.8-10.8) and neutrophils (absolute) 2.68x10E3/mcL (reference range: 2.1-7.6). AST had been increasing in the following days.



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On (b) (6) chest X-ray showed bilateral airspace opacification/consolidation.

On (b) (6) AST increased to 215 while ALT increased to 77.

On (b) (6) endotracheal intubation was performed. Chest X-ray image showed unchanged diffuse bilateral airspace disease.

On (b) (6) AST decreased to 70 and ALT was 48.

On (b) (6) at 04:15 (b) (6) days 16 hrs 10 min following the first investigational product, the patient was diagnosed with elevated AST which increased to 594 while ALT was 160. No corrective treatment was received in response to the event.

In the following days AST was gradually decreasing and on (b) (6) reached 127, while ALT was 193.

On (b) (6) AST was 43, while on (b) (6), it increased to 101.

On (b) (6), AST decreased to 42, and on the next day, increased to 204.

On (b) (6) AST decreased to 106. SpO2 was 91%, blood pressure 126/66 mmHg, pulse 55 and respiratory rate 25.

On (b) (6), at 11:12, SpO2 decreased to 68%, blood pressure to 58/29 mmHg, pulse was 90 and respiratory rate 24. At 17:25, (b) (6) (b) (6) days 5 hrs 20 min after the first administration of investigational product, the patient developed hypoxia and died. No corrective treatment was received in response to the event. The cause of death was reported as hypoxia. Primary cause of death was reported as asystole. Autopsy was not performed.

On 20-Jun-2020, the event of Elevated AST was downgraded from serious AESI to non-serious AESI by the Investigator.

Action taken with study drug in response to the events was not applicable.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

Causality assessment is as follows:

(b) (6)
Hypoxia: Severity = Grade 5; Investigator Causality = Not Related; Company Causality = Not Related
Investigator causality rationale: No other explanation provided.
Company causality rationale: A 57-year-old, female patient enrolled in the trial experienced hypoxia which ended fatally (b) (6) days after receiving



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the last dose of the study drug. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug is the most plausible cause for the development of hypoxia in this patient. Therefore, the event is assessed as not related to the study drug or to any clinical trial procedure.

Aspartate aminotransferase increased: Severity = Grade 2; Investigator Causality = Not Related; Company Causality = Related

Investigator causality rationale: No other explanation provided.

Company causality rationale: A 57-year-old female patient with severe or critical COVID-19 infection and worsening pneumonia experienced elevated AST, after receiving the study drug. Patient's baseline values were above reference ranges and increased significantly following study drug administration. Based on known potential effect of study drug on functional liver enzymes, causality for the event elevated AST is assessed as related to the study drug and not related to any clinical trial procedure. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation. Causality is confounded with underlying COVID-19 and reported concomitant medications azithromycin, ceftriaxone and hydroxychloroquine.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 26-May-2020

The Investigator provided the following updates: event asystole added, clinical course updated.

Follow up: 12-Jun-2020 and 15-Jun-2020 (processed together)

The Investigator provided the following updates: outcome, severity and seriousness criteria of event Elevated AST updated; event term for Asystole updated.

Follow-up: 20-Jun-2020

The Investigator provided the following updates: The event of elevated AST was downgraded to non-serious AESI, cause of death, outcome and severity was updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Thyroid disorder	14-Apr-2018		YES
Endotracheal intubation	(b) (6)	(b) (6)	NO
Anemia			YES



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Hypertension YES
 Obesity YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Aspartate aminotransferase	187	iU/L	0	40	N
Aspartate aminotransferase	70	iU/L	0	40	N
Aspartate aminotransferase	68	iU/L	0	40	N
Aspartate aminotransferase	48	iU/L	0	40	N
Aspartate aminotransferase	42	iU/L	0	40	N
Body temperature	101.7	degF			Y
Heart rate	90	beats/min			N
Neutrophil count	2.68	10 ³ /uL	2.1	7.6	N
Neutrophil count	13.97	10 ³ /uL	2.1	7.6	N
Respiratory rate	25	breaths/min			N
Alanine aminotransferase	49	iU/L	0	41	N
Aspartate aminotransferase	65	iU/L	0	40	N
Aspartate aminotransferase	101	iU/L	0	40	N
Aspartate aminotransferase	49	iU/L	0	40	N
Blood pressure measurement	137/86	mmHg			N
Heart rate	55	beats/min			N
Platelet count	187	10 ⁹ /L	150	450	N
Platelet count	492	10 ⁹ /L	150	450	N
Alanine aminotransferase	71	iU/L	0	41	N
Alanine aminotransferase	36	iU/L	0	41	N
Alanine aminotransferase	53	iU/L	0	41	N
Aspartate aminotransferase	594	iU/L	0	40	N
Aspartate aminotransferase	79	iU/L	0	40	N
Aspartate aminotransferase	60	iU/L	0	40	N
Blood pressure measurement	58/29	mmHg			N
Oxygen saturation	91	%			N
White blood cell count	14.04	10 ⁹ /L	4.8	10.8	N
Alanine aminotransferase	158	iU/L	0	41	N
Alanine aminotransferase	53	iU/L	0	41	N
Alanine aminotransferase	43	iU/L	0	41	N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	49	iU/L	0	41	N
Aspartate aminotransferase	104	iU/L	0	40	N
Aspartate aminotransferase	367	iU/L	0	40	N
Aspartate aminotransferase	56	iU/L	0	40	N
Oxygen saturation	68	%			N
Respiratory rate	19	breaths/min			N
Alanine aminotransferase	77	iU/L	0	41	N
Alanine aminotransferase	48	iU/L	0	41	N
Alanine aminotransferase	280	iU/L	0	41	N
Alanine aminotransferase	122	iU/L	0	41	N
Alanine aminotransferase	43	iU/L	0	41	N
Alanine aminotransferase	180	iU/L	0	41	N
Alanine aminotransferase	147	iU/L	0	41	N
Aspartate aminotransferase	185	iU/L	0	40	N
Aspartate aminotransferase	411	iU/L	0	40	N
Aspartate aminotransferase	82	iU/L	0	40	N
Aspartate aminotransferase	106	iU/L	0	40	N
Heart rate	103	beats/min			N
Oxygen saturation	89	%			N
Alanine aminotransferase	73	iU/L	0	41	N
Alanine aminotransferase	50	iU/L	0	41	N
Aspartate aminotransferase	169	iU/L	0	40	N
Aspartate aminotransferase	206	iU/L	0	40	N
Aspartate aminotransferase	215	iU/L	0	40	N
Aspartate aminotransferase	43	iU/L	0	40	N
Aspartate aminotransferase	204	iU/L	0	40	N
Blood bilirubin	0.28	mg/dL	0	1.2	N
Blood pressure measurement	126/66	mmHg			N
Body temperature	101.6	degF			Y
Chest X-ray					Y
Platelet count	269	10 ⁹ /L	150	450	N
Respiratory rate	24	breaths/min			N
White blood cell count	3.88	10 ⁹ /L	4.8	10.8	N
White blood cell count	15.11	10 ⁹ /L	4.8	10.8	N
Alanine aminotransferase	193	iU/L	0	41	N
Alanine aminotransferase	92	iU/L	0	41	N
Alanine aminotransferase	67	iU/L	0	41	N
Alanine aminotransferase	160	iU/L	0	41	N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Aspartate aminotransferase	393	iU/L	0	40	N
Aspartate aminotransferase	127	iU/L	0	40	N
Aspartate aminotransferase	131	iU/L	0	40	N
Chest X-ray					Y
Chest X-ray					Y

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	AZITHROMYCIN	500 MG/QD	Intravenous (not otherwise specified)	500 mg, QD	COVID-19	06-Apr-2020	12-Apr-2020	39135 MIN
2	CEFTRIAXONE	2000 MG/QD	Intravenous (not otherwise specified)	2000 mg, QD	Pneumonia	06-Apr-2020	13-Apr-2020	39135 MIN
3	HYDROXYCHLOROQUIN E		Oral	400 mg Q12 x 1 day; 200 mg Q12 X 4 days	COVID-19	06-Apr-2020	11-Apr-2020	39135 MIN

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17795162

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ESP **Event Date:** 03-Apr-2020 **Outcomes:** DE,OT, **Application Type:** ANDA

FDA Rcvd Date: 15-May-2020 **Mfr Rcvd Date:** 09-May-2020 **Mfr Control #:** ES-BAUSCH-BL-2020-014022 **Application #:** 040069

Patient Information:

Age: 62 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	DEXAMETASONA		20 MG/	Intravenous (not otherwise specified)		COVID-19 pneumonia	29-Mar-2020	01-Apr-2020
2	AZITROMICINA			Oral		COVID-19 pneumonia	27-Mar-2020	01-Apr-2020
3	CEFTRIAXONA		2 G/	Intravenous (not otherwise specified)		Product used for unknown indication	27-Mar-2020	01-Apr-2020
4	DEXAMETASONA			Intravenous (not otherwise specified)	dose reduced			
5	ENOXAPARINA			Subcutaneous	Dose Reduced			
6	ENOXAPARINA		80 MG/	Subcutaneous		Thrombosis prophylaxis	01-Apr-2020	03-Apr-2020
7	HIDROXICLOROQUINA		400 MG/	Oral		COVID-19 pneumonia	27-Mar-2020	02-Apr-2020
8	ROACTEMRA			Intravenous (not otherwise specified)	600 mg in total	COVID-19 pneumonia	27-Mar-2020	27-Mar-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	DEXAMETASONA	6 Day	Yes	NA				BAUSCH AND LOMB	
2	AZITROMICINA	8 Day	Yes	NA					
3	CEFTRIAXONA	8 Day	Yes	NA					



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FOIA Case Report Information

Case ID: 17795162

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC	
4 DEXAMETASONA	6 Day	Yes	NA				BAUSCH AND LOMB		
5 ENOXAPARINA	3 Day	Yes	NA						
6 ENOXAPARINA	3 Day	Yes	NA						
7 HIDROXICLOROQUINA	8 Day	Yes	NA						
8 ROACTEMRA	8 Day	Yes	NA						

Event Information:

Preferred Term (MedDRA ® Version: 23.1)

ReC

Anaemia

NA

Hypocoagulable state

NA

Hypofibrinogenaemia

NA

Thrombocytopenia

NA

Event/Problem Narrative:

This serious spontaneous case was downloaded from the EudraVigilance database as a L2A policy access case on 09/May/2020 from a physician via Spain Health authority, AGEMED (Spanish Agency of Medicines and Medical Products) (ES-AEMPS-628603) and concerned a patient of 62 years age and male gender.

Concurrent conditions: Not provided

Concomitant medications: Not provided

Past medications: Not provided

Medical history: Not provided

Company suspect product included:

Dexametasona, unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on 29/Mar/2020 to 01/Apr/2020, intravenous (not otherwise specified), at a dosage of 20 milligram, 1 in 24 hours; unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on an unknown date, intravenous (not otherwise specified), at a dosage of unit dose unknown, unknown frequency (dose reduced) for coronavirus disease (SARS COVID 19).



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FOIA Case Report Information

Case ID: 17795162

Other suspect products included:

Roactemra, unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on 27/Mar/2020 to 27/Mar/2020, intravenous (not otherwise specified), at a dosage of unit dose unknown, unknown frequency (600 mg in total) for SARS COVID 19.

Hidroxicloroquina, unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on 27/Mar/2020 to 02/Apr/2020, oral, at a dosage of 400 milligram, 1 in 24 hours for COVID-19 pneumonia.

Azitromicina, unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on 27/Mar/2020 to 01/Apr/2020, oral, at a dosage of unit dose unknown, unknown frequency for COVID-19 pneumonia.

Ceftriaxona, unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on 27/Mar/2020 to 01/Apr/2020, intravenous (not otherwise specified), at a dosage of 2 gram, 1 in 24 hours for unknown indication.

Enoxaparina, unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on 01/Apr/2020 to 03/Apr/2020, subcutaneous, at a dosage of 80 milligram, unknown frequency; unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on an unknown date, subcutaneous, at a dosage of unit dose unknown, unknown frequency (dose reduced) for high risk ETE.

On 03/Apr/2020, (latency: 6 days) the patient experienced hypofibrinogenemia and on same day, the patient recovered from the event. On the same day (latency: 6 days), the patient experienced hypocoagulable state.

On 08/Apr/2020 (latency: 11 days), the patient experienced trombopenia.

On 10/Apr/2020, the patient recovered from the event hypocoagulable state.

On 14/Apr/2020, (latency: 17 days) the patient experienced anemization not exteriorized (anaemia).

On (b) (6) the patient passed away due to respiratory insufficiency. It was unknown if an autopsy was performed.

Reported Term (Preferred Term): Onset Date-Cessation Date; Seriousness; Outcome:

Trombopenia (Thrombocytopenia): 08/Apr/2020-ongoing; serious (Other serious (Important Medical Events)); Not recovered/not resolved.

Hypofibrinogenemia (Hypofibrinogenaemia): 03/Apr/2020-03/Apr/2020; serious (Other serious (Important Medical Events)); Recovered/resolved.

Anemization not exteriorized (Anaemia): 14/Apr/2020-ongoing; serious (Other serious (Important Medical Events)); Not recovered/not resolved.

Hypocoagulable state (Hypocoagulable state): 03/Apr/2020-10/Apr/2020; serious (Other serious (Important Medical Events)); Recovered/resolved.

Action taken with company suspect product in response to the event, Dechallenge and Rechallenge:

Dexametasona/Trombopenia: Dose Reduced; Not Applicable; Not Applicable.

Dexametasona/Hypofibrinogenemia: Dose Reduced; Not Applicable; Not Applicable.



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FOIA Case Report Information

Case ID: 17795162

Dexametasona/Anemization not exteriorized: Dose Reduced; Not Applicable; Not Applicable.
Dexametasona/Hypocoagulable state: Dose Reduced; Not Applicable; Not Applicable.

Action taken with co-suspect product in response to the event:

Roactemra/Trombopenia: Drug discontinued
Roactemra/Hypofibrinogenemia: Drug discontinued
Roactemra/Anemization not exteriorized: Drug discontinued
Roactemra/Hypocoagulable state: Drug discontinued
Hidroxicloroquina/Trombopenia: Drug discontinued
Hidroxicloroquina/Hypofibrinogenemia: Drug discontinued
Hidroxicloroquina/Anemization not exteriorized: Drug discontinued
Hidroxicloroquina/Hypocoagulable state: Drug discontinued
Azitromicina/Trombopenia: Drug discontinued
Azitromicina/Hypofibrinogenemia: Drug discontinued
Azitromicina/Anemization not exteriorized: Drug discontinued
Azitromicina/Hypocoagulable state: Drug discontinued
Ceftriaxona/Trombopenia: Drug discontinued
Ceftriaxona/Hypofibrinogenemia: Drug discontinued
Ceftriaxona/Anemization not exteriorized: Drug discontinued
Ceftriaxona/Hypocoagulable state: Drug discontinued
Enoxaparina/Trombopenia: Dose Reduced
Enoxaparina/Hypofibrinogenemia: Dose Reduced
Enoxaparina/Anemization not exteriorized: Dose Reduced
Enoxaparina/Hypocoagulable state: Dose Reduced

Final therapy status:

Roactemra: Drug no longer administered.
Hidroxicloroquina: Drug no longer administered.
Dexametasona: Unknown.
Azitromicina: Drug no longer administered.
Ceftriaxona: Drug no longer administered.
Enoxaparina: Unknown.

Death information: Date of death: (b) (6) Cause of death: Respiratory insufficiency. Autopsy performed: Unknown.

Reporter causality assessment:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17795162

Dexametasona/Trombopenia: Not Reported.
Dexametasona/Hypofibrinogenemia: Not Reported.
Dexametasona/Anemization not exteriorized: Not Reported.
Dexametasona/Hypocoagulable state: Not Reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No Sender Organization: BAUSCH AND LOMB 503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17795162

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796109

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: BEL
Event Date: 27-Apr-2020
Outcomes: DE,OT,
Application Type: NDA
FDA Rcvd Date: 04-Jun-2020
Mfr Rcvd Date: 20-May-2020
Mfr Control #: BE-ADVANZ PHARMA-202004005128
Application #: 009768

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Hydroxychloroquine		2 DF/	Oral	2 Dosage Form, bid Capsule	COVID-19 pneumonia	27-Apr-2020	27-Apr-2020
2	Hydroxychloroquine		1 DF/	Oral	1 Dosage Form, bid,capsule	Product use in unapproved indication	28-Apr-2020	29-Apr-2020
3	Hydroxychloroquine		1 DF/	Oral	1 Dosage Form, bid,capsule	Product use in unapproved indication	28-Apr-2020	28-Apr-2020
4	Hydroxychloroquine		1 DF/	Oral	1 Dosage Form, bid, capsule		29-Apr-2020	01-May-2020
5	Hydroxychloroquine		2 DF/	Oral	2 Dosage Form, bid, Capsule	COVID-19 pneumonia	27-Apr-2020	27-Apr-2020
6	KEVZARA		400 MG/	Intravenous (not otherwise specified)	400 mg	COVID-19 pneumonia	29-Apr-2020	30-Apr-2020
7	KEVZARA					Product use in unapproved indication		
8	SARILUMAB AUTOINJECTOR			Unknown	UNK	COVID-19 pneumonia		
9	SARILUMAB AUTOINJECTOR					Interleukin level increased		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Hydroxychloroquine	2112 MINUTES	NA	NA	Unknown			CONCORDIA	
2	Hydroxychloroquine	2299 MINUTES	NA	NA	Unknown			CONCORDIA	
3	Hydroxychloroquine	2112 MINUTES	NA	NA	Unknown			CONCORDIA	
4	Hydroxychloroquine	2299 MINUTES	NA	NA	Unknown			CONCORDIA	



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Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler		OTC
5 Hydroxychloroquine	2299 MINUTES	NA	NA	Unknown			CONCORDIA		
6 KEVZARA		NA	NA	Unknown					
7 KEVZARA		NA	NA						
8 SARILUMAB AUTOINJECTOR		NA	NA						
9 SARILUMAB AUTOINJECTOR		NA	NA	Unknown					

Event Information:

Preferred Term (MedDRA ® Version: 23.1)

ReC

Condition aggravated

NA

Off label use

NA

Product use issue

NA

Respiratory failure

NA

Wrong technique in product usage process

NA

Event/Problem Narrative:

Case number 202004005128 is a business partner report (reference ID: 2020SA115641) sent by a physician on 29/Apr/2020.

Case Description: Based on additional information received on 02-May-2020, case has become serious due to addition of serious event death, with seriousness criteria as fatal.

Initial information from Belgium was received on 29-Apr-2020 regarding an unsolicited valid serious case received from a physician.

This case involves a 83 years old male patient who experienced aggravation of pulmonary failure, and who took sarilumab (Kevzara) at a dose of 400 mg, while he was treated with sarilumab delivered with the use of sarilumab autoinjector, hydroxychloroquine sulfate and hydroxychloroquine sulfate [Plaquenil]. It was reported that there was an urgent situation request for the treatment of a COVID-19 patient with sarilumab, hydroxychloroquine sulfate [Plaquenil], hydroxychloroquine sulfate and that the patient started taking sarilumab 200mg/1.14 ml injection at a dose of 400 mg subcutaneously in 100 ml of 0.9% NaCl.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796109

The patient's past medical history included hospitalisation with severe pulmonary dysfunction and IL-6 high, urinary plains, Inappetance, confusion, Asthenia, spo2 at 88% gradually decreasing to 70-75%, Agitation, 2 hospitalisation, Multistentent ischemic heart disease (OM1, proximal and average IVA, distal Cx, average Cx), Left ischemic stroke with sequelae of phasic disorders and trouble in walking, Leukoencephalopathy, cortico-subcortical atrophy, Benign prostate enlargement with urinary retention, Sigmoid diverticulosis, Renal cyst, Bilateral inguinal hernia cured by laparoscopy, thyroid nodule, L3 disc herniation treatment, Meniscectomy of the right knee, Dupuytren's disease, bilateral cataract operation, hypoxia and high C-reactive protein (high CRP).

The patient's past medical treatment(s) and family history were not provided.

At the time of the event, the patient had ongoing Type 2 diabetes, Retinopathy, Peripheral polyneuropathy (vertigo in particular), arteriopathy, high blood pressure, Spondylolisthesis degenerative L3 L4 with CLE, Beginning cognitive disorders with MMSE 25/30 in 2006 with periventricular leukoencephalopathy and pollen allergy.

Concomitant medications included azithromycin for COVID-19 pneumonia; cefuroxime; clopidogrel (Clopidogrel Sandoz) as anticoagulant; propranolol hydrochloride (Inderal) and perindopril both taken for hypertension arterial (HTA); morphine hydrochloride mixed with sodium chloride for sedation; paracetamol (Dafalgan Forte) for pain, fever and inflammation; paracetamol B Braun for pyrexia; enoxaparin sodium (Clexane) delivered via enoxaparin pre-filled syringe for anticoagulation; simvastatine for hyperlipidaemia; pantoprazole sodium sesquihydrate (Pantomed) as an antacid; insulin glargine (Basaglar) for diabetes; insulin aspart (Novorapid) for diabetes; haloperidol (Haldol) for agitation; midazolam hydrochloride in sodium chloride (midazolam B Braun) for insomnia; mirtazapine (Remergon) for depression; tamsulosin for prostate hypertrophy; ciprofloxacin hydrochloride (Ciproxin) for urinary plains; duloxetine hydrochloride (Cymbalta); perindopril erbumine (Coversyl); acetylsalicylic acid (Asaflow); tramadol hydrochloride (Contramal); sildenafil citrate (Sildenafil Sandoz); simvastatin (Zocor); mirtazapine; insulin glargine (Lantus), Aquapak Respiflich, and perfusions: glucose/NaCl (sodium chloride/ potassium phosphate, glucose/KCl (potassium chloride), glucose/NaCl/KCl, NaCl/potassium phosphate.

Smear test - On 24-Apr-2020: [positive for Severe SARS-CoV2 pneumonia in MRS by RT-PCR]; on (b) (6) [positive].

Computerised tomogram - On (b) (6) [Mediastin : Calcified atheromatosis of the thoracic aorta and coronary arteries. No mediastinal lymphadenopathy; some sequential calcified nodes.No pleuro-pericardial effusion. Tracheobronchial calcifications. Lung parenchyma: Multitude of vast areas of opacities in frosted glass with crazy paving of diffuse topography predominantly peripheral, and innumerable small confluent condensations in the two lower lobes. Bi-apical fibroretractile sequences.]

On (b) (6) at 09:41, the patient started taking hydroxychloroquine sulfate (Plaquenil) 200 mg capsule at a dose of 2 DF twice daily orally (lot details: unknown) for a severe SARS-Cov2 pneumonia and product use in unapproved indication.

On (b) (6) at 12:48, the patient started taking hydroxychloroquine sulfate 200 mg capsule at a dose of 2 DF twice daily orally (lot details: unknown) for a severe SARS-Cov2 pneumonia and Product use in unapproved indication.



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FOIA Case Report Information

Case ID: 17796109

Blood culture - On (b) (6) [negative]

Computerised tomogram thorax - On (b) (6) [High CoVid19 suspicion level: Multitude of vast areas of large frosted glass opacities with crazy paving of diffuse topography predominantly peripheral, and innumerable small confluent condensations in the two lower lobes. Bi-apical fibroretractile sequelae 70% of pulmonary parenchyma affected. Unfavorable evolution. Il6 measured at 866-high on an unknown date]

Oxygen saturation - On (b) (6) 75 %

On (b) (6) Gasometry : under NRBM FiO2 100% : 7.55 / 36/60 HCO3 32 - SaO2 92% - lactates 2.4, Saturation under FiO2 : 98 % under FiO2 100 % unknown date: Lungs: Crepitating major bibasal at the bases.

On (b) (6) hydroxychloroquine sulfate (Plaquenil) dosage was changed to 1 DF BID.

On (b) (6) at 10:00 hydroxychloroquine sulfate dosage was changed to 1 DF BID.

Consent was made under normal emergency procedure. They believed that the risk for non-treatment was higher than the risk of treatment with sarilumab. The risks and benefits have been extensively discussed with the patient (and his/her family), he/she signed an informed consent and agreed to start treatment with sarilumab. They have notified the Ethics Committee of our hospital of this urgent request. On (b) (6) (b) (6) the patient started taking sarilumab 200mg/1.14 ml injection at a dose of 400 mg subcutaneously in 100 ml of 0.9% NaCl (Unapproved dose administered; wrong technique in drug usage process, latency: same day from sarilumab, 2 days from the other co suspect drugs; lot details: unknown) delivered via sarilumab autoinjector for a severe SARS-Cov2 pneumonia and as anti IL6. On (b) (6) hydroxychloroquine sulfate (Plaquenil) dosage was changed to 1 DF twice daily. There was an urgent situation request for the treatment of a COVID-19 patient with sarilumab, hydroxychloroquine sulfate (Plaquenil), hydroxychloroquine sulfate (off label use; onset date and latency: unknown). The patient had aggravation of pulmonary failure on an unknown date (latency: unknown). Life expectancy was of more than 48 Hours. The patient died of it and COVID-19 pneumonia on (b) (6) and the death was not related to sarilumab. No autopsy was performed.

Action taken: unknown for aggravation of pulmonary failure and not applicable for the rest.

It was not reported if the patient received a corrective treatment.

Outcome: fatal for aggravation of pulmonary failure and not applicable for the rest.

Seriousness criteria: death of the patient and medically significant for aggravation of pulmonary failure.

Additional information received on 02-May-2020 from Physician:

New serious event death added. Text amended accordingly.

Version 0.0 comment: The case is assessed as non serious and listed as per the company RSI. The company considered the event of off label use to be possibly related to Hydroxychloroquine, as per WHO causality classification system, as per convention.



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FOIA Case Report Information

Case ID: 17796109

Follow-up information was received on 02/May/2020 (reference ID: 2020SA115641). Version 1.0 was created.

Additional information included: New event Death was added. Start/ stop date of Plaquenil and Azithromycin was added.

Version 1.0 comment: The case is assessed as serious and unlisted as per the company RSI. The company considered the event of Death to be unlikely to Plaquenil (Hydroxychloroquine sulfate) as event explained by underlying COVID-19 condition in hospitalized elderly patient. Company considered the event of off label use to be possibly related to Hydroxychloroquine, as per convention. More information regarding patient's medical history and autopsy report is required for a meaningful assessment of the case.

Query response was received from business partner on 18/May/2020. Version 2.0 was created.

The business partner had confirmed that the age of patient as unknown and treatment start date of hydroxychloroquine from (b) (6) to (b) (6) and further informed that no information available regarding the dose of hydroxychloroquine therapy, reason of patient's death and death details, patient's concomitant medications and any relevant laboratory data, medical history and family history of the patient, previous treatment /vaccinations.

version (2.0) comment: The case is assessed as serious and unlisted as per the company RSI. The company considered the event of Death to be unlikely to Plaquenil (Hydroxychloroquine sulfate) as event explained by underlying COVID-19 condition in hospitalized elderly patient. Company considered the event of off label use to be possibly related to Hydroxychloroquine, as per convention.

Follow up information was received from on 20-May-2020 and version (3.0) was created

Additional information included: Medical history, lab tests, new events (aggravation of pulmonary failure, unapproved dose administered and wrong technique in drug usage process)and concomitant drugs were added. Narrative was amended accordingly.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Seasonal allergy	01-Jul-1936		YES
Hernia repair	1987	1987	NO
Meniscus removal	1987	1987	NO
Dupuytren's contracture	2002	2002	NO



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

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Atrophy	2006		
Laparoscopy	2006	2006	NO
Leukoencephalopathy	2006		
Cataract operation	Jan-2017	Jan-2017	NO
Pollakiuria	21-Apr-2020		
Asthenia	22-Apr-2020		
Confusional state	22-Apr-2020		
Decreased appetite	22-Apr-2020		
Hospitalisation	(b) (6)		
Agitation			
Antacid therapy			
Anticoagulant therapy			
Arterial disorder			YES
Benign prostatic hyperplasia			
C-reactive protein increased			
COVID-19 pneumonia			
Cognitive disorder			YES
Depression			
Diabetes mellitus			
Diverticulum intestinal			
Gait disturbance			
Hospitalisation			
Hyperlipidaemia			
Hypertension			



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Hypertension	YES
Hypoxia	
Inflammation	
Inguinal hernia	
Insomnia	
Interleukin level increased	
Ischaemic stroke	
Lung disorder	
Myocardial ischaemia	
Oxygen saturation decreased	
Pain	
Polyneuropathy	YES
Pyrexia	
Renal cyst	
Retinopathy	YES
Sedation	
Spondylolisthesis	YES
Thyroid mass	
Type 2 diabetes mellitus	YES
Urinary retention	
Urinary tract pain	
Vertigo	YES



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FOIA Case Report Information

Case ID: 17796109

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Oxygen saturation	75	%			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ASAFLOW							
2	AZITHROMYCIN			UNK		27-Apr-2020	01-May-2020	
3	AZITHROMYCIN			UNK	COVID-19 pneumonia	26-Apr-2020	01-May-2020	
4	BASAGLAR			UNK	Diabetes mellitus	26-Apr-2020	30-Apr-2020	
5	CIPROXIN				Urinary tract pain			
6	CLEXANE			60/0.6 mg/mL		26-Apr-2020		
7	CLEXANE			60/0.6 mg/mL	Anticoagulant therapy	26-Apr-2020		
8	CLOPIDOGREL SANDOZ			UNK	Anticoagulant therapy			
9	CONTRAMAL							
10	COVERSYL			UNK				
11	CYMBALTA							
12	Cefuroxime			UNK		26-Apr-2020	29-Apr-2020	
13	DAFALGAN FORTE				Inflammation			
14	DAFALGAN FORTE				Pyrexia			
15	DAFALGAN FORTE			UNK	Pain	26-Apr-2020		



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FOIA Case Report Information

Case ID: 17796109

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
16 HALDOL			2 mg/mL	Agitation	27-Apr-2020		
17 INDERAL			UNK	Hypertension	27-Apr-2020		
18 LANTUS			UNK				
19 MIDAZOLAM B BRAUN			5 mg/mL	Insomnia	30-Apr-2020	30-Apr-2020	
20 MIRTAZAPINE			UNK				
21 MORPHINE HYDROCHLORIDE			UNK	Sedation	29-Apr-2020		
22 NOVORAPID			UNK	Diabetes mellitus	26-Apr-2020		
23 PANTOMED			UNK	Antacid therapy	26-Apr-2020		
24 PARACETAMOL B BRAUN			UNK	Pyrexia	28-Apr-2020		
25 PERINDOPRIL			UNK	Hypertension	27-Apr-2020	29-Apr-2020	
26 REMERGON			UNK	Depression	26-Apr-2020	28-Apr-2020	
27 SILDENAFIL SANDOZ							
28 SIMVASTATINE			UNK	Hyperlipidaemia	26-Apr-2020	28-Apr-2020	
29 SODIUM CHLORIDE			UNK		29-Apr-2020	30-Apr-2020	
30 SODIUM CHLORIDE			UNK, morphine hydrochloride mixed with sodium chloride		29-Apr-2020		
31 SODIUM CHLORIDE			UNK, midazolam hydrochloride in sodium chloride		30-Apr-2020	30-Apr-2020	
32 TAMSULOSIN			UNK	Benign prostatic hyperplasia	26-Apr-2020		
33 ZOCOR			UNK				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796109

Reporter Source:

Study Report?: No

Sender Organization: ADVANZ PHARMA

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796734

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Event Date:** 18-Apr-2020 **Outcomes:** DE,DS,HO,OT, **Application Type:** BLA

FDA Rcvd Date: 05-Jun-2020 **Mfr Rcvd Date:** 29-May-2020 **Mfr Control #:** US-SA-2020SA115037 **Application #:** 761037

Patient Information:

Age: **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	REGN mAb1 200 mg	COVID-19	17-Apr-2020	17-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	31 Hour	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Anaemia	NA
COVID-19	NA
Mental status changes	NA
Staphylococcal sepsis	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796734

Event/Problem Narrative:

Initial information from the Company sponsored study 6R88-COV-2040 was received on 21-Apr-2020 and 23-Apr-2020 (processed together). Patient ID: (b) (6) Site: (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

A 73-year-old, Caucasian, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

The patient experienced Acute hypoxic respiratory failure secondary to Covid-19 on (b) (6) Staph septicemia and Change in mental status on (b) (6) and Worsening anemia on (b) (6) and serious AESI on (b) (6) after receiving study drug.

Patients relevant medical history included acute respiratory failure with hypoxia.

No relevant concomitant medications were reported.

On 07-Apr-2020, nasopharyngeal swab was positive for SARS-CoV-2 Virus.

On 08-Apr-2020, earliest symptoms of pneumonia were noted, and the patient was hospitalized on (b) (6) On the same day, chest X-ray was performed with no result reported. Supplemental oxygen was applied via non-rebreather mask. Electrocardiogram was normal. The highest temperature recorded within 24 hours prior to study drug dosing was 38.6 C (degrees Celsius).

On (b) (6) rales/crackles on lung auscultation were not present at Baseline. Peripheral oxygen saturation (SpO2) was 90%, temperature was 37.4 C, blood pressure 110/52 mmHg, pulse 78 beats per minute (bpm) and respiratory rate was 44 respirations per minute (rpm). The patient was alert. Results of the biochemistry tests were as follows: alanine aminotransferase (ALT) 52 U/L (reference range: 12-59), aspartate aminotransferase (AST) 93 U/L (15-37), total bilirubin 0.6 mg/dl (0-1.1). Results of the hematology tests were as follows: platelets 256 (no units were reported), white blood cells (WBC) 9.93/nL (4.5 11), neutrophils (absolute): 9.14/nL (2-6.6), red blood cells (RBC) 3.91x10¹²/L (4.2-5.7) and haemoglobin 12.3 g/dL (14-17). In the following days RBC and haemoglobin levels were gradually decreasing.

On (b) (6) after (b) (6) of latency, the patient was transferred to intensive care unit. The patient had worsening hypoxemia and experienced acute hypoxic respiratory failure secondary to COVID-19, (saturation 70% to 85%). Due to worsening respiratory status, the patient agreed to a trial of intubation, during which he had significant oxygen desaturation, but it was short lived. Hypoxemia quickly improved. SpO2 was 89% with respiration rate of 30 rpm. The patient received methylprednisolone, 40 mg, twice daily, intravenously, as a corrective treatment for acute hypoxic respiratory failure secondary to Covid-19.

On (b) (6) SpO2 was 96%, respiratory rate was 28 rpm and the patient were unresponsive. Other reported measurements did not vary



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significantly from baseline values. Arterial blood gas analysis was performed with following results: pH 7.19-7.26, partial CO₂ pressure (PaCO₂) 39-59 mmHg and partial oxygen pressure (PaO₂) 95-183 mmHg. In the following days SpO₂ was 94-97%.

On (b) (6) after (b) (6) latency, the patient developed staph septicaemia (grade 3; medically significant), the event assessed as adverse event of special interest and experienced change in mental status (grade 3; disability). WBC was 8.67 and neutrophils were 6.88. Blood culture that was taken off central line grew gram positive cocci in clusters. The change in mental status precluded extubation. The patient received Zosyn (piperacillin/tazobactam) at dose of 4.5 g three times a day and vancomycin at a dose of 1500 mg both intravenously as a corrective treatment for septicaemia, and unspecified medication and procedure as a corrective treatment for change in mental status.

On (b) (6) variable mental status was complicating weaning attempts.

On (b) (6) WBC increased to 13.30 and neutrophils to 11.48.

On (b) (6) the patient was not tolerating spontaneous awakening trials due to confusion, agitation and delirium.

On (b) (6) the patient started receiving Acetaminophen (paracetamol) at a dose of 650 mg, as needed, orally, for indication Staph septicaemia. On the same day, he was placed on tracheostomy and percutaneous gastrostomy tube due to change in mental status.

On (b) (6) WBC increased to 17.33 and neutrophils to 15.52 and in the following days, they remained elevated. On the same day, the patient started receiving vancomycin at a dose of 1500 mg, daily, intravenously until (b) (6) and piperacillin-tazobactam at a dose of 4.5 g, three times per day, intravenously until (b) (6) for indication Staph septicaemia.

On (b) (6) vancomycin was given at a dose of 1500 mg, two times per day, intravenously for indication Staph septicaemia.

On (b) (6) daptomycin at dose of 800 mg, intravenously, was introduced as corrective treatment for septicaemia, until (b) (6)

On (b) (6) after (b) (6) days 11 hrs 22 min the patient developed worsening anemia (Severity: Grade 3, medically significant). Hemoglobin decreased to 6.9 g/dL and RBC to 2.16. The patient was unresponsive. Corrective treatment included blood transfusion.

On (b) (6) treatment assignment blind was broken for regulatory reporting purposes.

On (b) (6) at 21:40, the patient passed away and cause of death was reported as Acute hypoxic respiratory failure secondary to Covid-19 ((grade 5) (seriousness criteria of death and hospitalization)).

Action taken with study drug in response to the event was not applicable.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796734

Corrective treatment: methylprednisolone for acute hypoxic respiratory failure secondary to Covid-19, Zosyn (piperacillin/tazobactam) and vancomycin for staph septicaemia, and unspecified medication and procedure as a corrective treatment for change in mental status, blood transfusion for anemia

Outcome: was fatal for acute hypoxic respiratory failure secondary to Covid-19; not recovered for rest of all events

Causality is as follows:

For COVID-19:

Relationship with IP according to investigator: Not Related

Investigator causality rationale: No alternative explanation was provided.

Relationship with IP according to company: Not reportable

Company causality rationale: A 73-year-old, Caucasian, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced acute hypoxic respiratory failure secondary to Covid-19 with subsequent death, (b) (6) after receiving the study drug. The event of acute hypoxic respiratory failure secondary to Covid-19 is assessed as not related to study drug or any clinical trial procedure. The event is secondary to progression of COVID-19 infection and pneumonia further aggravated by preexisting acute respiratory failure with hypoxia.

For Staphylococcal sepsis:

Relationship with IP according to investigator: Not Related

Investigator causality rationale: No alternative explanation was provided.

Relationship with IP according to company: Related

Company causality rationale: A 73-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced Staphylococcal sepsis (b) (6) days after receiving the study drug. Blood culture that was taken off central line grew gram positive cocci in clusters. Based on a plausible temporal association between study drug administration and the reported event and higher rate of bacterial infections observed in patients treated with sarilumab, causality for the event Staphylococcal sepsis is assessed as related to study drug. The event is not related to any clinical trial procedure. Patient's underlying severe COVID 19 infection and use of catheters are confounders.

For Mental status changes:

Relationship with IP according to investigator: Not Related

Investigator causality rationale: No alternative explanation was provided.

Relationship with IP according to company: Not reportable

Company causality rationale: A 73-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced mental status changes (b) (6) days after receiving the study drug. The event of mental status changes is assessed as not related to study drug. The event is secondary to progression of COVID-19 infection and pneumonia further aggravated by comorbidities like acute respiratory failure with hypoxia and concurrent Staphylococcal sepsis. The event mental status changes is not related to any clinical trial procedure.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796734

For Anaemia:

Relationship with IP according to investigator: Not Related

Investigator causality rationale: Other suspected causes included chronic COVID-19 disease.

Relationship with IP according to company: Not reportable

Company causality rationale: A 73-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced worsening anemia ^{(b) (6)} days after receiving the study drug. Patient's baseline RBC and haemoglobin values were below reference ranges. The event is assessed as not related to study drug. The event is secondary to progression of COVID-19 infection and pneumonia further aggravated by comorbidities like acute respiratory failure with hypoxia and concurrent Staphylococcal sepsis. The event worsening anemia is not related to any clinical trial procedure.

Causality assessment for initially reported event Acute respiratory distress syndrome is as follows:

(b) (6)

For Acute respiratory distress syndrome:

Relationship with IP according to investigator: Not Related

Investigator causality rationale: No alternative explanation was provided.

Relationship with IP according to company: Not reportable

Company causality rationale: A 73-year-old, Caucasian, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced ARDS ^{(b) (6)} after receiving the study drug. The event of ARDS is assessed as not related to study drug. The event is secondary to progression of COVID-19 infection and pneumonia further aggravated by preexisting acute respiratory failure with hypoxia. The event ARDS is not related to any clinical trial procedure.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 29-Apr-2020 and 01-May-2020 (processed together)

The Investigator provided the following updates: new events added, concomitant medications, medical history, relevant tests and clinical course updated.

Follow up: 06-May-2020

The Investigator provided the following updates: Investigator causality to study drug for Staphylococcal sepsis updated, new event added, clinical course updated, concomitant medications added.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796734

Follow up: 29-May-2020:

The Investigator provided the following updates: Event term (for event Acute hypoxic respiratory failure secondary to Covid-19) updated. Concomitant medication information, clinical course and medical history updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute respiratory failure	(b) (6)		YES
Atypical pneumonia	(b) (6)		YES
Mitral regurgitation			YES
Paroxysmal supraventricular tachycardia			YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood pressure					Y
Absolute neutrophil count	11.98	/nL	2	6.6	Y
Oxygen saturation	90	%			Y
Partial arterial pressure of carbon dioxide	59	mmHg			Y
RBC count	3.91	10*12/L	4.2	5.7	Y
Respiratory rate	44	breaths/min			Y
Respiratory rate	28	breaths/min			Y



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796734

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
SARS-CoV-2 test		n			Y
Absolute neutrophil count	11.48	/nL	2	6.6	Y
Absolute neutrophil count	15.52	/nL	2	6.6	Y
Platelet count	256	UNK			Y
White blood cells	17.33	/nL	4.5	11	Y
Electrocardiogram					Y
Haemoglobin	12.3	g/dL	14	17	Y
Respiratory rate	30	breaths/min			Y
Body temperature	37.4	Cel			Y
Heart rate	78	beats/min			Y
PaO2	104	mmHg			Y
Chest X-ray					Y
Absolute neutrophil count	9.14	/nL	2	6.6	Y
White blood cells	13.30	/nL	4.5	11	Y
Aspartate aminotransferase	93	U/L	15	37	Y
Blood culture					Y
Haemoglobin	6.9	g/dL	14	17	Y
Alanine aminotransferase	52	U/L	12	59	Y
Oxygen saturation	96	%			Y
Blood bilirubin	0.6	mg/dL	0	1.1	Y
Oxygen saturation	89	%			Y
RBC count	2.16	10 ¹² /L	4.2	5.7	Y
White blood cells	9.93	/nL	4.5	11	Y
White blood cells	8.67	/nL	4.5	11	Y

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	1000 MG/Q6H		1000 mg, QID	Analgesic therapy	19-Apr-2020	19-Apr-2020	10 DAY
2	ACETAMINOPHEN	650 MG/	Oral	650 mg, PRN	Pyrexia	29-Apr-2020		10 DAY
3	ACETAMINOPHEN				Septicemia staphylococcal			10 DAY
4	AZITHROMYCIN	250 MG/QD		250 mg, QD	COVID-19	15-Apr-2020	18-Apr-2020	3 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

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	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
5	CEFTRIAXONE	1 G/QD		1 g, QD	Pneumonia	17-Apr-2020	19-Apr-2020	8 DAY
6	DIVALPROEX	250 MG/Q8H		250 mg, Q8H	Epilepsy	05-May-2020	07-May-2020	
7	HYDROXYCHLOROQUIN E	1000 MG/		1000 mg	Fever	19-Apr-2020	19-Apr-2020	2 DAY
8	HYDROXYCHLOROQUIN E	400 MG/Q12H		400 mg, BID		15-Apr-2020	15-Apr-2020	2 DAY
9	HYDROXYCHLOROQUIN E	200 MG/Q12H		200 mg, BID	COVID-19	16-Apr-2020	18-Apr-2020	2 DAY
10	LEVOPHED			1-50mcg/ml continous		19-Apr-2020		6 DAY
11	LEVOPHED				Blood pressure	19-Apr-2020		6 DAY
12	METHYLPREDNISOLON /00049601/			40 UNK	Respiratory failure	18-Apr-2020	19-Apr-2020	7 DAY
13	PIPERACILLIN TAZOBACTAM PA	4.5 G/QD		4.5 g, QID	Pneumonia	19-Apr-2020	22-Apr-2020	6 DAY
14	PLAQUENIL	400 MG/Q12H		400 mg, BID	COVID-19	15-Apr-2020	15-Apr-2020	3 DAY
15	REMDESIVIR	200 MG/		200 mg. oto	Antiviral treatment	19-Apr-2020	19-Apr-2020	6 DAY
16	REMDESIVIR	100 MG/QD		100 mg, QD (1-50mcg/min, continous)		20-Apr-2020	28-Apr-2020	6 DAY
17	ROCEPHIN	1 G/QD		1 g, QD	Pneumonia	17-Apr-2020	19-Apr-2020	1 DAY
18	TYLENOL	650 MG/		650 mg, PRN	Fever	15-Apr-2020		3 DAY
19	VANCOMYCIN	1000 MG/Q12H		1000 mg, BID		17-Apr-2020	21-Apr-2020	1 DAY
20	VANCOMYCIN	1500 MG/Q12H	Intravenous (not otherwise specified)	1500 mg, BID	Pneumonia	01-May-2020		1 DAY
21	VANCOMYCIN	1500 MG/QD	Intravenous (not otherwise specified)	1500 mg, QD	Staphylococcal sepsis	25-Apr-2020	01-May-2020	1 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796734

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796912

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ARM Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 18-May-2020 Mfr Rcvd Date: 13-May-2020 Mfr Control #:AM-ROCHE-2602535 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ACTEMRA			Intravenous (not otherwise specified)		COVID-19			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC

Death NA

Event/Problem Narrative:

AER 2602535 is a spontaneous case, received on 13/May/2020 from a consumer in Armenia. It concerns a patient of unknown demographics who died whilst being treated with tocilizumab (Actemra).

The patient's medical history, past drugs, concurrent conditions and concomitant medications and risk factors were not reported.

On an unknown date, the patient started therapy with intravenous tocilizumab injection (lot number: unknown, dose and frequency not reported) for covid-19. On an unknown date, the patient died due to unknown cause. After injection of tocilizumab patient died. It was not reported if an autopsy was performed or not.

At the time of death, therapy with tocilizumab was not provided.

The consumer did not report a causality between death and tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796912

No further information was reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** ROCHE **503B Compounding
Outsourcing Facility?:**



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17796912

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17797597

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: CAN Event Date: 11-May-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 18-Jun-2020 Mfr Rcvd Date: 15-Jun-2020 Mfr Control #: CA-ROCHE-2600439 Application #: 125276

Patient Information:

Age: 63 YR Sex: Male Weight: 80 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		1X	Intravenous (not otherwise specified)	vol:100 ml, which was most recent dose time: 18:04	COVID-19 pneumonia	02-May-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	9 Day	NA	NA	MJM08256,MJM09876,MJM26603,MJM27359				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC
 Retroperitoneal haemorrhage NA

Event/Problem Narrative:

AER 2600439 is a clinical study case, received on 12/May/2020 from a physician in Canada and concerns a 63 year old male patient (patient number: (b) (6)) who died due to severe retro-peritoneal bleed whilst enrolled in (b) (6) (b) (6)

The patient's concurrent conditions included paralysis, hypotension, hyperglycemia, hypertension, constipation, infection, agitation, nausea, type 2 diabetes mellitus, acute respiratory distress syndrome, mechanical ventilation, extracorporeal life support and bilateral air space changes on chest X-ray. Concomitant medications included propofol, fentanyl, rocuronium, norepinephrine, heparin, insulin human (Humulin R), labetalol, vasopressin, senna spp. (Senna), meropenem, lansoprazole, macrogol (Polyethylene Glycol), vitamins (Multivitamin), furosemide, amlodipine, hydralazine, metoprolol, quetiapine, bisacodyl, methylprednisolone, hydrocortisone, ondansetron, hydromorphone, metoclopramide, zinc gluconate, ascorbic acid, tobramycin, vancomycin, cefazolin and caspofungin. Medical history or past drugs were not reported.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17797597

(b) (6)
(b) (6) On 11/May/2020, at 11:00, he had septic shock and an increasing transfusion requirement. His hemoglobin was 66 platelet count was 43, white blood cell count was 67.7, creatinine was 123 and urea was 28 (unit and normal range not reported for all). His computed tomogram (CT) scan showed a large right severe retro-perineum bleed 16.8 X 17 X 22.5 cm. Bleeding was considered spontaneous as he supported with ECMO (extracorporeal membrane oxygenation) and on systemic anticoagulation. He became hemodynamically unstable and had cardiac arrest. He was treated with unspecified medications. On (b) (6) he died due to severe retro-peritoneal bleed (initial severity: grade 4). An autopsy was not performed.

The physician assessed severe retro-peritoneal bleed as a serious adverse event of special interest.

The physician assessed severe retro-peritoneal bleed as related to blinded tocilizumab, disease under study, unspecified concurrent illness and unspecified concomitant medication.

The company assessed fatal retro-peritoneal bleed as related to blinded tocilizumab considering temporal association and as role of tocilizumab cannot be excluded, other confounding factors could be concurrent conditions of hyperglycemia and hypertension, concomitant medication of methylprednisolone and hydrocortisone and study disease as strong confounding factors.

No further information was provided.

Additional information was received 19/May/2020 and the following information was added to the case: Secondary reporter (consumer), patient weight (80 kg) and concurrent condition (Type 2 diabetes).

Additional information was received on 29/May/2020. The following information was added to the case: Initial severity was updated to grade 4 (previously grade 5) and concurrent conditions (acute respiratory distress syndrome, mechanical ventilation, extracorporeal life support and bilateral air space changes on chest X-ray).

Additional information was received on 15/Jun/2020. The following information was added to the case: Additional reporter and event description was added.

Analysis of similar events. (PT: fatal Retroperitoneal haemorrhage)

On 15/MAY/2020, the Roche safety database was searched with MedDRA higher level term of Peritoneal and retroperitoneal haemorrhages for tocilizumab. The search was based on blinded/non-blinded data.

No previously submitted IND reports were identified.

In addition, 3 Non IND reports of serious cases with similar events were reported.

The index case AER 2600439 concerns a 63 year old male patient who developed Severe retro-peritoneal bleed 9 days after the first and the



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17797597

most recent dose of tocilizumab. The investigator assessed event retro-peritoneal bleed as related to blinded tocilizumab considering temporal association and as role of tocilizumab cannot be excluded, other confounding factors could be concurrent conditions of hyperglycemia and hypertension, concomitant medication of methylprednisolone, hydrocortisone and study disease as strong confounding factors. Based on review of available data, the sponsor cannot establish or exclude the possibility of a cause-and-effect relationship between administration of tocilizumab and the occurrence of Severe retro-peritoneal. After review of the clinical details of the index case and similar previous cases, the sponsor does not believe that changes to the conduct of the clinical trial are warranted in response to this case report at this time.

Relevant Medical History:

BILATERAL AIR SPACE CHANGES ON CHEST X-RAY

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute respiratory distress syndrome			YES
Agitation			
Constipation			
Hyperglycaemia			
Hypertension			
Hypotension			
Infection			
Life support			YES
Mechanical ventilation			YES
Nausea			
Paralysis			
Type 2 diabetes mellitus			YES



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17797597

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Platelet count	43	unit not reported			N
Blood urea	28	unit not reported			N
Haemoglobin	66	unit not reported			N
White blood cell count	67.7	unit not reported			N
Blood creatinine	123	unit not reported			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	AMLODIPINE	10 MG/QD	Unknown		Hypertension	26-Apr-2020	27-Apr-2020	15 DAY
2	ASCORBIC ACID	500 MG/QD	Unknown		Nutritional supplementation	06-May-2020	11-May-2020	5 DAY
3	BISACODYL	10 MG/BID	Unknown		Constipation	27-Apr-2020	01-May-2020	14 DAY
4	CASPOFUNGIN	70 MG/QD	Unknown		Infection	10-May-2020	11-May-2020	1 DAY
5	CEFAZOLIN	1 G/TID	Unknown		Infection	09-May-2020	11-May-2020	2 DAY
6	FENTANYL				Analgesic therapy			
7	FENTANYL	100 UG/	Unknown		Sedation	11-May-2020		
8	FUROSEMIDE	20 MG/BID	Unknown			25-Apr-2020	08-May-2020	16 DAY
9	HEPARIN	1750 IU/	Unknown			25-Apr-2020	10-May-2020	16 DAY
10	HUMULIN R	19.5 IU/	Unknown		Hyperglycaemia	25-Apr-2020	11-May-2020	16 DAY
11	HYDRALAZINE	20 MG/	Unknown		Hypertension	27-Apr-2020	30-Apr-2020	14 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17797597

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
12 HYDROCORTISONE	50 MG/	Unknown			09-May-2020	11-May-2020	2 DAY
13 HYDROMORPHONE	2 MG/	Unknown		Analgesic therapy	06-May-2020	09-May-2020	5 DAY
14 LABETALOL	1 MG/	Unknown		Hypertension	30-Apr-2020	04-May-2020	11 DAY
15 LANSOPRAZOLE	30 MG/QD	Unknown		Prophylaxis	25-Apr-2020	11-May-2020	16 DAY
16 MEROPENEM	1 G/TID	Unknown		Infection	24-Apr-2020	27-Apr-2020	35 DAY
17 MEROPENEM	1 G/TID	Unknown			06-Apr-2020	11-May-2020	35 DAY
18 METHYLPREDNISOLON E	160 MG/QD	Unknown			29-Apr-2020	02-May-2020	12 DAY
19 METHYLPREDNISOLON E	80 MG/QD	Unknown			03-May-2020	06-May-2020	12 DAY
20 METOCLOPRAMIDE	10 MG/TID	Unknown		Constipation	06-May-2020	11-May-2020	5 DAY
21 METOPROLOL	25 MG/TID	Unknown		Hypertension	27-Apr-2020	30-Apr-2020	14 DAY
22 NOREPINEPHRINE	.6 UG/	Unknown		Hypotension	11-May-2020		
23 ONDANSETRON	4 MG/QD	Unknown		Nausea	06-May-2020	06-May-2020	5 DAY
24 POLYETHYLENE GLYCOL [MACROGOL]	117 G/BID	Unknown		Constipation	25-Apr-2020	11-May-2020	16 DAY
25 PROPOFOL	60 UG/	Unknown		Sedation	11-May-2020		
26 QUETIAPINE	75 MG/TID	Unknown		Agitation	27-Apr-2020	09-May-2020	14 DAY
27 ROCURONIUM	.7 MG/	Unknown		Paralysis	11-May-2020		
28 SENNA [SENNAL SPP.]	34 MG/BID	Unknown		Constipation	24-Apr-2020	11-May-2020	17 DAY
29 TOBRAMYCIN	380 MG/QD	Unknown		Infection	06-May-2020	11-May-2020	5 DAY
30 VANCOMYCIN	1.25 G/BID	Unknown		Infection	06-May-2020	11-May-2020	5 DAY
31 VASOPRESSIN	6 IU/	Unknown		Hypotension	06-May-2020	11-May-2020	5 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17797597

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
32 ZINC GLUCONATE	388 MG/QD	Unknown		Nutritional supplementation	06-May-2020	11-May-2020	5 DAY

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17798009

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 18-May-2020
Mfr Rcvd Date: 13-May-2020
Mfr Control #: US-ROCHE-2601732
Application #: 125276

Patient Information:

Age: 89 YR
Sex: Female
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19	May-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	NOT PROVIDED				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
COVID-19	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2601732 is a spontaneous case, received on 13/May/2020 from a consumer via company representative in the USA. It concerns a 89 year old female patient who had off label use and died due to COVID-19 whilst being treated with tocilizumab (Actemra).

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On (b) (6) the patient received therapy with tocilizumab (dosing regimen was not reported) for COVID-19 (off label use). She was in hospital for one week. She died due to COVID-19 on (b) (6) Autopsy information was not provided.

The reporter did not provide the causal relationship of COVID-19 to tocilizumab.

No further information was provided.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17798009

Relevant Medical History:

None

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17798212

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 31-Mar-2020 Outcomes: DE,

Application Type: ANDA

FDA Rcvd Date: 18-May-2020 Mfr Rcvd Date: 10-May-2020 Mfr Control #: ES-BAUSCH-BL-2020-014076

Application #: 040069

Patient Information:

Age: 26 YR

Sex: Female

Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	DEXAMETASONA		20 MG/QD	Intravenous (not otherwise specified)	20 MG DIA	Product used for unknown indication	28-Mar-2020	01-Apr-2020
2	AZITROMICINA		500 MG/QD	Oral	500 MG DIA	COVID-19 pneumonia	23-Mar-2020	24-Mar-2020
3	DEXKETOPROFENO		25 MG/Q8H	Intravenous (not otherwise specified)	25 MG EVERY 8 HOURS	Product used for unknown indication	27-Mar-2020	01-Apr-2020
4	ENOXAPARINA		40 MG/QD	Subcutaneous	40MG DIA	Product used for unknown indication	27-Mar-2020	01-Apr-2020
5	HIDROXICLOROQUINA		400 MG/QD	Oral	400 MG DIA	COVID-19 pneumonia	23-Mar-2020	01-Apr-2020
6	TOCILIZUMAB		600 MG/	Intravenous (not otherwise specified)	Total dose: 600 mg	Severe acute respiratory syndrome	29-Mar-2020	29-Mar-2020
7	TOCILIZUMAB					COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	DEXAMETASONA	4 Day	NA	NA				BAUSCH AND LOMB	
2	AZITROMICINA	9 Day	NA	NA					
3	DEXKETOPROFENO	5 Day	NA	NA					
4	ENOXAPARINA	5 Day	NA	NA					
5	HIDROXICLOROQUINA	9 Day	NA	NA					



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17798212

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC	
6 TOCILIZUMAB	3 Day	NA	NA						
7 TOCILIZUMAB	3 Day	NA	NA						

Event Information:

Preferred Term (MedDRA ® Version: 23.1)

Coagulopathy

ReC

NA

Event/Problem Narrative:

This serious spontaneous case was downloaded from the EudraVigilance database as a L2A policy access case on 10/May/2020 from a physician via Spain Health Authority, The Spanish Agency of Medicines and Medical Devices (AEMPS) (ES-AEMPS-628824) and concerned a patient of 26 years age and female gender.

Concurrent conditions: Severe acute respiratory syndrome, SRAS COVID-19.

Concomitant medications: Not provided

Past medications: Not provided

Medical history: C-section

Company suspect products include:

Dexametasona, unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on 28/Mar/2020 till 01/Apr/2020, intravenous (not otherwise specified), at a dosage of 20 milligram, 1 in 1 days for unknown indication.

Other suspect products include:

Enoxaparina, unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on 27/Mar/2020 till 01/Apr/2020, subcutaneous, at a dosage of 40 milligram, 1 in 1 days for unknown indication.

Tocilizumab, unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on 29/Mar/2020 till 29/Mar/2020, intravenous (not otherwise specified), at a dosage of 600 milligram, unknown frequency for Severe acute respiratory syndrome, SRAS COVID-19.

Dexketoprofeno, unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on 27/Mar/2020 till 01/Apr/2020, intravenous (not otherwise specified), at a dosage of 25 milligram, 1 in 8 hours for unknown indication.

Hidroxicloroquina, unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on 23/Mar/2020 till 01/Apr/2020, oral, at a dosage of 400 milligram, 1 in 1 days for COVID-19 pneumonia.

Azitromicina, unknown formulation (Batch number: unknown; Expiry Date: Not provided) started on 23/Mar/2020 till 24/Mar/2020 oral, at a



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dosage of 500 milligram, 1 in 1 days for COVID-19 pneumonia.

On 31/Mar/2020 (latency: 4 days), the patient experienced coagulopathy. On (b) (6) the patient passed away and the cause of death was Multiple organ failure, Coagulopathy and Coronavirus disease 2019 (COVID-19). It was unknown whether the autopsy was performed.

Reported Term (Preferred Term): Onset Date-Cessation Date; Seriousness; Outcome:
Coagulopathy (Coagulopathy): 31/Mar/2020- Not Applicable; serious (Death); Fatal.

Action taken with company suspect product in response to the event, Dechallenge and Rechallenge:
Dexametasona/Coagulopathy: Drug discontinued; Not Applicable; Not Applicable.

Action taken with co-suspect product in response to the event:

Enoxaparina/Coagulopathy: Dosage maintained
Tocilizumab/Coagulopathy: Drug discontinued
Dexketoprofeno/Coagulopathy: Drug discontinued
Hidroxicloroquina/Coagulopathy: Drug discontinued
Azitromicina/Coagulopathy: Drug discontinued

Final therapy status at the time of death:
Dexametasona: Drug no longer administered.
Enoxaparina: Drug no longer administered.
Tocilizumab: Drug no longer administered.
Dexketoprofeno: Drug no longer administered.
Hidroxicloroquina: Drug no longer administered.
Azitromicina: Drug no longer administered.

Death information: Date of death: (b) (6) Cause of death: Multiple organ failure, Coagulopathy and Coronavirus disease 2019 (COVID-19): Autopsy performed: Unknown.

Reporter causality assessment:
Dexametasona/Coagulopathy: Not Reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?



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Caesarean section	(b) (6)	(b) (6)	NO
COVID-19 pneumonia			UNKNOWN
Severe acute respiratory syndrome			UNKNOWN

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No	Sender Organization: BAUSCH AND LOMB	503B Compounding Outsourcing Facility?:

Literature Text:



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FOIA Case Report Information

Case ID: 17798241

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ITA **Event Date:** **Outcomes:** DE, **Application Type:** BLA

FDA Rcvd Date: 18-May-2020 **Mfr Rcvd Date:** 11-May-2020 **Mfr Control #:** IT-ROCHE-2602963 **Application #:** 125276

Patient Information:

Age: **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		8 MG/KG/Q12H	Intravenous (not otherwise specified)		COVID-19 pneumonia		
2	TOCILIZUMAB					Acute respiratory distress syndrome		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		Unk	NA	UNKNOWN				
2	TOCILIZUMAB		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1)	ReC
Intentional product use issue	NA
Off label use	NA
Septic shock	NA



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Case ID: 17798241

Event/Problem Narrative:

AER 2602963 is a literature - non-interventional study case, received on 11/May/2020 from a physician in Italy. It concerns a patient of unspecified demographics who received tocilizumab intentionally for unlabeled indication and died due to septic shock whilst enrolled in a prospective series study of patients with confirmed COVID-19 pneumonia and acute respiratory distress syndrome (ARDS) requiring ventilatory support to determine whether administration of tocilizumab (TCZ), was associated with improved outcome.

Between 09/Mar/2020 and 20/Mar/2020, 100 consecutive patients admitted to authors hospital were prospectively studied. The median age was 62 years (range: 57-71) and most patients were male (male/female: 88/12). Comorbidities were present in more than half of patients with arterial hypertension being the most common one (46%), followed by obesity (31%), diabetes (17%) and cardiovascular disease (16%). Other comorbidities were chronic kidney disease (11%), chronic obstructive pulmonary disease (9%) and malignancy (6%). There were patients with overweight (34%). On admission the most common symptoms were fever (85%), dyspnea (73%) and cough (55%) with a median time from illness onset and hospital admission of 6 [range: 4-8] days. Other symptoms included dyspnea (73%) and diarrhea (9%). Patients were selected based on disease severity and absence of contraindication to TCZ, including a suspected or confirmed bacterial infection, an active diverticulitis or gastrointestinal tract perforation, neutropenia (0.500×10^3 cells/uL) and thrombocytopenia (50×10^3 cells/uL). Respiratory disease severity was assessed by a locally developed bedside respiratory severity scale, the Brescia COVID-19 Respiratory Severity Scale (BCRSS), a 9-category ordinal severity scale ranging from 0 (asymptomatic patient) to 8 (a critically ill patient with tracheal intubation, mechanical ventilation and advanced intensive care unit (ICU) management. BCRSS classifies the patients severity based on the need for oxygen supplementation and ventilatory support, offering a step-up therapeutic approach for the use of antiviral and anti-inflammatory drugs. In all patients SARS-CoV-2 infection was confirmed by real time-polymerase chain reaction (PCR) on nasopharyngeal swab and pneumonia was documented by chest x-ray or computed tomography. The most common radiological findings were bilateral pulmonary infiltration, ground glass opacities and consolidations. All the patients were treated with a standard pharmacological protocol, including antiviral drugs (lopinavir 400 mg and ritonavir 100 mg twice a day or remdesivir 100 mg/day), antibiotic prophylaxis (azithromycin, ceftriaxone or piperacillin/tazobactam), hydroxychloroquine 400 mg/day and dexamethasone 20 mg/day and received non-invasive ventilation (NIV) or mechanical ventilation with tracheal intubation (BCRSS score ≥ 3). Patients received TCZ based on rapidly progressive respiratory failure, refractory to pharmacological therapy and ventilatory support. TCZ was administered at a dosage of 8 mg/kg (max 800 mg) by two consecutive intravenous infusions 12 hours apart. A third infusion, 24 hours apart from the second was optional based on clinical response. Median time from hospital admission and TCZ infusion was 5 day (range: 3-8) and median days between onset of symptoms and TCZ infusion was 12 days (range: 9-14). All patients treated with TCZ had acute respiratory failure requiring ventilatory support (BCRSS ≥ 3). Fifty-seven patients were treated with NIV (BCRSS =3) notably, these patients were treated in the general ward as no ICU beds and ventilators were available. Forty-three patients were treated in the ICU after tracheal intubation and mechanical ventilation with a BCRSS before treatment of 7 [range: 5-8]. Eighty-seven patients (87%) received 2 infusions of TCZ, 13 patients (13%) 3 infusions. Clinical and laboratory data of all patients were collected at hospital admission, shortly before TCZ administration and 10 days after. At 24-72 hours after TCZ administration, 58 patients (58%) showed a rapid improvement of clinical and respiratory condition, 37 (37%) stabilized compared to the rapidly declining pre-TCZ condition, and 5 (5%) worsened (of whom 4 died). At 10 days, the respiratory condition was improved or stabilized in 77 (77%) patients, of whom 61 showed a significant clearing of diffuse bilateral opacities on chest x-ray and 15 were discharged from the hospital. Respiratory condition worsened in 23 (23%) patients, of whom 20 died. Of the 57 patients treated outside the ICU, 37 (65%) improved and suspended NIV (BCRSS 1 [range: 0-2]), 7 (12%) patients remained stable in NIV, and 13 (23%) patients worsened (10 died, 3



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were admitted to ICU). Of the 43 patients treated in ICU, 32 (74%) improved (17 of them were taken off the ventilator and were discharged to the ward), 1 (2%) remained stable (BCRSS class 5) and 10 (24%) died (all of them had BCRSS $\geq$ 7 before TCZ). Laboratory findings were collected, at the time of hospital admission, before TCZ administration (1-12 hour prior) and post TCZ administration (10 days after administration) and all the data presented as median values. In all patients (n=100) laboratory findings as follows [at the time of admission, before TCZ administration and post TCZ administration]: white blood cell count [6.0x 10³ macro/L (range: 4.5-8.4), 8.8 (6.5-11.4) and 11.3 (8.0-15.3)], neutrophils [4.9x 10³ macro/L (range: 3.3-7.8), 6.7 (4.9-9.7) and 8.9 (5.8-11.8)], lymphocytes [0.78x 10³ macro/L (range: 0.51-1.10), 0.62 (0.41-0.84) and 0.79 (0.61-1.16)], platelets [177x 10³ macro/L (range: 141-224, 220 (174-294) and 205 (142-289)], haemoglobin [13.6 g/dL (range: 12.8-14.8), 12.4 (11.1-13.6) and 12.6 (11.3-13.8)], C-reactive protein [97 mg/L (range: 38-159), 113 (45-169) and 2 (1-5)], ferritin [1004 macrog/L (range: 268-3730), 1689 (981-3533) and 1352 (806-2422)], D-Dimer [525 ng/mL (range: 283-1100), 979 (456-3640) and 2331 (887-3801)], fibrinogen [508 mg/dL (range: 421-627), 520 (436-714) and 217 (150-285)], aspartate aminotransferase [55 U/L (range: 41-82), 47 (35-72) and 43 (30-69)], alanine aminotransferase [39 U/L (range: 26-62), 43 (28-61) and 75 (44-129)], lactate dehydrogenase [413 U/L (range: 281-542), 428 (293-537) and 390 (319-531)], triglycerides [106 mg/dL (range: 91-135), 160 (113-219) and 189 (164-220)], cholesterol [112 mg/dL (range: 89-134), 120 (107-139) and 271 (220-355)], creatine kinase [161 U/L (range: 87-279), 105 (50-190) and 87 (39-181)] and troponin T [18 ng/L (range: 13-21), 11 (8-23) and 25 (16-49)]. In improved or stable patients (n=77) laboratory findings as follows [at the time of admission, before TCZ administration and post TCZ administration]: white blood cell count [5.7x 10³ macro/L (range: 4.4-8.3), 7.9 (6.0-10.8) and 10.9 (7.6-15.0)], neutrophils [4.4x 10³ macro/L (range: 3.0-7.3), 6.1 (4.4-9.0) and 7.9 (4.6-11.3)], lymphocytes [0.84x 10³ macro/L (range: 0.53-1.2), 0.69 (0.43-0.86) and 0.81 (0.61-1.30)], platelets [179x 10³ macro/L (range: 139-224), 224 (181-296) and 205 (154-297)], haemoglobin [13.8 g/dL (range: 12.8-14.8), 12.3 (11.1-13.3) and 12.4 (10.9-13.5)], C-reactive protein [81 mg/L (range: 38-138), 113 (43-170) and 2 (1-4)], ferritin [905 macrog/L (range: 270-1705), 1568 (946-2664) and 1308 (814-2397)], D-Dimer [383 ng/mL (range: 263-613), 746 (443-3444) and 2210 (729-3257)], fibrinogen [508 mg/dL (range: 458-653), 520 (473-713) and 203 (148-274)], aspartate aminotransferase [53 U/L (range: 41-77), 46 (33-64) and 41 (30-64)], alanine aminotransferase [39 U/L (range: 27-60), 39 (27-54) and 76 (44-130)], lactate dehydrogenase [402 U/L (range: 285-513), 418 (288-481) and 376 (317-504)], triglycerides [104 mg/dL (range: 92-129), 144 (102-207) and 190 (163-219)], cholesterol [112 mg/dL (range: 94-127), 116 (107-126) and 269 (215-336)], creatine kinase [172 U/L (range: 79-336), 104 (46-91) and 85 (38-164)], and troponin T [18 ng/L (range: 13-21), 10 (7-15) and 19 (15-55)]. In worsened or deceased patients (n=23) laboratory findings as follows [at the time of admission, before TCZ administration and post TCZ administration]: white blood cell count [7.0x 10³ macro/L (range: 4.9-9.7), 9.7 (7.4-15.4) and 13.8 (9.4-25.9)], neutrophils [6.1x10³ macro/L (range: 3.8-8.6, 9.5 (6.4-14.3) and 11.4 (10.1-25.8)], lymphocytes [0.55x 10³ macro/L (range: 0.46-0.83), 0.43 (0.32-0.72) and 0.72 (0.52-1.10)], platelets [172x 10³ macro/L (range: 145-219), 214 (141-266) and 137 (102-323)], haemoglobin [13.6 g/dL (range: 12.6-14.7), 12.4 (11.4-14.7) and 13.6 (12.4-14.5)], C-reactive protein [145 mg/L (range: 57-205), 118 (71-164) and 5 (5-7)], ferritin [3733 macrog/L (range: 1937-5020), 3283 (988-4247) and 1863 (790-6261)], D-Dimer [3854 ng/mL (range: 968-5250), 2407 (760-5250) and 5250 (3328-5250)], fibrinogen [482 mg/dL (range: 352-587), 530 (350-765) and 218 (168-316)], aspartate aminotransferase [61 U/L (range: 48-117), 52 (41-80) and 69 (44-77)], alanine aminotransferase [40 U/L (range: 24-73), 59 (31-78) and 63 (42-96)], lactate dehydrogenase [570 U/L (range: 247-764), 544 (365-749) and 565 (406-870)], triglycerides [109 mg/dL (range: 88-153), 206 (147-233) and 303 (228-432)], cholesterol [117 mg/dL (range: 87-156), 133 (123-141) and 178 (175-222)], creatine kinase [152 U/L (range: 123-208), 116 (70-156) and 167 (93-188)], and troponin T [18 ng/L (range: 14-40), 23 (17-51) and 42 (26-42)]. Interleukin-6 (IL6) data available for 42 patients. in improved or stabled patients before TCZ administration was 16 (9-94) and post TCZ was 1679 (335-2227). In worsened or deceased patients pre TCZ administration value was 56 (25-157) and post



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TCZ value was 5000 (5000-5000). At the time of TCZ administration, all patients presented lymphopenia (below 1×10^3 cells/uL) and high levels of inflammatory markers, including C-reactive protein (CRP), fibrinogen, ferritin and interleukin 6 (IL-6). Ten days after, the lymphocyte count increased, especially in improved patients. CRP, fibrinogen and ferritin levels decreased toward the range of normality, while D-Dimer and IL-6 levels increased both in improved and worsened patients. During 10 days of followup, three patients had adverse events.

This case concerns 2nd patient of 3 patients who developed adverse events.

The patient's concomitant medications included hydroxychloroquine and dexamethasone.

On an unspecified date, the patient started therapy with intravenous tocilizumab infusion 8 mg/kg for COVID-19 pneumonia (off label use, intentional use for unlabeled indication) with acute respiratory distress syndrome. During the followup period, the patient died due to severe septic shock. No autopsy information was provided.

The authors described fatal septic shock as an adverse event during therapy with tocilizumab.

Further information has been requested.

Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, Franceschini F, Foca E, Andreoli L and Latronico N
Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy.
Autoimmunity reviews 2020; DOI: 10.1016/J.AUTREV.2020.102568

This case one of is cross referenced with AERs: 2602984 (summary case), 2599700, 2602963 and 2602967 (same literature article).

Relevant Medical History:

Unknown

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events



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Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Polymerase chain reaction					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	DEXAMETHASONE	20 MG/	Unknown					
2	HYDROXYCHLOROQUIN E	40 MG/	Unknown					

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text: Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, Franceschini F, Foca E, Andreoli L and Latronico N Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy.. Autoimmunity reviews 2020;:-.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17798503

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 05-Apr-2020
Outcomes: DE,LT,
Application Type: BLA
FDA Rcvd Date: 25-May-2020
Mfr Rcvd Date: 15-May-2020
Mfr Control #: US-SA-2020SA098975
Application #: 761037

Patient Information:

Age: 50 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	400 mg, single, 1X	COVID-19	04-Apr-2020	04-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	10343 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
Aspartate aminotransferase increased	NA
Multiple organ dysfunction syndrome	NA
Pneumonia pseudomonal	NA

Event/Problem Narrative:

Based on additional information received on 14-Apr-2020, event of pseudomonas pneumonia was updated to serious fatal and reporter causality for multi organ failure was updated to related.

Based on additional information received on 12-Apr-2020, this non-serious case was upgraded to serious due to addition of fatal event of multiorgan system failure.

Initial information from the Company sponsored study ^{(b) (6)} was received on 05-Apr-2020.

Patient ID ^{(b) (6)} Site: ^{(b) (6)} Country: United States.

Study title: ^{(b) (6)}



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(b) (6)

A 50-year-old, Hispanic, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6)

The patient AST increased on (b) (6) and pseudomonas pneumonia on (b) (6) and multi organ failure on (b) (6)

No relevant medical history was reported.

No relevant concomitant medications were reported.

On (b) (6) the patient experienced earliest symptoms of pneumonia and was admitted to the hospital. SARS-CoV-2 reverse transcription polymerase chain reaction (RT-PCR) test was performed from the nasopharyngeal swab, and the patient was SARS-CoV-2 Virus positive. Chest X-ray showed multifocal bilateral airspace opacities.

On (b) (6) the patient was transferred to intensive care unit (ICU). Electrocardiogram (ECG) was abnormal, with sinus tachycardia and abnormal rhythm. Chest X-ray showed progression of bilateral diffuse heterogeneous airspace opacities with peripheral predominance and similar severe bilateral widespread parenchymal opacities.

On (b) (6) chest X-ray showed extensive bilateral lung opacities with air bronchograms, increased compared to the prior imaging.

On (b) (6) rales/crackles were present were present at lung auscultation. Highest body temperature measured within 24 hours prior to dosing was 101.7 degrees Fahrenheit (F). The patient was using supplemental oxygen by invasive mechanical ventilation with fraction of inspired oxygen (FiO2) set to 60% and oxygen flow rate of 10.2 L/min. Oxygen saturation (SpO2) was 93%. Chest X-ray showed diffuse bilateral lung consolidation, decreased on the left and increased on the right.

On (b) (6) at 04:36, (b) (6) hrs. 24 min after taking study drug, aspartate aminotransferase increased (AST) (intensity: grade 2). No results were provided. No correct treatment was applied. The event was assessed as non-serious adverse event of special interest (AESI). SpO2 increased to 95%.

On (b) (6) at 04:02, the event was considered resolved, when AST level was 101. Alanine aminotransferase (ALT) was 96 and total bilirubin 0.6 mg/dl (reference range 0.1-1.5). Chest X ray showed that extensive airspace disease has progressively worsened and increased.

On (b) (6) at 01:06, (b) (6) days 8 hrs. 54 min after the administration of study drug, respiratory culture was positive for 1 plus Pseudomonas aeruginosa and the patient was diagnosed with pseudomonas pneumonia (grade 4; AESI, seriousness: life threatening) (Clinically significant invasive 2/3, (b) (6) date: (b) (6) Severity: bacterial or fungal infections). AST decreased further to 60. ALT was 85.



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Chest X-ray showed progression of bilateral diffuse airspace consolidation with relative sparing of the lung apices. On the same day the patient received vancomycin at a dose of 2000 mg, daily via intravenous route (as a corrective treatment for Pseudomonas pneumonia). Details regarding blood culture tests were not reported.

On (b) (6) SpO2 93 %, ALT and AST were within referent ranges.

On (b) (6) SpO2 decreased to 58%. Chest X-ray showed bilateral airspace disease with consolidation. Some areas were improved while other areas have progressed. Bilateral airspace disease and consolidation.

On (b) (6) SpO2 was 78%.

On (b) (6) SpO2 was 88%, pulse increased to 140 beats bpm (per minute), blood pressure was 95/62 mmHg and respiratory rate was 34 rpm (respirations per minute). On the same day, (b) (6) days 4 hrs. 23 min after the administration of study drug, despite maximal care, the patient died due to multiorgan system failure at 20:35 (Grade: 5) and pseudomonas pneumonia. Information regarding corrective treatment was not provided. Autopsy was not performed.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

On (b) (6), the event Psuedomonas pneumonia (onset: (b) (6)) was downgraded to non-serious non-AESI and inactivated by the investigator.

Action taken with study drug in response to the events was not applicable.

Corrective treatment: vancomycin for pseudomonas pneumonia, none for AST increased, not reported for multi organ failure

Outcome: recovered for AST increased, fatal for multiorgan system failure, not recovered for pseudomonas pneumonia.

Seriousness criteria: fatal for multiorgan system failure, life threatening for pseudomonas pneumonia

For Pneumonia pseudomonal (onset (b) (6)):
Relationship with IP according to investigator: reasonable possibility.
Relationship with IP according to company: reportable.

Investigator causality rationale: Per Principal Investigator (PI).

Company causality rationale: A 50-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced



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pseudomonas pneumonia confirmed by respiratory culture was positive for Pseudomonas aeruginosa (b) (6) days after receiving study drug. Based on a plausible temporal association between study drug administration and the reported events and a known fact that higher rate of bacterial infections was observed in patients treated with sarilumab, causality for the event is assessed as related to study drug. The event is not related to any clinical trial procedure. Other possible confounder is bacterial superinfection in a setting of pre-existing worsening infection where the patient had already been compromised such as patient's COVID-19 pneumonia.

For Multiple organ dysfunction syndrome:

Relationship with IP according to investigator: reasonable possibility

Investigator causality rationale: Per Principal Investigator (PI). Previous Investigator causality assessment on 12-Apr-2020 was Not Related with same rationale.

Relationship with IP according to company: not reportable.

Company causality rationale: A 50-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced multi organ system failure and subsequent death, after receiving the study drug. The event multi organ system failure is assessed as not related to study drug or any clinical trial procedure since it is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age.

For Aspartate aminotransferase increased:

Relationship with IP according to investigator: reasonable possibility

Investigator causality rationale: Per Principal Investigator (PI).

Relationship with IP according to company: reportable.

Company causality rationale: A 50-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced AST increased (b) (6) days after receiving study drug. Based on a plausible temporal relationship between study drug and the reported event and known potential effect of study drug on functional liver enzymes, causality for the event AST increased is assessed as related to study drug. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation. The event AST increased is not related to any clinical trial procedure.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow-up: 12-Apr-2020:

The Investigator provided the following updates: new events of Pseudomonas pneumonia and Multiorgan system failure, event course, relevant tests and corrective treatment added.

Follow-up: 14-Apr-2020:

The Investigator provided the following updates: seriousness, outcome and end date for event Pseudomonas pneumonia updated, causality assessment to study drug for event Multiorgan system failure updated.

Follow up: 08-May-2020

The investigator provided the following updates: new event of Pseudomonas pneumonia added; cause of death updated.



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Follow up: 15-May-2020 and 18-May-2020

The investigator provided the following updates: Pseudomonas pneumonia (onset date (b) (6)) seriousness criteria updated; outcome updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	96	UNK			Y
Chest X-ray					Y
Culture					Y
Bilirubin total	0.6	mg/dL	0.1	1.5	N
Chest X-ray					Y
Chest X-ray					Y
Pulse rate	140	beats/min			Y
Oxygen saturation	93	%			N
Aspartate aminotransferase	101	UNK			Y
Chest X-ray					Y
Respiratory rate	34	breaths/min			N
Chest X-ray					Y
Viral test					N
Alanine aminotransferase	85	UNK			Y



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase					Y
Aspartate aminotransferase	60	UNK			Y
Aspartate aminotransferase	60	UNK			Y
Aspartate aminotransferase					Y
Blood pressure	95/62	mmHg			Y
Oxygen saturation	58	%			N
Chest X-ray					Y
Chest X-ray					Y
Electrocardiogram					Y
Oxygen saturation	78	%			N
Alanine aminotransferase	85	UNK			Y
Aspartate aminotransferase					Y
Chest X-ray					Y
Oxygen saturation	95	%			N
Oxygen saturation	90	%			N
Oxygen saturation	93	%			N
Oxygen saturation	88	%			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17798851

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 02-Apr-2020 Outcomes: DE,HO, Application Type: ANDA

FDA Rcvd Date: 18-May-2020 Mfr Rcvd Date: 10-May-2020 Mfr Control #: ES-TEVA-2020-ES-1235527 Application #: 040081

Patient Information:

Age: 72 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	HIDROXICLOROQUINA (2143A)		400 MG/	Oral	400 MG DAY	COVID-19 pneumonia	26-Mar-2020	02-Apr-2020
2	LINEZOLID (1279A)		600 MG/Q12H	Intravenous (not otherwise specified)	1200 Milligram Daily;		28-Mar-2020	16-Apr-2020
3	MEROPENEM (7155A)		1 G/Q8H	Intravenous (not otherwise specified)	3 Gram Daily;		04-Apr-2020	19-Apr-2020
4	METAMIZOL (111A)		2 G/Q8H	Intravenous (not otherwise specified)	6 Gram Daily;		13-Apr-2020	16-Apr-2020
5	PIPERACILINA TAZOBACTAM 4G/0,5G		1 DF/	Intravenous (not otherwise specified)	1 Dosage form, C/8H		04-Apr-2020	07-Apr-2020
6	ROACTEMRA 20 mg/ml, CONCENTRADO PARA SOLUCION PARA PERFUSION		600 MG/		600mg	Acute respiratory distress syndrome	27-Mar-2020	27-Mar-2020
7	ROACTEMRA 20 mg/ml, CONCENTRADO PARA SOLUCION PARA PERFUSION					COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	HIDROXICLOROQUINA (2143A)	22 Day	Yes	NA	Unknown			TEVA	
2	LINEZOLID (1279A)	20 Day	Yes	NA	Unknown			TEVA	



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17798851

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC	
3 MEROPENEM (7155A)	13 Day	Yes	NA	Unknown					
4 METAMIZOL (111A)	4 Day	Yes	NA	Unknown					
5 PIPERACILINA TAZOBACTAM 4G/0,5G	13 Day	Yes	NA	Unknown					
6 ROACTEMRA 20 mg/ml, CONCENTRADO PARA SOLUCION PARA PERFUSION	21 Day	Yes	NA	Unknown					
7 ROACTEMRA 20 mg/ml, CONCENTRADO PARA SOLUCION PARA PERFUSION	21 Day	Yes	NA	Unknown					

Event Information:

Preferred Term (MedDRA @ Version: 23.1)

ReC

Drug reaction with eosinophilia and systemic symptoms

NA

Hypofibrinogenaemia

NA

Upper gastrointestinal haemorrhage

NA

Event/Problem Narrative:

10-May-2020, Spontaneous, Health authority Serious report (Report duplicates - AGEMED: ES-AEMPS-627000)

A Physician reported the case of a 72-Years-old Male patient who received HIDROXICLOROQUINA (2143A) (HYDROXYCHLOROQUINE, Product cannot be excluded as a Teva product), LINEZOLID (1279A) (LINEZOLID, Product cannot be excluded as a Teva product), PIPERACILINA TAZOBACTAM 4g/0,5g (PIPERACILLIN SODIUM, TAZOBACTAM SODIUM, Product cannot be excluded as a Teva product), MEROPENEM (7155A) (MEROPENEM, not Teva's product), ROACTEMRA 20 mg/ml, CONCENTRADO PARA SOLUCION PARA PERFUSION (TOCILIZUMAB, not Teva's product), METAMIZOL (111A) (METAMIZOLE MAGNESIUM, not Teva's product). The patient took HIDROXICLOROQUINA (2143A) for COVID-19 PNEUMONIA (HYDROXYCHLOROQUINE, Oral, from 26-Mar-2020, until 02-Apr-2020, 400 MG DAY) batch: Unknown, LINEZOLID (1279A) (LINEZOLID, Intravenous (not otherwise specified), from 28-Mar-2020, until 16-Apr-2020, 1200Milligram per day) batch: Unknown, PIPERACILINA TAZOBACTAM 4g/0,5g (PIPERACILLIN SODIUM; TAZOBACTAM SODIUM, Intravenous (not otherwise specified), from 04-Apr-2020, until 07-Apr-2020, 1 Dosage form, C/8H) batch: Unknown, ROACTEMRA 20 mg/ml, CONCENTRADO PARA SOLUCION PARA PERFUSION for ADULT RESPIRATORY STRESS SYNDROME, COVID-19 PNEUMONIA (TOCILIZUMAB, from 27-Mar-2020, until 27-Mar-2020, 600mg) batch: Unknown, MEROPENEM (7155A)



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17798851

(MEROPENEM, Intravenous (not otherwise specified), from 04-Apr-2020, until 19-Apr-2020, 3Gram per day) batch: Unknown, METAMIZOL (111A) (METAMIZOLE MAGNESIUM, Intravenous (not otherwise specified), from 13-Apr-2020, until 16-Apr-2020, 6Gram per day) batch: Unknown.

While on the suspect medications, the patient experienced DRESS SYNDROME(Serious , since (b) (6)); UPPER GASTROINTESTINAL HEMORRHAGE(Serious , since (b) (6)); HYPOFIBRINOGENEMIA(Serious , since (b) (6) until (b) (6) (b) (6)) .

At the time of the report the outcome of the AEs was: DRESS SYNDROME:Not recovered/not resolved, HYPOFIBRINOGENEMIA:Recovered/resolved, UPPER GASTROINTESTINAL HEMORRHAGE:Recovering/resolving. Action taken with suspect drugs: HIDROXICLOROQUINA (2143A) - Drug discontinued; LINEZOLID (1279A) - Drug discontinued; PIPERACILINA TAZOBACTAM 4g/0,5g - Drug discontinued; ROACTEMRA 20 mg/ml, CONCENTRADO PARA SOLUCION PARA PERFUSION - Drug discontinued; MEROPENEM (7155A) - Drug discontinued; METAMIZOL (111A) - Drug discontinued.

The patient's medical history was not reported.

On (b) (6) the patient died. The patient died from SEPTIC SHOCK, COVID-19 PNEUMONIA. It is unknown whether an autopsy was performed.

The patient's concomitant medication were unspecified.

The patient's past medication were unspecified.

Lab tests were not reported.

This case was considered serious based on the following criteria: (Hospitalization Required)

Because this is a spontaneous case, regulatory distribution will be handled as though it is a related case.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17798851

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: TEVA

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17799090

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 03-Apr-2020 Outcomes: DE,OT, Application Type: ANDA

FDA Rcvd Date: 18-May-2020 Mfr Rcvd Date: 10-May-2020 Mfr Control #: ES-TEVA-2020-ES-1235781 Application #: 065150

Patient Information:

Age: 62 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	AZITROMICINA (7019A)		500 MG/QD	Oral	500 Milligram Daily;	COVID-19 pneumonia	27-Mar-2020	01-Apr-2020
2	CEFTRIAXONA (501A)		2 G/	Intravenous (not otherwise specified)	2 Gram Daily;		27-Mar-2020	01-Apr-2020
3	DEXAMETASONA (722A)		20 MG/	Intravenous (not otherwise specified)	20 MG	COVID-19	29-Mar-2020	01-Apr-2020
4	ENOXAPARINA (2482A)		80 MG/	Subcutaneous	80 MG	Thrombosis prophylaxis	01-Apr-2020	03-Apr-2020
5	HIDROXICLOROQUINA (2143A)		400 MG/	Oral	400 Milligram Daily;	COVID-19 pneumonia	27-Mar-2020	02-Apr-2020
6	ROACTEMRA		600 MG/	Intravenous (not otherwise specified)	600 MG	COVID-19 pneumonia	27-Mar-2020	27-Mar-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	AZITROMICINA (7019A)	13 Day	Yes	NA	Unknown				
2	CEFTRIAXONA (501A)	13 Day	Yes	NA	Unknown				
3	DEXAMETASONA (722A)	11 Day	Yes	NA	Unknown				
4	ENOXAPARINA (2482A)	8 Day	Yes	NA	Unknown				
5	HIDROXICLOROQUINA (2143A)	13 Day	Yes	NA	Unknown			TEVA	
6	ROACTEMRA	13 Day	Yes	NA	Unknown				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17799090

Event Information:

Preferred Term (MedDRA Version: 23.1)

ReC

Anaemia

NA

Hypocoagulable state

NA

Hypofibrinogenaemia

NA

Thrombocytopenia

NA

Event/Problem Narrative:

10-May-2020, Spontaneous, Health authority Serious report(Report duplicate - AGEMED: ES-AEMPS-628603)

A Physician reported the case of a 62-Years-old Male patient who received AZITROMICINA (7019A) (AZITHROMYCIN, Product cannot be excluded as a Teva product), HIDROXICLOROQUINA (2143A) (HYDROXYCHLOROQUINE, Product cannot be excluded as a Teva product), ROACTEMRA (not Teva's product), DEXAMETASONA (722A) (DEXAMETHASONE, not Teva's product), CEFTRIAXONA (501A) (CEFTRIAXONE, not Teva's product), ENOXAPARINA (2482A) (ENOXAPARIN, not Teva's product).

The patient took AZITROMICINA (7019A) for COVID-19 PNEUMONIA (AZITHROMYCIN, Oral, from 27-Mar-2020, until 01-Apr-2020, 500 Milligram per day) batch: Unknown, HIDROXICLOROQUINA (2143A) for COVID-19 PNEUMONIA (HYDROXYCHLOROQUINE, Oral, from 27-Mar-2020, until 02-Apr-2020, 400Milligram per day) batch: Unknown, ROACTEMRA for SRAS COVID 19 (Intravenous (not otherwise specified), from 27-Mar-2020, until 27-Mar-2020, 600 MG) batch: Unknown, DEXAMETASONA (722A) for SRAS COVID19 (DEXAMETHASONE, Intravenous (not otherwise specified), from 29-Mar-2020, until 01-Apr-2020, 20 MG) batch: Unknown, CEFTRIAXONA (501A) (CEFTRIAXONE, Intravenous (not otherwise specified), from 27-Mar-2020, until 01-Apr-2020, 2Gram per day) batch: Unknown, ENOXAPARINA (2482A) for HIGH RISK ETE (ENOXAPARIN, Subcutaneous, from 01-Apr-2020, until 03-Apr-2020, 80 MG) batch: Unknown. While on the suspect medications, the patient experienced THROMBOCYTOPENIA(Serious , since 08-Apr-2020); HYPOFIBRINOGENEMIA(Serious , since 03-Apr-2020, until 03-Apr-2020); ANAEMIA(Serious , since 14-Apr-2020); HYPOCOAGULABLE STATE(Serious , since 03-Apr-2020, until 10-Apr-2020) .

At the time of the report the outcome of the AEs were: THROMBOCYTOPENIA: Not recovered/not resolved, HYPOCOAGULABLE STATE:Recovered/resolved, ANAEMIA: Not recovered/not resolved, HYPOFIBRINOGENEMIA: Recovered/resolved.

Action taken with suspect drugs: AZITROMICINA (7019A) - Drug discontinued; HIDROXICLOROQUINA (2143A) - Drug discontinued; ROACTEMRA - Drug discontinued; DEXAMETASONA (722A) - Dose Reduced; CEFTRIAXONA (501A) - Drug discontinued; ENOXAPARINA (2482A) - Dose Reduced.

The patient's medical history was not reported.

On ^{(b) (6)} the patient died. The patient died from RESPIRATORY INSUFFICIENCY. It is unknown whether an autopsy was performed..

The patient's concomitant medication were unspecified.

The patient's past medication were unspecified.

Lab tests were not reported.

This case was considered serious based on the following criteria: (Other Serious (Important Medical Events))

Because this is a spontaneous case, regulatory distribution will be handled as though it is a related case.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17799090

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: TEVA

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17800626

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ITA **Event Date:** **Outcomes:** DE, **Application Type:** BLA

FDA Rcvd Date: 19-May-2020 **Mfr Rcvd Date:** 11-May-2020 **Mfr Control #:** IT-ROCHE-2599700 **Application #:** 125276

Patient Information:

Age: **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		8 MG/KG/Q12H	Intravenous (not otherwise specified)		COVID-19 pneumonia		
2	TOCILIZUMAB					Acute respiratory distress syndrome		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		Unk	NA	UNKNOWN				
2	TOCILIZUMAB		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1)	ReC
Intentional product use issue	NA
Off label use	NA
Septic shock	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17800626

Event/Problem Narrative:

AER 2599700 is a literature - non-interventional study case, received on 11/May/2020 from a physician in Italy. It concerns a patient of unspecified demographics who received tocilizumab intentionally for unlabeled indication and died due to septic shock whilst enrolled in a prospective series study of patients with confirmed COVID-19 pneumonia and acute respiratory distress syndrome (ARDS) requiring ventilatory support to determine whether administration of tocilizumab (TCZ), was associated with improved outcome.

Between 09/Mar/2020 and 20/Mar/2020, 100 consecutive patients admitted to authors hospital were prospectively studied. The median age was 62 years (range: 57-71) and most patients were male (male/female: 88/12). Comorbidities were present in more than half of patients with arterial hypertension being the most common one (46%), followed by obesity (31%), diabetes (17%) and cardiovascular disease (16%). Other comorbidities were chronic kidney disease (11%), chronic obstructive pulmonary disease (9%) and malignancy (6%). There were patients with overweight (34%). On admission the most common symptoms were fever (85%), dyspnea (73%) and cough (55%) with a median time from illness onset and hospital admission of 6 [range: 4-8] days. Other symptoms included dyspnea (73%) and diarrhea (9%). Patients were selected based on disease severity and absence of contraindication to TCZ, including a suspected or confirmed bacterial infection, an active diverticulitis or gastrointestinal tract perforation, neutropenia (0.500×10^3 cells/uL) and thrombocytopenia (50×10^3 cells/uL). Respiratory disease severity was assessed by a locally developed bedside respiratory severity scale, the Brescia COVID-19 Respiratory Severity Scale (BCRSS), a 9-category ordinal severity scale ranging from 0 (asymptomatic patient) to 8 (a critically ill patient with tracheal intubation, mechanical ventilation and advanced intensive care unit (ICU) management. BCRSS classifies the patients severity based on the need for oxygen supplementation and ventilatory support, offering a step-up therapeutic approach for the use of antiviral and anti-inflammatory drugs. In all patients SARS-CoV-2 infection was confirmed by real time-polymerase chain reaction (PCR) on nasopharyngeal swab and pneumonia was documented by chest x-ray or computed tomography. The most common radiological findings were bilateral pulmonary infiltration, ground glass opacities and consolidations. All the patients were treated with a standard pharmacological protocol, including antiviral drugs (lopinavir 400 mg and ritonavir 100 mg twice a day or remdesivir 100 mg/day), antibiotic prophylaxis (azithromycin, ceftriaxone or piperacillin/tazobactam), hydroxychloroquine 400 mg/day and dexamethasone 20 mg/day and received non-invasive ventilation (NIV) or mechanical ventilation with tracheal intubation (BCRSS score ≥ 3). Patients received TCZ based on rapidly progressive respiratory failure, refractory to pharmacological therapy and ventilatory support. TCZ was administered at a dosage of 8 mg/kg (max 800 mg) by two consecutive intravenous infusions 12 hours apart. A third infusion, 24 hours apart from the second was optional based on clinical response. Median time from hospital admission and TCZ infusion was 5 day (range: 3-8) and median days between onset of symptoms and TCZ infusion was 12 days (range: 9-14). All patients treated with TCZ had acute respiratory failure requiring ventilatory support (BCRSS ≥ 3). Fifty-seven patients were treated with NIV (BCRSS =3) notably, these patients were treated in the general ward as no ICU beds and ventilators were available. Forty-three patients were treated in the ICU after tracheal intubation and mechanical ventilation with a BCRSS before treatment of 7 [range: 5-8]. Eighty-seven patients (87%) received 2 infusions of TCZ, 13 patients (13%) 3 infusions. Clinical and laboratory data of all patients were collected at hospital admission, shortly before TCZ administration and 10 days after. At 24-72 hours after TCZ administration, 58 patients (58%) showed a rapid improvement of clinical and respiratory condition, 37 (37%) stabilized compared to the rapidly declining pre-TCZ condition, and 5 (5%) worsened (of whom 4 died). At 10 days, the respiratory condition was improved or stabilized in 77 (77%) patients, of whom 61 showed a significant clearing of diffuse bilateral opacities on chest x-ray and 15 were discharged from the hospital. Respiratory condition worsened in 23 (23%) patients, of whom 20 died. Of the 57 patients treated outside the ICU, 37 (65%) improved and suspended NIV (BCRSS 1 [range: 0-2]), 7 (12%) patients remained stable in NIV, and 13 (23%) patients worsened (10 died, 3



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were admitted to ICU). Of the 43 patients treated in ICU, 32 (74%) improved (17 of them were taken off the ventilator and were discharged to the ward), 1 (2%) remained stable (BCRSS class 5) and 10 (24%) died (all of them had BCRSS $\geq$ 7 before TCZ). Laboratory findings were collected, at the time of hospital admission, before TCZ administration (1-12 hour prior) and post TCZ administration (10 days after administration) and all the data presented as median values. In all patients (n=100) laboratory findings as follows [at the time of admission, before TCZ administration and post TCZ administration]: white blood cell count [6.0x 10³ macro/L (range: 4.5-8.4), 8.8 (6.5-11.4) and 11.3 (8.0-15.3)], neutrophils [4.9x 10³ macro/L (range: 3.3-7.8), 6.7 (4.9-9.7) and 8.9 (5.8-11.8)], lymphocytes [0.78x 10³ macro/L (range: 0.51-1.10), 0.62 (0.41-0.84) and 0.79 (0.61-1.16)], platelets [177x 10³ macro/L (range: 141-224, 220 (174-294) and 205 (142-289)], haemoglobin [13.6 g/dL (range: 12.8-14.8), 12.4 (11.1-13.6) and 12.6 (11.3-13.8)], C-reactive protein [97 mg/L (range: 38-159), 113 (45-169) and 2 (1-5)], ferritin [1004 macrog/L (range: 268-3730), 1689 (981-3533) and 1352 (806-2422)], D-Dimer [525 ng/mL (range: 283-1100), 979 (456-3640) and 2331 (887-3801)], fibrinogen [508 mg/dL (range: 421-627), 520 (436-714) and 217 (150-285)], aspartate aminotransferase [55 U/L (range: 41-82), 47 (35-72) and 43 (30-69)], alanine aminotransferase [39 U/L (range: 26-62), 43 (28-61) and 75 (44-129)], lactate dehydrogenase [413 U/L (range: 281-542), 428 (293-537) and 390 (319-531)], triglycerides [106 mg/dL (range: 91-135), 160 (113-219) and 189 (164-220)], cholesterol [112 mg/dL (range: 89-134), 120 (107-139) and 271 (220-355)], creatine kinase [161 U/L (range: 87-279), 105 (50-190) and 87 (39-181)] and troponin T [18 ng/L (range: 13-21), 11 (8-23) and 25 (16-49)]. In improved or stable patients (n=77) laboratory findings as follows [at the time of admission, before TCZ administration and post TCZ administration]: white blood cell count [5.7x 10³ macro/L (range: 4.4-8.3), 7.9 (6.0-10.8) and 10.9 (7.6-15.0)], neutrophils [4.4x 10³ macro/L (range: 3.0-7.3), 6.1 (4.4-9.0) and 7.9 (4.6-11.3)], lymphocytes [0.84x 10³ macro/L (range: 0.53-1.2), 0.69 (0.43-0.86) and 0.81 (0.61-1.30)], platelets [179x 10³ macro/L (range: 139-224), 224 (181-296) and 205 (154-297)], haemoglobin [13.8 g/dL (range: 12.8-14.8), 12.3 (11.1-13.3) and 12.4 (10.9-13.5)], C-reactive protein [81 mg/L (range: 38-138), 113 (43-170) and 2 (1-4)], ferritin [905 macrog/L (range: 270-1705), 1568 (946-2664) and 1308 (814-2397)], D-Dimer [383 ng/mL (range: 263-613), 746 (443-3444) and 2210 (729-3257)], fibrinogen [508 mg/dL (range: 458-653), 520 (473-713) and 203 (148-274)], aspartate aminotransferase [53 U/L (range: 41-77), 46 (33-64) and 41 (30-64)], alanine aminotransferase [39 U/L (range: 27-60), 39 (27-54) and 76 (44-130)], lactate dehydrogenase [402 U/L (range: 285-513), 418 (288-481) and 376 (317-504)], triglycerides [104 mg/dL (range: 92-129), 144 (102-207) and 190 (163-219)], cholesterol [112 mg/dL (range: 94-127), 116 (107-126) and 269 (215-336)], creatine kinase [172 U/L (range: 79-336), 104 (46-91) and 85 (38-164)], and troponin T [18 ng/L (range: 13-21), 10 (7-15) and 19 (15-55)]. In worsened or deceased patients (n=23) laboratory findings as follows [at the time of admission, before TCZ administration and post TCZ administration]: white blood cell count [7.0x 10³ macro/L (range: 4.9-9.7), 9.7 (7.4-15.4) and 13.8 (9.4-25.9)], neutrophils [6.1x 10³ macro/L (range: 3.8-8.6, 9.5 (6.4-14.3) and 11.4 (10.1-25.8)], lymphocytes [0.55x 10³ macro/L (range: 0.46-0.83), 0.43 (0.32-0.72) and 0.72 (0.52-1.10)], platelets [172x 10³ macro/L (range: 145-219), 214 (141-266) and 137 (102-323)], haemoglobin [13.6 g/dL (range: 12.6-14.7), 12.4 (11.4-14.7) and 13.6 (12.4-14.5)], C-reactive protein [145 mg/L (range: 57-205), 118 (71-164) and 5 (5-7)], ferritin [3733 macrog/L (range: 1937-5020), 3283 (988-4247) and 1863 (790-6261)], D-Dimer [3854 ng/mL (range: 968-5250), 2407 (760-5250) and 5250 (3328-5250)], fibrinogen [482 mg/dL (range: 352-587), 530 (350-765) and 218 (168-316)], aspartate aminotransferase [61 U/L (range: 48-117), 52 (41-80) and 69 (44-77)], alanine aminotransferase [40 U/L (range: 24-73), 59 (31-78) and 63 (42-96)], lactate dehydrogenase [570 U/L (range: 247-764), 544 (365-749) and 565 (406-870)], triglycerides [109 mg/dL (range: 88-153), 206 (147-233) and 303 (228-432)], cholesterol [117 mg/dL (range: 87-156), 133 (123-141) and 178 (175-222)], creatine kinase [152 U/L (range: 123-208), 116 (70-156) and 167 (93-188)], and troponin T [18 ng/L (range: 14-40), 23 (17-51) and 42 (26-42)]. Interleukin-6 (IL6) data available for 42 patients. in improved or stabled patients before TCZ administration was 16 (9-94) and post TCZ was 1679 (335-2227). In worsened or deceased patients pre TCZ administration value was 56 (25-157) and post



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TCZ value was 5000 (5000-5000). At the time of TCZ administration, all patients presented lymphopenia (below 1×10^3 cells/uL) and high levels of inflammatory markers, including C-reactive protein (CRP), fibrinogen, ferritin and interleukin 6 (IL-6). Ten days after, the lymphocyte count increased, especially in improved patients. CRP, fibrinogen and ferritin levels decreased toward the range of normality, while D-Dimer and IL-6 levels increased both in improved and worsened patients. During 10 days of followup, three patients had adverse events.

This case concerns 1st patient of 3 patients who developed adverse event.

The patients concomitant medications included hydroxychloroquine and dexamethasone.

On an unspecified date, the patient started therapy with intravenous tocilizumab infusion 8 mg/kg for COVID-19 pneumonia (off label use, intentional use for unlabeled indication) with acute respiratory distress syndrome. During the followup period, the patient died due to severe septic shock. No autopsy information was provided.

The authors described fatal septic shock as adverse event during therapy with tocilizumab.

Further information has been requested.

Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, Franceschini F, Foca E, Andreoli L and Latronico N
Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy.
Autoimmunity reviews 2020; doi: 10.1016/J.AUTREV.2020.102568

This case is cross referenced with AERs: 2602984 (summary case), 2599700, 2602963 and 2602967 (same literature article).

Relevant Medical History:

Unknown

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17800626

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Polymerase chain reaction					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	DEXAMETHASONE	20 MG/	Unknown					
2	HYDROXYCHLOROQUIN E	40 MG/	Unknown					

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:

Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, Franceschini F, Foca E, Andreoli L and Latronico N Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy.. Autoimmunity reviews 2020;:-.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17805686

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 10-May-2020
Outcomes: DE,HO,LT,
Application Type: BLA
FDA Rcvd Date: 25-Jun-2020
Mfr Rcvd Date: 16-Jun-2020
Mfr Control #: US-SA-2020SA126157
Application #: 761037

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	400 mg, 1X	COVID-19	06-May-2020	06-May-2020
2	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	400 mg, 1X		07-May-2020	07-May-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	7627 MINUTES	NA	NA				SANOFI	
2	SARILUMAB	7627 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Alanine aminotransferase increased	NA
Aspartate aminotransferase increased	NA
Multiple organ dysfunction syndrome	NA
Multiple organ dysfunction syndrome	NA
Pneumonia	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17805686

Event/Problem Narrative:

Based on information received on 29-May-2020, the events AST increased (onset (b) (6)), ALT increase (onset (b) (6)) and AST increase (onset (b) (6)) were downgraded from non-serious AESIs to non-serious non-AESIs and inactivated, as the reported events information was merged with previously reported events with the same PT.

Based on additional information received on 13-May-2020, case initially considered as non-serious was upgraded to serious by addition of event Pneumonia and case upgraded from non-susar to susar.

Initial information received on 11-May-2020 regarding a solicited valid serious case received from (lp) regeneron-usa gsa-ppc under reference number (b) (6) on 11-May-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6)
Patient ID: (u) (v) Site: (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

A 65-year-old, Black, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6) The patient experienced non-serious adverse event of special interest (AESI) ALI increased and AST increased on (b) (6) serious AESI pneumonia on (b) (6) and SAEs Multiorgan failure on (b) (6) and (b) (6) after receiving study drug.

Relevant medical history included hypertension and chronic kidney disease.

No relevant concomitant medications were reported.

On 24-Apr-2020, the patient had earliest onset of symptoms of pneumonia.

On 02-May-2020, chest X-ray showed moderate new diffuse bilateral lung opacities, which could reflect pneumonia or edema.

On 04-May-2020 chest X-ray showed increased lung opacities which remained asymmetric, greater on the right side, with some improvement in the left midlung; extensive bilateral pulmonary infiltrates were noted. The highest temperature measured within 24 hours prior to dosing was 38.9 degrees Celsius (C).

On (b) (6) patients blood pressure was 158/73 mmHg, oxygen saturation (SpO2) was 91 %, body temperature 38.5 C, pulse 129 beats per minute (bpm) and respiratory rate 28 respirations per minute (rpm). Biochemistry and hematology results included alanine aminotransferase (ALT) 46 U/L (10-65), aspartate aminotransferase (AST) 38 U/L (10-45), total bilirubin 0.3 mg/dl (0.2-1.1), creatinine 1.31 mg/dl (0.7-1.3), white blood cells (WBC) 12.7 K/uL (3.8-11), absolute neutrophil count 11.95 K/uL (1.9-7.4) and platelets 380 K/uL (150-400). CT scan showed extensive regions of consolidation in both lungs upper and lower lobe. The patient was using oxygen supplementation by non-rebreather mask and invasive mechanical ventilation, and vasopressors and required treatment in intensive care unit. Rales/crackles were not present on lung auscultation. Chest X-ray revealed extensive regions of consolidation in both lungs, upper and lower lobes;



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remainder the lungs, particularly upper lobes demonstrated uniform ground-glass infiltrative character. On the next day, chest X-ray presented with increasing consolidation in the right midlung, with peripheral ground-glass opacity throughout the left lung. In the following days, AST and ALT levels were gradually increasing.

On (b) (6) ALT was 121 and AST was 84.

On (b) (6) chest X-ray showed improved perihilar infiltrates and persistent diffuse mixed interstitial and alveolar opacity. Same day at 06:19, (b) (6) days 13 hrs. 26 min after administration of study drug, the patient experienced increased ALT (Grade 2) and AST (Grade 3), with values of 226 and 255, respectively. Corrective treatment included monitoring. These events were considered as non-serious adverse events of special interest (AESI) ALT or AST increase).

On (b) (6) ALT increased to 264 and AST decreased to 208. Respiratory rate was 42 rpm.

On (b) (6) (b) (6) days 7 hrs. 7 min after administration of study drug, the patient developed pneumonia (Grade 4). The event was assessed as life threatening and AESI (Clinically significant invasive bacterial or fungal infections) leading to hospitalization. Unspecified culture tested positive for Acinetobacter baumannii complex. SpO2 was 90%. The patient received unspecified medication as corrective treatment for the event.

On (b) (6) ALT decreased to 163, and AST to 78. Chest X-ray showed mildly worsened bilateral pulmonary opacities. SpO2 was 87% and respiratory rate was 45 rpm.

On (b) (6) (b) (6) days 7 hrs 7 min after the administration of study drug, the patient started experiencing life-threatening multiorgan failure (Grade 4). The patient was placed on constant vasopressors, as corrective treatment, and monitored. Chest X-ray revealed slightly worsened diffuse bilateral airspace disease. ALT and AST were 110 and 58, respectively.

On (b) (6) chest X-ray presented with slight improvement of aeration of the lung apices and otherwise stable diffuse bilateral opacities. ALT and AST increased to 136 and 119, respectively.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

On (b) (6) SpO2 decreased to 75%. ALT and AST were 117 and 88, respectively. Multiorgan failure was deemed resolved.

On (b) (6) the patient developed severe acute hypoxic respiratory failure due to COVID pneumonia that ultimately was refractory to all therapies. Vital signs and laboratory tests were as follows: SpO2 62%, respiratory rate 40 rpm, blood pressure 84/53 mmHg, creatinine 5.02, ALT 92, AST 68, WBC 19.2 and neutrophils 15.67. On the same day at 22:38, (b) (6) days 5 hrs 45 min after the administration of study drug, the event multiorgan failure increased in severity (Grade 5) and the patient died due to multiorgan failure. Autopsy was not performed.

At the time of death, pneumonia, elevated AST and ALT had not resolved.

Action taken with study drug in response to the events was not applicable.



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For both the events of multiorgan failure:

Relationship with IP according to investigator: no reasonable possibility

Investigator causality rationale: Per Principal Investigator not related.

Relationship with IP according to company: not reportable

Company causality rationale: 65-year-old, male patient with severe or critical COVID-19 and worsening pneumonia experienced multiorgan failure, (b) (6) days after receiving the last dose of the study drug. After additional (b) (6) days, the event of multiorgan failure increased in severity and the patient died due to multiorgan failure. The events of multiorgan failure are assessed as not related to study drug or to any clinical trial procedure. The events are secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and comorbidities such as hypertension and chronic kidney disease.

For Pneumonia:

Relationship with IP according to investigator: reasonable possibility

Investigator causality rationale: Per Principal Investigator related.

Relationship with IP according to company: reportable

Company causality rationale: A 65-year-old, male patient with severe or critical COVID-19 experienced pneumonia (b) (6) days after receiving the last dose of the study drug. Based on a plausible temporal association between study drug administration and the reported event and a known fact that higher rate of infections was observed in patients treated with sarilumab, causality for the event pneumonia is assessed as related to study drug. The event is not related to any clinical trial procedure.

Alanine aminotransferase increased and Aspartate aminotransferase increased:

Relationship with IP according to investigator: reasonable possibility

Investigator causality rationale: Related per Principal Investigator (PI). No alternative explanation was provided.

Relationship with IP according to company: reportable

Company causality rationale: A 65-year-old, male patient enrolled in the trial experienced increased AST and increased ALT, after receiving the study drug. Patient's baseline AST and ALT values were within reference ranges and increased significantly (b) (6) days after receiving the last dose of the study drug. Based on a plausible temporal association between study drug administration and the reported events and known potential effect of study drug on functional liver enzymes, causality for both events is assessed as related to study drug and not related to any clinical trial procedure. It was observed that higher rate of patients treated with sarilumab experience transaminases elevation.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up received date: 13-May-2020:

The Investigator provided the following updates: new events with all relevant information added. Relevant tests, study drug re-dose administration date, event outcome and resolution date, severity, and clinical course updated.

Follow up: 18-May-2020 and 19-May-2020 (processed together)

The Investigator provided the following updates: new events added, clinical course, cause of death and outcome for events ALT increased



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and AST increased updated.

Follow up: 29-May-2020 and 01-Jun-2020 (processed together):

The Investigator provided the following updates: onset and resolution date of events ALT and AST increased updated, the events AST increased (onset (b) (6)), ALT increase (onset (b) (6)) and AST increase (onset (b) (6)) downgraded from non-serious AEs to non-serious non-AEs and inactivated, clinical course updated.

Follow-up: 16-Jun-2020:

The Investigator provided the following updates: event outcome, event stop date and SAE criteria for the event Pneumonia updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Chronic kidney disease stage 3			YES	
Hypertension			YES	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Chest X-ray					Y
Absolute neutrophil count	15.67	10 ³ /uL	1.9	7.4	N
Alanine aminotransferase	163	U/L	10	65	N
Alanine aminotransferase	110	U/L	10	65	N
Bilirubin total	0.3	mg/dL	0.2	1.1	N
Creatinine	5.02	mg/dL	0.7	1.31	N
Blood pressure	158/73	mmHg			N
Chest X-ray					Y
Chest X-ray					Y
Oxygen saturation	87	%			N
Platelet count	380	10 ³ /uL	150	400	N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	226	U/L	10	65	N
Alanine aminotransferase	117	U/L	10	65	N
Aspartate aminotransferase	68	U/L	10	45	N
Creatinine	1.31	mg/dL	0.7	1.31	N
CT scan					Y
Pulse rate	129	beats/min			N
Respiratory rate	28	breaths/min			N
Respiratory rate	45	breaths/min			N
White blood cell count	19.2	10 ³ /uL	3.8	11	N
Aspartate aminotransferase	255	U/L	10	45	N
Aspartate aminotransferase	78	U/L	10	45	N
Aspartate aminotransferase	58	U/L	10	45	N
Chest X-ray					Y
Oxygen saturation	62	%			N
Respiratory rate	35	breaths/min			N
Alanine aminotransferase	136	U/L	10	65	N
Aspartate aminotransferase	38	U/L	10	45	N
Aspartate aminotransferase	139	U/L	10	45	N
Blood pressure	84/53	mmHg			N
Oxygen saturation	91	%			N
Alanine aminotransferase	214	U/L	10	65	N
Alanine aminotransferase	92	U/L	10	65	N
Body temperature	38.5	Cel			N
Chest X-ray					Y
Absolute neutrophil count	11.95	10 ³ /uL	1.9	7.4	N
Oxygen saturation	75	%			N
White blood cell count	12.7	10 ³ /uL	3.8	11	N
Alanine aminotransferase	46	U/L	10	65	N
Alanine aminotransferase	121	U/L	10	65	N
Alanine aminotransferase	264	U/L	10	65	N
Aspartate aminotransferase	208	U/L	10	45	N
Aspartate aminotransferase	92	U/L	10	45	N
Chest X-ray					Y
Chest X-ray					Y
Chest X-ray					Y
Culture NOS					Y
Aspartate aminotransferase	119	U/L	10	45	N



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FOIA Case Report Information

Case ID: 17805686

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Aspartate aminotransferase	84	U/L	10	45	N
Oxygen saturation	90	%			N
Respiratory rate	42	breaths/min			N
Respiratory rate	40	breaths/min			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	PLASMA	218.6 ML/1X	Intravenous (not otherwise specified)	218.6 mL, 1X	COVID-19	03-May-2020	04-May-2020	9 DAY

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17807391

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 09-Apr-2020 Outcomes: DE,LT, Application Type: BLA

FDA Rcvd Date: 01-Jul-2020 Mfr Rcvd Date: 22-Jun-2020 Mfr Control #:US-SA-2020SA095069 Application #: 761037

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	200 mg injection	COVID-19	03-Apr-2020	03-Apr-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	13370 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Acute respiratory failure	NA
Alanine aminotransferase increased	NA
Aspartate aminotransferase increased	NA
Pneumonia pseudomonal	NA
Pneumothorax	NA
Pseudomonal bacteraemia	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17807391

Event/Problem Narrative:

Initial information received on 09-Apr-2020 regarding a solicited valid serious case received from (lp) regeneron-usa gsa-pcp under reference 2020-29994 on 09-Apr-2020 and transmitted to Sanofi on 12-APR-2020, in the scope of company sponsored study (b) (6)

Patient ID: (b) (6) Site: (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

A 75-year-old, Asian, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

The patient experienced SAE (Acute respiratory failure with hypoxia [Acute respiratory failure] (previously reported as Worsening of Acute respiratory failure with hypoxia, initially reported as Acute respiratory failure with hypoxia): Death; Onset date: (b) (6) Severity: Grade 5; Outcome: Fatal; Event resolved on: (b) (6)), before receiving study drug, and SAE (Pneumothorax right-sided [Pneumothorax]: Life-threatening; Onset date: (b) (6) Severity: Grade 4; Outcome: Recovered/ Resolved; Event resolved on: (b) (6)), serious AESI (Sepsis, pseudomonas bacteremia and pneumonia [Pneumonia pseudomonal] (Initially reported as Sepsis [Sepsis]): Life threatening; Serious AESI (clinically significant invasive bacterial or fungal infections) Onset date: (b) (6) Severity: Grade 4; Outcome: Not recovered/Not resolved; Event resolved on: Ongoing) and non-serious AESIs (AST increased [Aspartate aminotransferase increased]: Non-serious AESI (ALT or AST increase); Onset date: (b) (6) Severity: Grade 3; Outcome: Recovered / Resolved; Event resolved on: (b) (6)) (ALT increased [Alanine aminotransferase increased]: Non-serious AESI (ALT or AST increase); Onset date: (b) (6) Severity: Grade 3; Outcome: Recovered / Resolved; Event resolved on: (b) (6)) (Pseudomonas aeruginosa bacteremia gram negative bacilli on blood cultures Pseudomonas aeruginosa [Pseudomonal bacteraemia] (initially reported as Gram negative bacilli on blood cultures [Bacteraemia]): Non-serious AESI (Clinically significant invasive bacterial or fungal infections); Onset date: (b) (6) Severity: Grade 3; Outcome: Not recovered/Not resolved; Event resolved on: Ongoing), after receiving study drug.

The patient's relevant medical history included diabetes with hyperglycaemia.

Concomitant medications reported included Methylprednisone (methylprednisolone), acetaminophen, hydroxychloroquine, and azithromycin.

On (b) (6) the patient experienced earliest symptoms of pneumonia (chills and a dry cough) without rales/crackles present on lung auscultation. The highest temperature that was recorded within 24 hours prior to dosing was 37.0 degree C (Celsius), measured orally. The patient has required treatment in intensive care unit, used invasive ventilation and vasopressors.

On (b) (6) the patient was intubated due to continued respiratory distress. He received antibiotics and plaquenil. He also completed a course of IV steroids. He was later found to have copious secretions with worsening hypoxic and a bronchoscopy was done which showed minimal secretions at that point in time. He had imaging done which demonstrated a large R sided pneumothorax and a chest tube was



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subsequently placed. He continued to remain intubated with very poor mental status despite weaning sedation. Palliative care was consulted and after a meeting, decision was made to transition patient to a DNR B active treatment with no escalation of care. Later on after further discussions, plan was for a one way extubation and comfort care.

On (b) (6) before administration of study drug the patient started experiencing acute respiratory failure with hypoxia. Arterial blood gas analysis was performed and following results were captured: arterial blood pH was 7.21, partial pressure of carbon dioxide (PaCO₂) was 49mmHg, partial pressure of oxygen (PaO₂) was 105 mmHg and arterial oxygen saturation (SaO₂) was 97%. Patient's peripheral capillary oxygen saturation (SpO₂) was 94%, blood pressure was 121/64 mmHg, pulse 59 beats per minute (bpm), respiratory rate 17 respirations per minute (rpm) and temperature 36.6 degrees Celsius (C), measured axillary. Blood chemistry results included alanine aminotransferase (ALT) 18 U/L (reference range: 12-59), aspartate aminotransferase (AST) 30U/L (reference range: 15-37), carbon dioxide (bicarbonate) 22 (unreported units and reference ranges) and total bilirubin 0.8 mg/dl (reference range: 0-1.1). Patient's haematology results included: platelets 261 (unreported units and reference ranges), white blood cells (WBC) 10.70/nL (reference range: 4.5-11) and neutrophils (absolute) 9.69/nL (reference range: 2-6.6).

Between (b) (6) and (b) (6) the arterial blood gas analysis results did not change significantly: arterial blood pH was between 7.24-7.40, PaCO₂ was between 38-45 mmHg, PaO₂ was between 72-102 mmHg, and SaO₂ was between 94-97%.

On (b) (6) patient's WBC count was 10.88/nL and neutrophils 10.13/nL

On (b) (6) patient's WBC count was 4.86/nL and neutrophils 3.83/nL

On (b) (6), a chest X-ray scan was performed, and the result was abnormal, but not clinically significant. Patient's WBC count was 8.27/nL and neutrophils 7.66/nL. The patient underwent bronchoscopy secondary to mucus plugging and growth of pseudomonas was noted from these cultures.

On (b) (6) patient's SpO₂ was 99%, bicarbonate 24, WBC count 15.11/nL, neutrophils 12.99/nL and PaO₂ increased to 148 mmHg, and other results did not significantly change.

On (b) (6) chest X-ray (b) (6) days 18 hrs. 7 min after administration of study drug new life-threatening right-sided pneumothorax was noted, and the patient had chest tube placed. Patient's SpO₂ decreased to 93% and bicarbonate remained at 24. WBC count was 12.00/nL and neutrophils 10.99/nL.

On (b) (6) at 04:58 (b) (6) days 11 hrs. 48 min after administration of study drug the patient had significant increase in alanine aminotransferase (ALT) 387 U/L and (b) (6) days 11 hrs. 48 min after administration of study drug aspartate aminotransferase (AST) 329 U/L. WBC count was 14.15/nL and neutrophils 12.07/nL. At 09:16, (b) (6) days 16 hrs. 6 min after administration of study drug Pseudomonas aeruginosa was noted on blood cultures. No MRSA was detected on blood culture.



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On (b) (6) the patient started receiving Merrem (meropenem trihydrate), at a dose of 1-2 g every eight hours, intravenously, as a corrective treatment for Pseudomonas aeruginosa infection. His WBC count was 11.14/nL and neutrophils 9.47/nL.

On (b) (6) (b) (6) days 6 hrs. 50 min after administration of study drug the patient developed Sepsis, pseudomonas bacteremia and pneumonia. WBC was 13.13/nL and neutrophils 10.77/nL.

On (b) (6) Merrem was replaced with cefepime, at a dose of 2 g every eight hours, intravenously.

On (b) (6) the patient recovered from the event AST increased. AST was 33 U/L.

On (b) (6) the patient recovered from the event ALT increased. ALT was 60 U/L.

On (b) (6) blood pressure reached 121/81mmHg, pulse rate was 81bpm, respiratory rate was 27rpm. Patient was extubated with comfort care orders placed. Shortly after, patient passed away peacefully at 22:40. Cause of death was acute respiratory failure with hypoxia.

Action taken with study drug in response to the events was not applicable. The patient died on (b) (6) Cause of death was acute respiratory failure with hypoxia. Autopsy was not performed.

On (b) (6) event Pseudomonas aeruginosa bacteremia gram negative bacilli on blood cultures Pseudomonas aeruginosa was downgraded from serious-AESI to non-serious AESI, because event didn't meet any seriousness criteria.

Causality assessment is as follows:

(b) (6)

Acute respiratory failure: Severity = Grade 5; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 75-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced acute respiratory failure with hypoxia and subsequent death. The reported event is assessed as not related to study drug or any clinical trial procedure since it is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age.

Pneumonia pseudomonal: Severity = Grade 4; Investigator causality = Related; Company Causality = Not Related

Investigator causality rationale: Related due to the known risk of secondary infections with anti-IL6 treatment.



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Company causality rationale: A 75-year-old male patient enrolled in the trial experienced sepsis, Pseudomonas bacteraemia and pneumonia, with positive blood culture (b) (6) days after receiving single dose of study drug. Patient's baseline neutrophil count was above normal, suggesting the presence of an infection even before study drug administration. Causality for the event is assessed as not related to study drug or any clinical trial procedure. The event is a secondary bacterial infection confounded with progression of patient's underlying COVID-19 disease and subsequent hospitalization and mechanical ventilation aggravated by patient's advanced age and comorbidities like diabetes, as well as concurrent use of corticosteroids like methylprednisone.

Pneumothorax: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 75-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced pneumothorax right-sided, (b) (6) days after receiving the study drug. The event pneumothorax right-sided is assessed as not related to study drug or any clinical trial procedure. The event is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age.

Pseudomonal bacteraemia: Severity = Grade 3; Investigator Causality = Related; Company Causality = Not Related

Investigator causality rationale: Related due to the known risk of secondary infections with anti-IL6 treatment.

Company causality rationale: A 75-year-old male patient enrolled in the trial experienced Pseudomonas bacteraemia, with positive blood culture (b) (6) days after receiving single dose of study drug. Patient's baseline neutrophil count was above normal, suggesting the presence of an infection even before study drug administration. Causality for the event is assessed as not related to study drug or any clinical trial procedure. The event is a secondary bacterial infection confounded with progression of patient's underlying COVID-19 disease and subsequent hospitalization and mechanical ventilation aggravated by patient's advanced age and comorbidities like diabetes, as well as concurrent use of corticosteroids like methylprednisone.

Previous company causality assessment was Related with following rationale:

A 75-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced positive blood culture for Pseudomonas aeruginosa, (b) (6) days after receiving the study drug. Patient's baseline WBC count was within reference ranges whereas neutrophil count was above reference ranges, suggesting infection even before study drug administration. However, based on plausible temporal relationship between the event and study drug and known potential risk for bacterial infections in patient's treated with sarilumab, causality for the event is assessed as related to study drug and not related to any clinical trial procedure. Other possible confounder is underlying COVID-19 disease aggravated by patient's advanced age and underlying diabetes and concomitant medications used, particularly methylprednisolone, which is known to cause immunosuppression, and increased risk of serious infections.



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Alanine aminotransferase increased: Severity = Grade 3; Investigator Causality = Related; Company Causality = Related

Aspartate aminotransferase increased: Severity = Grade 3; Investigator Causality = Related; Company Causality = Related

Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 75-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced ALT increased, and AST increased (b) (6) days after receiving the study drug. Patient's baseline values were above reference ranges and increased significantly after study drug administration. Based on a plausible temporal relationship between study drug administration and the reported events and known potential effect of study drug on functional liver enzymes, causality for both events, ALT increased, and AST increased, is assessed as related to study drug and not related to any clinical trial procedure. Causality is confounded with progression of COVID-19 infection and concomitant use of acetaminophen, hydroxychloroquine, and azithromycin.

Causality assessment for previously reported events, on (b) (6) was as follows:

Bacteraemia: Severity = Grade 3; Investigator Causality = Related; Company Causality = Related

Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 75-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced positive blood culture for gram-negative bacilli, (b) (6) days after receiving the study drug. Patient's baseline and subsequent WBC and neutrophil count were not provided. Based on plausible temporal relationship between the event and study drug and known potential risk for bacterial infections in patient's treated with sarilumab, causality for the event is assessed as related to study drug and not related to any clinical trial procedure. Other possible confounder is underlying COVID-19 disease aggravated by patient's age.

Sepsis: Severity = Grade 4; Investigator Causality = Related; Company Causality = Related

Investigator causality rationale: Related due to the known risk of secondary infections with anti-IL6 treatment.

Company causality rationale: A 75-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced sepsis, (b) (6) days after receiving the study drug. Following study drug administration and before sepsis, the patient's blood culture was positive for *Pseudomonas aeruginosa*. Patient's baseline WBC count was within reference ranges whereas neutrophil count was above reference ranges, suggesting infection even before study drug administration. However, based on a plausible temporal relationship between the event and study drug and known potential risk for bacterial infections in patient's treated with sarilumab, causality for the event is assessed as related to study drug and not related to any clinical trial procedure. Other possible confounder is underlying COVID-19 disease aggravated by patient's advanced age and underlying diabetes and concomitant medications used, particularly methylprednisolone, which is known to cause immunosuppression, and increased risk of serious infections.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17807391

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 13-Apr-2020

The Investigator provided the following updates: new events added with all relevant information, study drug administration date and time updated.

Follow up: 17-Apr-2020 and 20-Apr-2020 (processed together)

The Investigator provided the following updates: new events added with all relevant information.

Follow up: 28-Apr-2020 and 30-Apr-2020 (processed together)

The Investigator provided the following updates: event term updated and rationale for causality assessment in relationship to study drug provided (Gram negative bacilli on blood cultures), corrective treatment (Pneumothorax right-sided) provided.

Follow up: 11-May-2020, 12-May-2020, 14-May-2020, 15-May-2020 and 18-May-2020(processed together)

The investigator provided the following updates: stop date added, outcome updated (Pneumothorax right-sided; AST increased; ALT increased; Sepsis; Pseudomonas aeruginosa bacteremia gram negative bacilli on blood cultures Pseudomonas aeruginosa); Worsening acute respiratory failure with hypoxia event term updated; stop date added (ALT increased, AST increased); clinical course.

Follow up: 19-May-2020

The Investigator provided the following updates: event Pseudomonas aeruginosa bacteremia gram negative bacilli on blood cultures Pseudomonas aeruginosa downgraded, event outcome updated (Pseudomonas aeruginosa bacteremia gram negative bacilli on blood cultures Pseudomonas aeruginosa and Sepsis), event term and onset date updated (Acute respiratory failure with hypoxia) and clinical course updated.

FU 22-Jun-2020: event term updated (event Sepsis, pseudomonas bacteremia and pneumonia), concomitant medications updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Pneumonia	(b) (6)		YES
ARDS	(b) (6)		YES
Respiratory failure	(b) (6)		YES



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17807391

Diabetes YES
 Hypertension YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
CO2	46	mmHg			N
O2 saturation	94	%			N
O2 saturation	99	%			N
O2 saturation					Y
PaO2	77	mmHg			N
WBC	15.11	10 ⁹ /L	4.5	11	N
Alanine aminotransferase	18	U/L	12	59	N
Alanine aminotransferase	387	U/L	12	59	N
Bicarbonate	24	UNK			Y
CO2	41	mmHg			N
CO2	41	mmHg			N
O2 saturation	97	%			N
PaO2	72	mmHg			N
WBC	12	10 ⁹ /L	4.5	11	N
Aspartate aminotransferase	33	U/L	15	37	N
Blood culture					Y
Arterial blood pH	7.40	UNK			Y
Arterial blood pH	7.33	UNK			Y
Blood pressure	121/64	mmHg			N
Pulse rate	59	beats/min			N
O2 saturation	94	%			N
WBC	10.70	10 ⁹ /L	4.5	11	N
WBC	14.15	10 ⁹ /L	4.5	11	N
WBC	13.13	10 ⁹ /L	4.5	11	N
Bicarbonate	22	UNK			Y
Arterial blood pH	7.21	UNK			Y
Blood pressure	121/81	mmHg			N
O2 saturation	93	%			N
Platelet count	261	UNK			Y
Aspartate aminotransferase	329	U/L	15	37	N
Arterial blood pH	7.32	UNK			Y



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17807391

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Arterial blood pH	7.39	UNK			Y
Chest X-ray					Y
Pulse rate	81	beats/min			N
Respiratory rate	17	breaths/min			N
Alanine aminotransferase	60	U/L	12	59	N
Aspartate aminotransferase	30	U/L	15	37	N
Arterial blood pH	7.24	UNK			Y
CO2	49	mmHg			N
CO2	45	mmHg			N
Monocyte count	1.12	/nL	0.2	0.8	N
Absolute neutrophil count	9.69	10 ⁹ /L	2	6.6	N
O2 saturation	94	%			N
Respiratory rate	27	breaths/min			N
Bicarbonate	24	UNK			Y
Bicarbonate	24	UNK			Y
Bilirubin	0.8	mg/dL	0	1.1	N
CO2	38	mmHg			N
Chest X-ray					Y
Absolute neutrophil count	10.77	10 ⁹ /L	2	6.6	N
O2 saturation	97	%			N
O2 saturation	94	%			N
PaO2	105	mmHg			N
PaO2	68	mmHg			N
PaO2	148	mmHg			N
WBC	13.4	10 ⁹ /L	4.5	11	N
Bacterial test					N
PaO2	102	mmHg			N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	AZITHROMYCIN	500 MG/	Intravenous (not otherwise specified)	500 mg, OTO	Corona virus infection	31-Mar-2020	31-Mar-2020	13 DAY
2	AZITHROMYCIN	250 MG/QD	Oral	250 mg, QD		01-Apr-2020	04-Apr-2020	13 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17807391

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
3	CEFEPIME	2000 MG/Q12H	Intravenous (not otherwise specified)	2000 mg, BID	Acute respiratory failure	07-Apr-2020	09-Apr-2020	6 DAY
4	HYDROXYCHLOROQUIN E	400 MG/Q12H	Oral	400 mg, BID	Malaria	01-Apr-2020	01-Apr-2020	12 DAY
5	HYDROXYCHLOROQUIN E	200 MG/Q12H	Oral	200 mg, BID		01-Apr-2020	05-Apr-2020	12 DAY
6	MEROPENEM	2 G/Q8H	Intravenous (not otherwise specified)	2 g, TID	Acute respiratory failure	11-Apr-2020	14-Apr-2020	2 DAY
7	METHYLPREDNISOLON E	125 MG/Q12H	Intravenous (not otherwise specified)	125 mg, BID	Acute respiratory failure	03-Apr-2020	03-Apr-2020	10 DAY
8	METHYLPREDNISOLON E	20 MG/QD	Intravenous (not otherwise specified)	20 mg, QD		12-Apr-2020	12-Apr-2020	10 DAY
9	METHYLPREDNISOLON E	10 MG/QD	Intravenous (not otherwise specified)	10 mg, QD		13-Apr-2020	16-Apr-2020	10 DAY
10	METHYLPREDNISOLON E	60 MG/Q12H	Intravenous (not otherwise specified)	60 mg, BID		03-Apr-2020	05-Apr-2020	10 DAY
11	METHYLPREDNISOLON E	20 MG/	Intravenous (not otherwise specified)	20 mg UNK		09-Apr-2020	11-Apr-2020	10 DAY
12	METHYLPREDNISOLON E	40 MG/Q12H	Intravenous (not otherwise specified)	40 mg, BID		05-Apr-2020	09-Apr-2020	10 DAY
13	TYLENOL	650 MG/Q8H	Other	650 mg, tid, NG	Fever	07-Apr-2020		6 DAY
14	VANCOMYCIN	1000 MG/Q12H	Intravenous (not otherwise specified)	1000 mg, BID	Ant biotic therapy	09-Apr-2020	11-Apr-2020	4 DAY

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17807391

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17807469

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ROM Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 20-May-2020 Mfr Rcvd Date: 27-Apr-2020 Mfr Control #:RO-ROCHE-2594071 Application #: 125276

Patient Information:

Age: 77 YR Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA			Unknown	6 vials of 400 mg (total dose) from 08/May/2020 to 10/mMy/2020	COVID-19	May-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2594071 is a spontaneous case, received on 27/Apr/2020 from a pharmacist via company representative in Romania. It concerns a 77 year old patient (gender unspecified) who died while been treated with treated with tocilizumab (Roactemra).

Patient's medical history, concurrent conditions, past drugs or concomitant medications were not reported.

On an unknown date in May/2020 (reported as date between 08/May/2020 and 10/May/2020), the patient started therapy with tocilizumab 6 vials of 400 mg (total dose) (lot number: unknown) for covid 19 infection (off label use). The patient died on an unspecified date between (b) (6) and (b) (6). The cause of death was not mentioned. It was not stated if autopsy was performed or not.

At the time of death, it was not reported of therapy with tocilizumab was ongoing or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17807469

The reporter did not report the causality of event death with tocilizumab.

No further information was reported.

Additional information was received on 11/May/2020. Following information was added to the case: Total tocilizumab dose updated to 6 vials of 400 mg. New event : death with associated event description.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17807469

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17808058

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ESP **Event Date:** 02-Apr-2020 **Outcomes:** DE,HO, **Application Type:** NDA

FDA Rcvd Date: 20-May-2020 **Mfr Rcvd Date:** 19-May-2020 **Mfr Control #:** ES-PFIZER INC-2020198873 **Application #:** 050706

Patient Information:

Age: 72 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	MEROPENEM		1 G/TID	Intravenous (not otherwise specified)	1 g, 3x/day (every 8 hours)		04-Apr-2020	19-Apr-2020
2	HYDROXYCHLOROQUIN E		400 MG/	Oral	400 mg, daily	COVID-19 pneumonia	26-Mar-2020	02-Apr-2020
3	LINEZOLID		600 MG/BID	Intravenous (not otherwise specified)	600 mg, 2x/day (every 12 hours)		28-Mar-2020	16-Apr-2020
4	METAMIZOLE		2 G/TID	Intravenous (not otherwise specified)	2 g, 3x/day (2 g every 8 hours)		13-Apr-2020	16-Apr-2020
5	PIPERACILLIN/TAZOBAC TAM		1 DF/TID	Intravenous (not otherwise specified)	1 DF, 3x/day (every 8 hours)		04-Apr-2020	07-Apr-2020
6	ROACTEMRA		600 MG/		600 mg, single	Adult respiratory stress syndrome	27-Mar-2020	27-Mar-2020
7	ROACTEMRA					COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	MEROPENEM	12 Day	Yes	NA	Unknown			PFIZER	
2	HYDROXYCHLOROQUIN E	7 Day	Yes	NA	Unknown				
3	LINEZOLID	5 Day	Yes	NA	Unknown			PFIZER	
4	METAMIZOLE		Yes	NA	Unknown				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17808058

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
5 PIPERACILLIN/TAZOBAC TAM		Yes	NA	Unknown				
6 ROACTEMRA	6 Day	Yes	NA	Unknown				
7 ROACTEMRA	6 Day	Yes	NA					

Event Information:

Preferred Term (MedDRA @ Version: 23.1)

ReC

Drug reaction with eosinophilia and systemic symptoms

NA

Hypofibrinogenaemia

NA

Upper gastrointestinal haemorrhage

NA

Event/Problem Narrative:

This is a spontaneous report from a contactable physician downloaded from the European Medicines Agency (EMA) EudraVigilance- WEB [ES-AEMPS-627000]. A 72-year-old male patient started to receive meropenem (manufacturer unspecified), intravenous from 04Apr2020 to 19Apr2020 at 1 g, 3x/day (every 8 hours) for an unspecified indication; linezolid (manufacturer unspecified), intravenous from 28Mar2020 to 16Apr2020 at 600 mg, 2x/day (every 12 hours) for an unspecified indication; tocilizumab (ROACTEMRA), via an unspecified route of administration from 27Mar2020 to 27Mar2020 at 600 mg, single for acute respiratory distress syndrome and covid-19 pneumonia; piperacillin;tazobactam (manufacturer unspecified), intravenous from 04Apr2020 to 07Apr2020 at 1 DF, 3x/day (every 8 hours) for an unspecified indication; metamizole (manufacturer unspecified), intravenous from 13Apr2020 to 16Apr2020 at 2 g, 3x/day (2 g every 8 hours) for an unspecified indication; hydroxychloroquine (manufacturer unspecified), oral from 26Mar2020 to 02Apr2020 at 400 mg, daily for covid-19 pneumonia. The patient's medical history and concomitant medications were not reported. The patient experienced hypofibrinogenemia on (b) (6). The patient experienced DRESS syndrome (drug reaction with eosinophilia and systemic symptoms) and upper gastrointestinal hemorrhage on (b) (6). The patient was hospitalized for all events. The action taken in response to the events for meropenem was permanently withdrawn on (b) (6), for linezolid was permanently withdrawn on (b) (6), for tocilizumab was permanently withdrawn on (b) (6), for piperacillin;tazobactam was permanently withdrawn on (b) (6) for metamizole was permanently withdrawn on (b) (6) and for hydroxychloroquine was permanently withdrawn on (b) (6). The outcome of the event hypofibrinogenemia was recovered on (b) (6). The outcome of the event upper gastrointestinal hemorrhage was recovering, while the outcome of the event DRESS syndrome was not recovered. The patient died on (b) (6) with cause of death was reported as septic shock and COVID-19 pneumonia. It was not known if autopsy was performed.

Pfizer is Marketing Authorization Holder of meropenem and linezolid in the reporter's country. This may be a duplicate report in situations



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

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where another Marketing Authorization Holder of meropenem and linezolid has submitted the same report to the regulatory authorities.

No follow-up attempts are possible. No further information is expected.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: PFIZER
**503B Compounding
Outsourcing Facility?:**



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17808058

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17808090

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 06-Apr-2020
Outcomes: DE,HO,LT,OT,
Application Type: BLA
FDA Rcvd Date: 28-May-2020
Mfr Rcvd Date: 19-May-2020
Mfr Control #: US-SA-2020SA096379
Application #: 761037

Patient Information:

Age: 61 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		1X	Intravenous (not otherwise specified)	REGN mAb1 400 mg 1X	COVID-19	06-Apr-2020	06-Apr-2020
2	SARILUMAB		1X	Intravenous (not otherwise specified)	1X, REGN88 or placebo, 200 mg or 400 mg single dose for 1 hour		13-Apr-2020	13-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	11549 MINUTES	NA	NA				SANOFI	
2	SARILUMAB	11549 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Acute kidney injury	NA
Alanine aminotransferase increased	NA
Aspartate aminotransferase increased	NA
Fungaemia	NA
Respiratory failure	NA
Shock	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17808090

Event/Problem Narrative:

Based on additional information received on 15-Apr-2020 and 16-Apr-2020 (both processed together), serious-related events death due to shock and fungemia were added with details. Consequently, the case was upgraded to SUSAR.

Solicited case from the 6R88-COV-2040 study received on 10-Apr-2020 and 12-Apr-2020 (both processed together)

Centre ID: (b) (6) Patient ID (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

A 61-year-old, Hispanic, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6) The patient experienced Hypoxic respiratory failure on (b) (6) Acute kidney injury on (b) (6) and Death due to shock on (b) (6) and fungemia on (b) (6) and elevated ALT and AST on (b) (6), after receiving study drug.

The patient's relevant medical history included diabetes mellitus, hyperlipidaemia, coronary artery disease and hypertension.

Relevant concomitant medications included azithromycin, doxycycline, hydroxychloroquine, acetaminophen and methylprednisolone.

On 27-Mar-2020., the patient had earliest onset of symptoms of pneumonia with no rales/crackles on lung auscultation present at baseline.

On (b) (6) the patient was hospitalized and nasopharyngeal swab was positive for SARS-CoV-2.

On (b) (6), electrocardiogram showed atrial fibrillation with rapid ventricular response and minimal voltage criteria for left ventricular hypertrophy, consider normal variant ST deviation and moderate T-wave abnormality, consider lateral ischemia.

On (b) (6) oxygen saturation (SpO₂) was 98%, blood pressure 107/68 mmHg, pulse 89 bpm, respiratory rate 20 rpm, temperature 36.1 C, alanine aminotransferase (ALT) 32 U/l (1-45), aspartate aminotransferase (AST) 54 U/l (1-40), creatinine 1.4 mg/dl (0.5-1), lactate dehydrogenase (LDH) 570 (60-200) U/l, total bilirubin 0.6 mg/dl (0.1-1.2), uric acid 12.8 mg/dl (3.5-7.2), platelets 195, white blood cells (WBC) 10.53/nl (3.9-10.6), neutrophils (absolute) 9.78/nl (1.9-8.7). On the same day, same day after the first study drug administration, the patient experienced hypoxic respiratory failure (intensity: Grade 4). The event was assessed as life threatening leading to hospitalization. An X-ray showed progression of acute viral infection compatible with COVID-19 pneumonia and the patient was put on non-invasive ventilation.

On (b) (6) the patient was intubated. SpO₂ was 91%, respiratory rate 22.

On (b) (6) patient's SpO₂ was 93%, respiratory rate 22 and his creatinine increased to 2.7.



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On (b) (6) days 8 hrs 46 min after the first study drug administration, SpO2 was 91%, the patient experienced acute kidney injury (intensity: Grade 4) and his creatinine increased to 4.2, while his urine output decreased. The event was assessed as life threatening. Information on corrective was not provided.

On (b) (6) SpO2 was 100%, creatinine was 5.8 and continuous renal replacement therapy was initiated.

On (b) (6) creatinine decreased to 2.1. On the same day (b) (6) days 8 hrs 46 min after the first study drug administration, the patient's blood culture showed fungemia (intensity: Grade 4). The event was assessed as life-threatening leading to hospitalization.

On (b) (6) the patient received a single dose of 70 mg of IV caspofungin for the fungal sepsis. On the same day (b) (6) days 8 hrs 46 min after the first administration of study drug, the patient experienced elevated ALT (intensity: Grade 4) at 2952 and AST at more than 7000 (intensity: Grade 4). The events were assessed as life-threatening, serious adverse event of special interest and medically significant. Information on corrective was not provided. The patient experienced shock (intensity: Grade 5) and passed away on the same day at 15:43.

On (b) (6) treatment assignment blind was broken for regulatory reporting purposes.

Outcome: fatal for shock; not recovered for all other events

Action taken with study drug in response to the events was not applicable.

For Shock:

Relationship to study drug according to investigator: reasonable possibility.

Investigator causality rationale: Invasive fungal infections an adverse event of interest. Other suspected causes included Fungemia.

Relationship to study drug according to company: not reportable.

Company causality rationale: A 61-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced shock and subsequent death (b) (6) days after receiving the study drug. The patient experienced fungemia (b) (6) days before. The event of shock is assessed to be unrelated to the study drug in spite of a plausible temporal association between study drug and the reported event. The event is most possibly associated with progression of underlying COVID-19 disease aggravated by patient's age and comorbidities of diabetes mellitus, CAD and hypertension.

For Respiratory failure:

Relationship to study drug according to investigator: no reasonable possibility.

Investigator causality rationale: Secondary to COVID-19 pneumonia.

Relationship to study drug according to company: not reportable.

For Acute kidney injury:



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Relationship to study drug according to investigator: no reasonable possibility.
Investigator causality rationale: Likely due to COVID-19.
Relationship to study drug according to company: not reportable.

For both Respiratory failure and Acute Kidney Injury

Company causality rationale: A 61-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced hypoxic respiratory failure and acute kidney injury, after receiving the study drug. The events hypoxic respiratory failure and acute kidney injury are assessed as not related to study drug or any clinical trial procedure. The events are secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and comorbidities like diabetes mellitus, hyperlipidaemia, coronary artery disease, hypertension and concurrent use of azithromycin.

For Fungaemia:

Relationship to study drug according to investigator: reasonable possibility.

Investigator causality rationale: sequelae of COVID-19 infection

Relationship to study drug according to company: reportable

Company causality rationale: A 61-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced fungemia (b) (6) days after receiving the study drug. Patient's baseline WBC values were on the upper limit of reference ranges and started increasing after study drug administration. Based on plausible temporal association between study drug and the reported event, as well as known potential risk for fungal infections in patients treated with sarilumab, causality is assessed as related to study drug and not related to any clinical trial procedure.

For Aspartate aminotransferase increased and Alanine aminotransferase increased:

Relationship to study drug according to investigator: reasonable possibility.

Investigator causality rationale: AE of interest. Other suspected causes included shock liver, COVID-19 infection, critical illness.

Relationship to study drug according to company: reportable

Company causality rationale: A 61-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced elevated AST and ALT, one day after receiving the last dose of the study drug. Patient's baseline ALT values were within reference ranges and baseline AST values were slightly increased. Based on a plausible temporal relationship between study drug administration and the reported events and known potential effect of study drug on functional liver enzymes, causality for both events is assessed as related to study drug and not related to any clinical trial procedure. Significant confounding factors are shock liver and concomitant use of azithromycin, doxycycline, hydroxychloroquine, acetaminophen and methylprednisolone.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 15-Apr-2020 and 16-Apr-2020 (processed together):

The investigator provided the following updates: new events and death details added, additional study drug administration details added,



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FOIA Case Report Information

Case ID: 17808090

action taken updated, clinical course updated.

Follow up: 11-May-2020 and 12-May-2020 (processed together):

The Investigator provided the following updates: new events added (elevated AST and ALT), primary cause of death updated.

Follow up: 19-May-2020: The Investigator provided the following updates: outcome of events updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Asthma			YES
Atrial fibrillation with rapid ventricular response			YES
Coronary artery disease			YES
Diabetes mellitus			YES
Hyperlipidemia			YES
Hypertension			YES
Obstructive sleep apnea hypopnea syndrome			YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Bilirubin total	0.6	mg/dL	0.1	1.2	N
Body temperature	36.1	Cel			Y



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Respiratory rate	20	breaths/min			N
White blood cells	10.53	nL	3.6	10.6	N
Aspartate aminotransferase	54	U/L	1	40	N
Creatinine	5.8	mg/dL	0.5	1	N
Oxygen saturation	93	%			N
Creatinine	2.7	mg/dL	0.5	1	N
X-ray					Y
Creatinine	4.2	mg/dL	0.5	1	N
Oxygen saturation	100	%			N
Creatinine	2.1	mg/dL	0.5	1	N
Lactate dehydrogenase	570	U/L	60	200	N
Oxygen saturation	98	%			N
Oxygen saturation	91	%			N
Respiratory rate	22	breaths/min			N
Alanine aminotransferase	32	U/L	1	45	N
Aspartate aminotransferase	more than 7000	U/L	1	40	N
Uric acid	12.8	mg/dL	3.5	7.2	N
Oxygen saturation	91	%			N
Platelet count	195	UNK			Y
Respiratory rate	22	breaths/min			N
Blood pressure	107/68	mmHg			N
Heart rate	89	beats/min			N
Absolute neutrophil count	9.78	nL	1.9	8.7	N
Alanine aminotransferase	2952	U/L	1	45	N
Creatinine	1.4	mg/dL	0.5	1	N
Coronavirus test positive					Y
Electrocardiogram					Y

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/	Rectal	650 mg, PRN	Fever	08-Apr-2020	14-Apr-2020	9583 MIN
2	AMIODARONE		Intravenous (not otherwise specified)	1 mg/min continuous infusion	Arrhythmia	07-Apr-2020	08-Apr-2020	11023 MIN



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17808090

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
3	ASPIRIN [ACETYLSALICYLIC ACID]	81 MG/QD	Oral	81 mg, QD	Hypertension	03-Apr-2020	12-Apr-2020	16783 MIN
4	AZITHROMYCIN	500 MG/QD	Oral	500 mg, QD	COVID-19	02-Apr-2020	02-Apr-2020	18223 MIN
5	CEFTRIAZONE	1000 MG/QD	Intravenous (not otherwise specified)	1000 mg, QD	COVID-19 pneumonia	02-Apr-2020	09-Apr-2020	18223 MIN
6	DOXYCYCLINE	100 MG/Q12H	Oral	100 mg, BID	COVID-19 pneumonia	04-Apr-2020	09-Apr-2020	15343 MIN
7	HYDROXYCHLOROQUIN E	400 MG/Q12H	Oral	400 mg, Q12H	COVID-19	02-Apr-2020	02-Apr-2020	18223 MIN
8	HYDROXYCHLOROQUIN E	400 MG/QD	Oral	400 mg, QD		02-Apr-2020	07-Apr-2020	18223 MIN
9	IVERMECTIN				Prophylactic			9583 MIN
10	IVERMECTIN	21 MG/QD	Oral	21 mg, QD	Strongyloidiasis	08-Apr-2020	09-Apr-2020	9583 MIN
11	METHYLPREDNISOLON E	60 MG/QD	Intravenous (not otherwise specified)	60 mg, QD	Inflammation	09-Apr-2020	13-Apr-2020	8143 MIN
12	METHYLPREDNISOLON E SODIUM SUCCINATE	60 MG/Q12H	Intravenous (not otherwise specified)	60 mg, Q12H	Drug use for unknown indication	05-Apr-2020	06-Apr-2020	13903 MIN
13	NEO-SYNEPHRINE HYDROCHLORIDE				Arrhythmia			2383 MIN
14	NEO-SYNEPHRINE HYDROCHLORIDE		Intravenous (not otherwise specified)	100-400 mcg/min continuous infusion	Hypotension	13-Apr-2020	14-Apr-2020	2383 MIN
15	NOREPINEPHRINE		Intravenous (not otherwise specified)	1-30 mcg/min continuous infusion	Hypotension	11-Apr-2020	14-Apr-2020	5263 MIN
16	NOREPINEPHRINE				Arrhythmia			5263 MIN
17	NORVASC	10 MG/QD	Oral	10 mg, QD	Arrhythmia	03-Apr-2020	06-Apr-2020	16783 MIN
18	VASOPRESSIN		Intravenous (not otherwise specified)	0.04 unites/min continuous infusion	Hypotension	07-Apr-2020	12-Apr-2020	11023 MIN



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17808090

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17808203

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 20-Apr-2020 Outcomes: DE,OT, Application Type: BLA

FDA Rcvd Date: 16-Jun-2020 Mfr Rcvd Date: 08-Jun-2020 Mfr Control #: IT-ROCHE-2604117 Application #: 125276

Patient Information:

Age: 69 YR Sex: Female Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		800 MG/	Intravenous (not otherwise specified)	Tocilizumab 8 mg/kg (up to a maximum of 800mg per dose). Second administration (same dose) optional	COVID-19 pneumonia	26-Mar-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	25 Day	Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC

Multiple organ dysfunction syndrome NA

Pancreatitis NA

Event/Problem Narrative:

AER 2604117 is a clinical study case, received on 14/May/2020 from a physician in Italy. It concerns a 69 year old female patient (patient number: (b) (6)) who developed multi organ failure and pancreatitis whilst enrolled in (b) (6) (b) (6)

Concurrent conditions included obesity ((BMI 41.6 kg/m2), rheumatoid arthritis, hypertension. No medical history, past drugs and concomitant medications were reported.

(b) (6)
 (b) (6) One month before treatment, she showed an increase of pancreatic enzymes (amylase 166 U/L and lipase 73 U/L) not further investigated. On (b) (6) she experienced



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vomiting and multi organ failure and pancreatitis (severity: grade 3) and on the same day, computerised tomogram abdomen, CT-scan performed, was compatible with pancreatitis with fluid collections, necrosis and hemorrhage. Pancreatic enzymes were normal. Due to the event she was transferred in surgery department for observation. On (b)(6) CT-scan performed, showed a worsening of pancreatitis with increase of fluid collections. No other symptoms were reported. On (b)(6) it showed she had worsening of pancreatitis (severity: grade 3). On (b)(6), she was died. The underlying cause of death remained unclear (sudden death, NOS). The event pancreatitis was still ongoing at death. It was unknown if an autopsy was performed or not.

At the time of the report, pancreatitis was persisting. It was not reported if therapy with tocilizumab was altered or not in response to the multi organ failure, pancreatitis.

The physician assessed the multi organ failure and pancreatitis as related to tocilizumab. According to the investigator, despite obesity in absence of concomitant additional risk factors for pancreatitis (e.g. gallstone disease) a relation between the event and tocilizumab cannot be ruled out and therefore the investigator assessed pancreatitis as possibly related to tocilizumab.

The company assessed pancreatitis as medically significant.

No further information has been reported.

AER 2602345 was identified as potential duplicate of AER 2604117 and all the information from AER 2602345 was added to AER 2604117, which remains the active case.

Approval given by DESAIV

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension			
Obesity			
Rheumatoid arthritis			

Medical History Product(s)	Start Date	End Date	Indications	Events



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FOIA Case Report Information

Case ID: 17808203

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Computerised tomogram abdomen					N
Computerised tomogram abdomen					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17808608

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 23-Mar-2020 Outcomes: DE,

Application Type: NDA

FDA Rcvd Date: 20-May-2020 Mfr Rcvd Date: 19-May-2020 Mfr Control #: ES-PFIZER INC-2020198882

Application #: 050784

Patient Information:

Age: 26 YR

Sex: Female

Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	AZITHROMYCIN		500 MG/QD	Oral	500 mg, 1x/day	COVID-19 pneumonia	23-Mar-2020	24-Mar-2020
2	DEXAMETHASONE		20 MG/QD	Intravenous (not otherwise specified)	20 mg, 1x/day		28-Mar-2020	01-Apr-2020
3	DEXKETOPROFEN		25 MG/TID	Intravenous (not otherwise specified)	25 mg, 3x/day (every 8 hours)		27-Mar-2020	01-Apr-2020
4	ENOXAPARIN		40 MG/QD	Subcutaneous	40 mg, 1x/day		27-Mar-2020	
5	HYDROXYCHLOROQUIN E		400 MG/QD	Oral	400 mg, 1x/day	COVID-19 pneumonia	23-Mar-2020	01-Apr-2020
6	TOCILIZUMAB		600 MG/	Intravenous (not otherwise specified)	600 mg, single	Severe acute respiratory syndrome	29-Mar-2020	29-Mar-2020
7	TOCILIZUMAB					COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	AZITHROMYCIN	8 Day	NA	NA				PFIZER	
2	DEXAMETHASONE	3 Day	NA	NA					
3	DEXKETOPROFEN	4 Day	NA	NA					
4	ENOXAPARIN	4 Day	NA	NA					
5	HYDROXYCHLOROQUIN E	8 Day	NA	NA					



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Case ID: 17808608

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC	
6 TOCILIZUMAB	2 Day	NA	NA						
7 TOCILIZUMAB	2 Day	NA	NA						

Event Information:

Preferred Term (MedDRA Version: 23.1)

ReC

Coagulopathy

NA

Off label use

NA

Product use in unapproved indication

NA

Event/Problem Narrative:

This is a spontaneous report from a contactable physician downloaded from the European Medicines Agency (EMA) EudraVigilance-WEB. This is a report received from the Spanish Regulatory Authority. Regulatory Authority report number was ES-AEMPS-628824.

A 26-year-old female patient started to receive azithromycin (MANUFACTURER UNKNOWN), oral from 23Mar2020 to 24Mar2020 at 500 mg, once a day for COVID-19 pneumonia; dexamethasone (MANUFACTURER UNKNOWN), intravenous from 28Mar2020 at 20 mg, once a day for an unspecified indication; enoxaparin (MANUFACTURER UNKNOWN), subcutaneous from 27Mar2020 at 40 mg, once a day for an unspecified indication, tocilizumab (MANUFACTURER UNKNOWN) intravenous on 29Mar2020 as a 600 mg, single dose for severe acute respiratory syndrome and COVID-19 pneumonia; dexketoprofen (MANUFACTURER UNKNOWN), intravenous from 27Mar2020 at 25 mg, three times a day (every 8 hours) for an unspecified indication; and hydroxychloroquine (MANUFACTURER UNKNOWN), oral from 23Mar2020 at 400 mg, once a day for COVID-19 pneumonia. Medical history included caesarean section on (b) (6). The patient concomitant medications were not reported. On 31Mar2020, the patient experienced coagulopathy. The action taken in response to the event for azithromycin was post-therapy as it was completed on 24Mar2020, for dexamethasone was permanently withdrawn on 01Apr2020, for enoxaparin was dose not changed, for tocilizumab was post-therapy as it was only given on 29Mar2020, for dexketoprofen was permanently withdrawn on 01Apr2020, and for hydroxychloroquine was permanently withdrawn on 01Apr2020. The clinical outcome of the coagulopathy was reported as fatal. The patient died on (b) (6). It was not reported if an autopsy was performed. The reported cause of death was multiple organ failure and COVID-19.

Pfizer is the Marketing Authorization Holder of azithromycin in the country of incidence or the country where the product was purchased (if different). This may be a duplicate report if another Marketing Authorization Holder of azithromycin has submitted the same report to the regulatory authorities.



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No follow-up attempts are possible. No further information is expected.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
C-section	(b) (6)	(b) (6)	NO

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



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FOIA Case Report Information

Case ID: 17808608

Reporter Source:

Study Report?: No

Sender Organization: PFIZER

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17809848

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 03-Apr-2020
Outcomes: DE,HO,LT,
Application Type: BLA
FDA Rcvd Date: 29-Jun-2020
Mfr Rcvd Date: 19-Jun-2020
Mfr Control #: US-SA-2020SA092868
Application #: 761037

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		400 MG/	Intravenous (not otherwise specified)	400 mg	COVID-19	02-Apr-2020	02-Apr-2020
2	SARILUMAB		400 MG/	Intravenous (not otherwise specified)	400 mg		17-Apr-2020	17-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	15 Day	Yes	NA				SANOFI	
2	SARILUMAB	15 Day	Yes	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Enterococcal bacteraemia	NA
Lactic acidosis	NA
Renal failure	NA
Septic shock	NA
Transaminases increased	NA



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FOIA Case Report Information

Case ID: 17809848

Event/Problem Narrative:

Based on follow up information received on 15-Apr-2020, a serious life-threatening related event of Increase AST/ALT was added. Hence the case was upgraded to suspected, unexpected serious adverse reaction (SUSAR).

Initial information received on 06-Apr-2020 regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference number 2020-28756 on 06-Apr-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6)

Centre ID (b) (6) Patient ID: (b) (6) Country: United States

Study title: (b) (6)

(b) (6)

A 77-year-old, Black, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6). The patient experienced septic shock [Septic shock]; Death; Onset date: (b) (6); Severity: Grade 5; Outcome: Fatal; Event fatal on: (b) (6); Renal failure (Renal failure): Life-threatening; Onset date: (b) (6); Severity: Grade 4; Outcome: Not recovered / Not resolved; Event ended on: Ongoing; Enterococcus faecalis bacteremia (Enterococcal bacteraemia): Life-threatening; Serious AESI (Clinically significant invasive bacterial or fungal infections); Onset date: (b) (6); Severity: Grade 4; Outcome: Recovered / Resolved; Event resolved on: (b) (6); Increase AST/ALT (Transaminases increased) Life threatening; Hospitalization; Serious AESI (ALT or AST increase); Onset date: (b) (6); Severity: Grade 4; Outcome: Not recovered / Not resolved; Event resolved on: Ongoing; Lactic acidosis (Lactic acidosis): Life threatening; Hospitalization; Onset date: (b) (6); Severity: Grade 4; Outcome: Not recovered / Not resolved; Event resolved on: Ongoing), all after receiving study drug.

Relevant medical history included hypertension, diabetes type 2, chronic kidney disease, stage III, renal cell carcinoma and left renal mass.

Relevant concomitant included hydroxychloroquine, aspirin and azithromycin.

On (b) (6) the patient was admitted to hospital and tested positive for SARS-CoV-2 virus from nasopharyngeal swab.

On (b) (6), the patient experienced earliest symptoms of pneumonia (fever/feverishness, cough, dyspnoea/short of breath), with rales/crackles on lung auscultation present at baseline and was transferred to intensive care unit (ICU). The patient was put on invasive mechanical ventilation, his temperature was 38.0 degree C.

On (b) (6) electrocardiogram (ECG) was performed, and showed non-specific wave abnormality.

On (b) (6) results of biochemistry were as follows: albumin - 2.1 g/dL (3.4-5), alkaline phosphatase (ALP) - 543 U/L (40-125), alanine



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aminotransferase (ALT) - 98 U/L (7-50), aspartate aminotransferase (AST) - 129 U/L (10-40), creatine phosphokinase (CPK) - 309 U/L (21-232), sodium - 152 mmol / L (135-145), glucose - 163 mg/dL (40-110), creatinine - 4.13 mg/dL (0.5-1.5), total bilirubin - 0.5 mg/dL (0-1.2), uric acid - 10.6 mg/dL (4-8). Haematology tests were performed, and following results were noted: platelets - 298 10⁹ /L (150-450), white blood cells (WBC) - 8.5 10⁹ /L (3.9-12), neutrophils (absolute) - 7.2 10⁹ /L (1.3-7.5), lymphocytes (absolute) - 0.2 10⁹ /L (1.3-4.2).

On (b) (6) (b) (6) hours and 36 minutes after the first investigational product (IP), the patient developed renal failure (intensity: grade 4) and started hemodialysis on the same day. The patient had history of chronic kidney disease. Nephrectomy for renal cell carcinoma and cryoablation for left renal mass were performed earlier in the hospital course.

On (b) (6) the patient started with norepinephrine at a dose of 20 mcg/min, titrated to effect in continuous infusion, intravenously.

On (b) (6) (b) (6) days after first dose of IP, the patient experienced Enterococcus faecalis bacteremia (severity: grade 4). As corrective treatment, the patient received vancomycin, 2250 mg intravenously, once and cefepime, 2 g, twice daily, intravenously.

On (b) (6), vancomycin was reintroduced at dose of 1250 mg daily, intravenously, for event enterococcus faecalis bacteremia. WBC increased to 10.7. Blood cultures became sterile. Earlier before, it was noted that the patient had a hypotension initially attributed to the heavy sedation required to manage his acute respiratory distress syndrome. On the same day, after he developed bacteremia and hypotension, the patient developed septic shock (latency: 10 days; grade 5). Despite sterile blood cultures he had persistent shock that did not improve with medical therapy.

On (b) (6) cefepime was stopped and WBC increased to 15.4, with absolute neutrophils reaching 13.2.

On (b) (6) ampicillin was introduced, at dose of 1 g, every 8 h, intravenously for enterococcus faecalis bacteremia. On the same day, all blood and urine culture information were negative, and the event enterococcus faecalis bacteremia resolved.

On (b) (6) platelets decreased to 94.

On (b) (6) (b) (6) days after first dose of IP the patient experienced increase in AST and ALT (ALT - 659 and AST - 940) and lactic acidosis (severity: grade 4 for both). AST/ALT peaked later in the day at 6603 and 4205 respectively and began to improve, but never returned to less than 5 times the upper limit of normal. No diagnostic testing for liver disease was able to be completed. In response to lactic acidosis, hemodialysis was changed to continuous veno-venous hemofiltration (CVVH) and transfusion of 1 unit of red blood cells was given. Imipenem-cilastatin was introduced at a dose of 500 mg every 8 hours, intravenously, for septic shock.

On (b) (6) micafungin at a dose of 100 mg and vancomycin at a dose of 1000 mg both daily via intravenous route, and vasopressin at a dose of 0.04 unit/min, continuous, intravenously, for septic shock. White blood cells values were 15.0 and neutrophils (absolute) 12.4.



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On the following day, ALT and AST increased to 3807 and 5145, respectively.

On (b) (6) treatment with ampicillin was discontinued. WBC was 18.6 and neutrophils (absolute) was 15.8.

On (b) (6) the patient started treatment with tobramycin, at dose of 560 mg, daily, intravenously, for septic shock.

On (b) (6) treatment with tobramycin was discontinued. WBC was 12.8, ALT was 768 and AST was 382.

On (b) (6) ALT was 575 and AST was 304.

On (b) (6), palliative extubation was performed to improve the patient's failure, however at 17:12, the patient died. Cause of death was reported as septic shock. Autopsy was not performed.

Action taken with study drug in response to the event Increase AST/ALT, was drug withdrawn, and in response to all other events was not applicable.

Corrective treatment: hemodialysis for renal failure; vancomycin, ampicillin, cefepime for enterococcus faecalis bacteremia, continuous veno-venous hemofiltration (CVVH) and transfusion of 1 unit of red blood cells for lactic acidosis, not reported for Increase AST/ALT and Imipenem-cilastatin, vancomycin, micafungin, vasopressin; tobramycin for septic shock

Outcome: fatal for septic shock; enterococcus faecalis bacteremia resolved on (b) (6) Not recovered for rest of the events

On (b) (6) treatment assignment blind was broken for regulatory reporting purposes

Causality assessment is as follows:

(b) (6)

Septic shock: Severity = Grade 5; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Not related, as septic shock identified after study drug administration. Other suspected causes included Covid 19 infection and possible bacterial superinfection.

Company causality rationale: A 77-year-old male patient enrolled in a trial experienced septic shock (b) (6) days after receiving first dose of study drug. Although blood culture and central venous catheter were positive for Enterococcus faecalis, culture tests were negative after the onset of the event. Causality for the event is assessed as not related to study drug or any clinical trial procedure. The event is associated with



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underlying COVID-19 disease aggravated by patient's advanced age and comorbidities like hypertension, diabetes type 2, chronic kidney disease, stage III, renal cell carcinoma and left renal mass.

Renal failure: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Not related. Acute kidney injury had been progressing prior to study drug administration. Others suspected cause was COVID-19 infection.

Company causality rationale: A 77-year-old, Black, male patient with severe or critical COVID-19 experienced renal failure, (b) (6) after receiving study drug. The patient had history of chronic kidney disease. Therefore in concurrence with the investigator, the event of renal failure is assessed as not related to study drug or any clinical trial procedure. The event is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and comorbidities like chronic kidney disease and renal cell carcinoma.

Enterococcal bacteraemia: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Not related. Other suspected cause included enterococcus faecalis bacteremia

Company causality rationale: A 77-year-old male patient enrolled in a trial experienced Enterococcus faecalis bacteraemia, (b) (6) days after receiving first dose of study drug. Blood culture and central venous catheter were positive for Enterococcus faecalis. Causality for the event is assessed as not related to study drug or any clinical trial procedure. The event is nosocomial infection associated with weakened general condition due to underlying COVID-19 disease aggravated by patient's advanced age and comorbidities like hypertension, diabetes type 2, chronic kidney disease, stage III, renal cell carcinoma and left renal mass.

Transaminases increased: Severity = Grade 4; Investigator Causality = Related; Company Causality = Related

Investigator causality rationale: Related - increase in AST/ALT within 24 hours of study drug administration. Other suspected cause was severe sepsis.

Lactic acidosis: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Unrelated - not a known side effect and more likely related to severe sepsis.

Company causality rationale: A 77-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced sepsis, lactic acidosis and increase AST/ALT, after receiving the study drug. The patient's WBC baseline values were within reference ranges



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and they've further increased following study drug administration. The events lactic acidosis and sepsis are assessed as not related to study drug or any clinical trial procedure since they are secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and comorbidities like diabetes type 2 and chronic kidney disease. Patient's baseline AST and ALT were slightly above reference ranges however, they've increased substantially following study drug administration. Concomitant medications hydroxychloroquine, aspirin and azithromycin may provide alternative aetiology for the increased transaminases. Causality for the event increase AST/ALT is assessed as related to study drug and not related to any clinical trial procedure, based on a plausible temporal relationship between study drug administration and the reported event and known potential effect of study drug on functional liver enzymes.

Causality assessment for previously reported event sepsis is as follows:

(b) (6)

Sepsis: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Not related. Other suspected cause was enterococcus faecalis bacteremia.

Company causality rationale: A 77-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced sepsis, lactic acidosis and increase AST/ALT, after receiving the study drug. The patient's WBC baseline values were within reference ranges and they've further increased following study drug administration. The events lactic acidosis and sepsis are assessed as not related to study drug or any clinical trial procedure since they are secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and comorbidities like diabetes type 2 and chronic kidney disease. Patient's baseline AST and ALT were slightly above reference ranges however, they've increased substantially following study drug administration. Concomitant medications hydroxychloroquine, aspirin and azithromycin may provide alternative aetiology for the increased transaminases. Causality for the event increase AST/ALT is assessed as related to study drug and not related to any clinical trial procedure, based on a plausible temporal relationship between study drug administration and the reported event and known potential effect of study drug on functional liver enzymes.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 15-Apr-2020 and 20-Apr-2020 (processed together)

The Investigator provided the following updates: events of Sepsis, Increase AST/ALT and Lactic acidosis added.

Follow up: 23-Apr-2020 and 29-Apr-2020 (processed together)

The Investigator provided the following updates: New event palliative extubation added. Medical history, severity and clinical course updated.



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Case ID: 17809848

Amendment updated.

Follow up: 11-May-2020, 12-May-2020 and 16-May-2020 (processed together)

The Investigator provided the following updates: outcomes, clinical course, action taken, relevant history, relevant concomitants, corrective treatment and rationale for causality assessment updated.

Follow up: 18-May-2020 and 19-May-2020 (processed together)

The Investigator provided the following updates: Event palliative extubation was downgraded, earliest symptoms of pneumonia updated, event Renal failure outcome added.

Follow up: 19-Jun-2020

The Investigator provided the following updates: new event (Septic shock) added. Cause of death updated. Event term, outcome and resolution date (for event enterococcus faecalis bacteremia) updated. Medical history, relevant test, lab test information, concomitant med information and clinical course updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Renal cell carcinoma	2011		UNKNOWN
Renal mass	2020		UNKNOWN
COVID-19 pneumonia	(b) (6)		YES
Anemia			YES
Benign prostatic hyperplasia			YES
Chronic back pain			YES
Chronic kidney disease stage 3			YES
Diabetes mellitus			YES
Erectile dysfunction			YES
Hyperlipidaemia			YES



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FOIA Case Report Information

Case ID: 17809848

Hypertension

YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	98	U/L	7	50	N
Aspartate aminotransferase	129	U/L	10	40	N
Aspartate aminotransferase	5145	U/L	10	40	N
Bilirubin total	0.5	mg/dL	0	1.2	N
Creatinine	4.13	mg/dL	0.5	1.5	N
Absolute neutrophil count	7.2	10 ⁹ /L	1.3	7.5	N
Absolute neutrophil count	15.8	10 ⁹ /L	1.3	7.5	N
Respiratory rate	45	breaths/min			N
White blood cell count	15.4	10 ⁹ /uL	3.9	12	N
Alanine aminotransferase	768	U/L	7	50	N
Chest X-ray					Y
White blood cell count	12.8	10 ⁹ /uL	3.9	12	N
Glucose	163	mg/dL	40	110	N
Electrocardiogram					Y
Alanine aminotransferase	659	U/L	7	50	N
Alanine aminotransferase	3807	U/L	7	50	N
Aspartate aminotransferase	304	U/L	10	40	N
Oxygen saturation	98	%			N
Platelet count	298	10 ⁹ /uL	150	450	N
White blood cell count	10.7	10 ⁹ /uL	3.9	12	N
White blood cell count	15.0	10 ⁹ /uL	3.9	12	N
White blood cell count	18.6	10 ⁹ /uL	3.9	12	N
Alanine aminotransferase	575	U/L	7	50	N
Aspartate aminotransferase	940	U/L	10	40	N
Aspartate aminotransferase	382	U/L	10	40	N
Body temperature	38	Cel			N
Absolute lymphocyte count	0.2	10 ⁹ /L	1.3	4.2	N
SARS-CoV-2 test					N
Albumin	2.1	g/dL	3.4	5	N
Alkaline phosphatase	543	U/L	40	125	N
Creatine phosphokinase	309	U/L	21	232	N
Sodium	152	mmol/L	135	145	N



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FOIA Case Report Information

Case ID: 17809848

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Absolute neutrophil count	13.2	10 ⁹ /L	1.3	7.5	N
Absolute neutrophil count	12.4	10 ⁹ /L	1.3	7.5	N
Body temperature	38	Cel			N
Pulse rate	89	beats/min			N
Platelet count	94	10 ⁹ /uL	150	450	N
Uric acid	10.6	mg/dL	4	8	N
Chest X-ray					Y
White blood cell count	8.5	10 ⁹ /uL	3.9	12	N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ASPIRIN [ACETYLSALICYLIC ACID]	81 MG/QD	Oral	81 mg, QD	Prophylaxis	25-Mar-2020	24-Apr-2020	24 DAY
2	AZITHROMYCIN	500 MG/QD	Intravenous (not otherwise specified)	500 mg, QD	Empiric treatment	14-Apr-2020	17-Apr-2020	4 DAY
3	HYDROXYCHLOROQUIN E	200 MG/Q12H	Oral	200 mg, q12h	COVID-19	26-Mar-2020	05-Apr-2020	23 DAY

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17809905

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 06-May-2020
Outcomes: DE,HO,LT,
Application Type: BLA
FDA Rcvd Date: 25-Jun-2020
Mfr Rcvd Date: 16-Jun-2020
Mfr Control #: US-SA-2020SA122428
Application #: 761037

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		1X	Intravenous (not otherwise specified)	REGN88 or placebo 200 mg or 400 mg, single or multiple	COVID-19	23-Apr-2020	23-Apr-2020
2	SARILUMAB		1X	Intravenous (not otherwise specified)	REGN88 or placebo 200 mg or 400 mg, single or multiple		30-Apr-2020	30-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	19 Day	Yes	NA				SANOFI	
2	SARILUMAB	19 Day	Yes	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Bacterial infection	NA
COVID-19 pneumonia	NA
Liver function test increased	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17809905

Event/Problem Narrative:

Initial information received on 07-May-2020 regarding a solicited valid serious case received from (LP) regeneron-usa gsa-pcp under reference 2020-36405 on 07-May-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6) Patient ID: (b) (6) Site: (b) (6) Country: United States.

Based on additional information received on 12-May-2020, overall company causality was updated from not reportable to reportable.

Study title: (b) (6)

(b) (6)

A 90-year-old, Caucasian, female patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

The patient experienced serious AESI (adverse event of special interest), namely, gram + rods in the blood on (b) (6) and elevated LFTs (AST and ALT) on (b) (6) and COVID-19 pneumonia on (b) (6) after receiving study drug.

Patient's relevant medical history included respiratory failure, septic shock, mitral regurgitation and coronary artery disease.

Relevant concomitant medications included hydroxychloroquine, prednisone and hydrocortisone

On 19-Apr-2020, the patient started experiencing earliest symptoms of pneumonia. Chest X-ray was performed and showed left pulmonary opacity with suspicion for a small left effusion, as well as right perihilar and right lower lung field opacity.

On (b) (6) assessment, the patient had chronic hypercapnic respiratory failure and fever. Her highest temperature recorded within 24 hours prior to dosing was 98.6 degrees Fahrenheit (F), measured axillary. The patient was on the invasive mechanical ventilation and required treatment in the intensive care unit. Her peripheral capillary oxygen saturation (SpO2) was 92%, blood pressure 131/74 mmHg, pulse 78 beats per minute (bpm), respiratory rate 26 respirations per minute (rpm), temperature 97.8 degrees F, and the patient was responsive to pain. Patient's blood chemistry results were: alanine aminotransferase (ALT) 122 IU/L (0-33), aspartate aminotransferase (AST) 122 IU/L (0-32) and total bilirubin 0.5 mg/dl (0-1.2). Patients haematology results included: platelets 184x10E9/L (150-450), white blood cells (WBC) 19.23x10E9/L (3.5-10.5) and neutrophils (absolute) 19.06x10E9/L (1.7-7). Chest X-ray revealed bilateral pulmonary infiltrates unchanged from previous examination and no pneumothorax.

On (b) (6) patients WBC count was 16.12x10⁹/L and neutrophils (absolute) 14.01x10⁹/L.

On (b) (6), (b) (6) days 4 hrs 37 min after the first administration of IP, patient's WBC count was 14.09x10E9/L. At 18:00, Gram + rods were found in her blood (Grade 4) and she started receiving piperacillin/tazobactam (Zosyn) at dose of 4.5 g, every eight hours, intravenously, was introduced as corrective treatment for Gram + rods in the blood. The event was assessed as life threatening and adverse event of special interest (Clinically significant invasive bacterial or fungal infections) leading to hospitalization. No further information provided regarding



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17809905

diagnostic procedures.

On (b) (6) patients WBC count was $12.78 \times 10^9/L$.

On (b) (6) (b) (6) days after the administration of study drug, the patient experienced elevation of liver function tests (LFTs), with ALT and AST (grade 3), measuring 634 and 798 respectively. The event was assessed to be life threatening and adverse event of special interest leading to hospitalization. The patient did not receive any corrective treatment in response to the event. On the same day, Zosyn was discontinued.

On (b) (6) the patient experienced elevation of liver function tests (LFTs), with ALT and AST measuring 508 and 447 respectively, and in following days, they continued to decrease.

On (b) (6) WBC was 23.62.

On (b) (6) ALT and AST were 148 and 43, respectively.

On (b) (6) ALT dropped to 35, and AST to 24. WBC was 13.32.

On (b) (6) at 21:19, (b) (6) days 8 hrs 6 min after the administration of the investigational product, the patient experienced COVID-19 pneumonia (severity : Grade 5, seriousness criteria : death). The patient died on (b) (6) at 21:19. The cause of death was COVID-19 pneumonia. Autopsy was not performed.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

Action taken with study drug in response to the event Gram + rods in the blood was drug withdrawn, and in response to Elevated LFTs (AST and ALT) and COVID-19 pneumonia was not applicable.

Corrective treatment: piperacillin/tazobactam (Zosyn) for gram + rods in the blood, not reported for COVID-19 pneumonia

Outcome: not recovered from gram + rods in the blood; recovering from elevated LFTs (AST and ALT), fatal for COVID-19 pneumonia

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

Causality assessment is as follows:

COVID 19 pneumonia:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: No alternative explanation was provided.

Relationship with IP according to company: not reportable.



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FOIA Case Report Information

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Company causality rationale: A 90-year-old, female patient enrolled in the trial, died due to COVID-19 pneumonia approximately (b) (6) after administration of the blinded study drug. The reported event is assessed as not related to study drug or any clinical trial procedure since it is secondary to progression of COVID-19 infection, complicated by patient's relevant medical history of mitral regurgitation and coronary artery disease and further aggravated by patient's advanced age.

For gram + rods in the blood:

Relationship with IP according to investigator: reasonable possibility.

Investigator causality rationale: No alternative explanation was provided.

Relationship with IP according to company: not reportable.

Company causality rationale: A 90-year-old female patient enrolled in the trial, experienced bacterial infection (b) (6) days after first and (b) (6) days after last administration of study drug. Considering already compromised health of this elderly patient with COVID 19 complicated by pneumonia and septic shock before study drug administration with a prior increased count of WBC and neutrophils on the day of study drug administration and concomitant use of prednisone and hydrocortisone, the event is assessed as not related to study drug or any clinical trial procedure.

For elevated LFTs (AST and ALT):

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: No alternative explanation was provided.

Relationship with IP according to company: reportable.

Company causality rationale:

A 90-year-old female patient with severe or critical COVID-19 and worsening pneumonia experienced increased liver function test, (b) (6) days after receiving the last dose of the study drug. Patient's baseline AST and ALT values were above reference ranges however, they've further increased following study drug administration. Based on a plausible temporal association between study drug administration and the reported event and known potential effect of study drug on functional liver enzymes, causality is assessed as related to study drug. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation. The event is not related to any clinical trial procedure. Causality was also confounded by concomitant drugs acetaminophen, hydroxychloroquine and hydrocortisone.

Relationship to study conduct or study procedure: The Investigator assessed the event Gram + rods in the blood as related and events Elevated LFTs (AST and ALT) and COVID 19 pneumonia as not related to study conduct or study procedure.

Follow up received date: 12-May-2020

The Investigator provided the following updates: new related serious event added, and case upgraded.

Follow up received date: 29-May-2020 and 03-Jun-2020 (processed together)

The Investigator provided the following updates: date of informed consent signing, outcome of event 'gram + rods in the blood' and relevant tests updated, new event 'death' added, clinical course updated.



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Follow up received date: 04-Jun-2020 and 05-Jun-2020 (processed together) The Investigator provided the following updates: verbatim of event 'Death' and reason of death updated.

Follow up received date: 11-Jun-2020
The Investigator provided the following updates: clinical course and autopsy details updated.

Follow up received date: 16-Jun-2020 and 20-Jun-2020 (processed together):
The Investigator provided the following updates: outcome for Gram + rods in the blood and Elevated LFTs (AST and ALT) updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Mitral regurgitation	Dec-2016		YES
Acute kidney injury	(b) (6)		YES
Respiratory failure	(b) (6)	(b) (6)	NO
Septic shock	(b) (6)		YES
Atrial fibrillation			YES
Coronary artery disease			YES
Fibromyalgia			YES

Medical History Product(s)	Start Date	End Date	Indications	Events
ACETAMINOPHEN			F bromyalgia	
ZITHROMAX				
ZOSYN	19-Apr-2020	19-Apr-2020	COVID-19	
PLAQUENIL [HYDROXYCHLOROQUINE SULFATE]	20-Apr-2020	20-Apr-2020	COVID-19	



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FOIA Case Report Information

Case ID: 17809905

VANCOCIN	19-Apr-2020	19-Apr-2020	COVID-19
PREDNISON			F bromyalgia
SOLU-CORTEF	20-Apr-2020	21-Apr-2020	

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	122	iU/L	0	33	N
Alanine aminotransferase	634	iU/L	0	33	N
Aspartate aminotransferase	24	iU/L	0	32	N
Bilirubin	0.5	mg/dL	0	1.2	N
Neutrophil count	12.06	10 ⁹ /L	1.7	7	N
Aspartate aminotransferase	798	iU/L	0	32	N
Aspartate aminotransferase	447	iU/L	0	32	N
Chest X-ray					Y
Pulse rate	78	beats/min			N
Neutrophil count	19.06	10 ⁹ /L	1.7	7	N
Alanine aminotransferase	508	iU/L	0	33	N
Aspartate aminotransferase	43	iU/L	0	32	N
Blood pressure	131/74	mmHg			N
Body temperature	98.6	degF			Y
White blood cell count	23.62	10 ⁹ /L	3.5	10.5	N
Neutrophil count	11.05	10 ⁹ /L	1.7	7	N
Oxygen saturation	92	%			N
White blood cell count	12.78	10 ⁹ /L	3.5	10.5	N
Body temperature	97.8	degF			Y
Chest X-ray					Y
Platelet count	184	10 ⁹ /L	150	450	N
White blood cell count	16.12	10 ⁹ /L	3.5	10.5	N
Aspartate aminotransferase	122	iU/L	0	32	N
White blood cell count	13.32	10 ⁹ /L	3.5	10.5	N
Alanine aminotransferase	148	iU/L	0	33	N
Alanine aminotransferase	35	iU/L	0	33	N
Neutrophil count	14.01	10 ⁹ /L	1.7	7	N
Respiratory rate	26	breaths/min			N
White blood cell count	19.23	10 ⁹ /L	3.5	10.5	N
White blood cell count	14.09	10 ⁹ /L	3.5	10.5	N



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FOIA Case Report Information

Case ID: 17809905

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	DIGOXIN	.125 UG/QD	Oral	0.125 g, qd; date of last administration: 22-Apr-2020	Atrial fibrillation			354 HR
2	PLAQUENIL [HYDROXYCHLOROQUINE PHOSPHATE]	200 MG/Q12H	Other	200 mg, bid, FEEDING TUBE	COVID-19	20-Apr-2020	24-Apr-2020	402 HR
3	PREDNISONE	20 MG/QD		20 mg, qd	Fibromyalgia	07-May-2020	02-Jun-2020	426 HR
4	SOLU-CORTEF	25 MG/Q12H	Intravenous (not otherwise specified)	25 mg, bid		23-Apr-2020	02-May-2020	402 HR
5	SOLU-CORTEF	20 MG/QD	Intravenous (not otherwise specified)	20 mg, qd		03-May-2020	04-May-2020	402 HR
6	SOLU-CORTEF	25 MG/Q6H	Intravenous (not otherwise specified)	25 mg, qid	COVID-19	21-Apr-2020	23-Apr-2020	402 HR
7	ZOSYN	4.5 G/Q8H	Intravenous (not otherwise specified)	4.5 g, tid	COVID-19	20-Apr-2020	24-Apr-2020	426 HR

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17810896

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 11-May-2020
Outcomes: DE,OT,
Application Type: BLA
FDA Rcvd Date: 12-Nov-2020
Mfr Rcvd Date: 30-Oct-2020
Mfr Control #: US-SA-2020SA131828
Application #: 761037

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	200 mg, 1X	COVID-19	14-Apr-2020	14-Apr-2020
2	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	200 mg, 1X		21-Apr-2020	21-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	35 Day	NA	NA				SANOFI	
2	SARILUMAB	35 Day	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Alanine aminotransferase increased	NA
Aspartate aminotransferase increased	NA
Respiratory failure	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17810896

Event/Problem Narrative:

Initial information received on 12-May-2020 and 15-May-2020 (processed together) regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference number (2020-37412) on 12-May-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6)

Patient ID (b) (6) Site (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

A 53-year-old, Hispanic, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6) The patient experienced serious AESIs Elevated AST and Elevated ALT on (b) (6) and serious acute hypoxemic respiratory failure on (b) (6) after receiving study drug.

The patient's relevant medical history included type 2 diabetes mellitus.

Relevant concomitant medication included remdesivir and hydroxychloroquine.

On 20-Mar-2020, the patient started experiencing earliest symptoms of pneumonia with rales/crackles on lung auscultations present at baseline.

On 05-Apr-2020, chest X-ray showed diffuse haziness of the right lung and peripheral left lung base.

On (b) (6) peripheral oxygen saturation (SpO₂) was 94%, and the patient was receiving supplemental oxygen via invasive mechanical ventilation as well as treatment in the intensive care unit. The highest temperature recorded within 24 hours prior to dosing was 100.8 degrees Fahrenheit (°F). On baseline, temperature was 99.7 Fahrenheit (F), blood pressure was 104/67 mmHg, pulse 72 bpm and respiratory rate was 28 rpm. Alanine aminotransferase (ALT) was 101 U/L (reference range: 9-50), aspartate aminotransferase (AST) was 99 U/L (10-37), total bilirubin was 0.8 mg/dl (0.2-1.3). Haematology results were as follows: platelets 359x10⁹/uL (156-325), white blood cells (WBC) 14.04x10⁹/uL (3.12-8.44), and neutrophils (absolute) 11.58 (reference range not reported). On the following days, ALT and AST levels were decreasing.

On (b) (6) patient's viral signs were as follows: SpO₂ 91%, blood pressure 131/67, pulse 103, respiratory rate 13, body temperature 37.5 °C measured orally. The patient was unresponsive.

On (b) (6) SpO₂ 94%, blood pressure increased to 163/82, pulse 99, respiratory rate 23, body temperature 98.8 °F.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17810896

On (b) (6) ALT was 24, and AST was 40, SpO2 was 96%, blood pressure was 147/71, pulse was 79, respiratory rate was 18, temperature was 36.9 °C.

On (b) (6) after (b) (6) days latency, the patient was diagnosed with elevated ALT and AST (both are grade: 4 and medically significant serious AESI). ALT increased to 634, and AST to 477. The patient received electrolyte repletion and continuous renal replacement therapies as corrective treatments for the events.

On (b) (6) ALT was 281 and AST 102.

On (b) (6) ALT decreased to 217, SpO2 was 100%, blood pressure was 124/70, pulse was 101, respiratory rate was 32, temperature was 38 degree C.

On (b) (6) ALT decreased to 138. On the following days, ALT and AST levels were decreasing.

On (b) (6) the patient's vital signs were: SpO2 was 92%, blood pressure was 104/62, pulse was 116, respiratory rate was 35, temperature was 37.4°C. The patient was unresponsive.

On (b) (6) after (b) (6) days latency, the patient experienced acute hypoxemic respiratory failure (Severity: Grade 5) for which no corrective treatment was used. On the same day at 06:36, the patient passed away. The patient died due to acute hypoxemic respiratory failure. Autopsy was not performed.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes

Action taken with study drug in response to the events was not applicable.

Corrective treatment: none for acute hypoxemic respiratory failure; electrolyte repletion and continuous renal replacement therapies for elevated AST, elevated ALT

Outcome: not recovered for elevated AST, elevated ALT and Fatal for acute hypoxemic respiratory failure.

Causality assessment is as follows:

Acute hypoxemic respiratory failure: Severity: Grade 5; Investigator Causality = Not Related; Company Causality = not related (not reportable).

Investigator causality rationale: The patient was in critical condition. Acute hypoxemic respiratory failure not related to study drug.



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FOIA Case Report Information

Case ID: 17810896

Company causality rationale: A 53-year-old, male patient enrolled in the trial experienced respiratory failure which ended fatally (b) (6) days after receiving the (b) (6) dose of the study drug. Based on the clinical course, the event is most likely secondary to progression of Covid-19 infection further aggravated by patient's prolonged hospitalization in ICU and mechanical ventilation. Therefore, the event is assessed as not related to the study drug or any clinical trial procedure.

Aspartate aminotransferase increased: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Related

Alanine aminotransferase increased: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Related

Investigator causality rationale: The patient was in critical condition. Elevated AST and ALT were related to illness. Other suspected cause included kidney injury in the setting of COVID-19 infection.

Company causality rationale: A 53-year-old, male patient with severe or critical COVID-19 experienced elevated AST and elevated ALT, after study drug administration. Baseline levels of both enzymes were above reference ranges and increased up significantly after receiving the last dose of the study drug. Confounding factor is concomitant use of remdesivir. Based on a known potential effect of study drug on the functional liver enzymes, contributing role of the suspect drug cannot be excluded and causality for both events is assessed as related to study drug and not related to any clinical trial procedure. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow-up: 18-May-2020. The Investigator provided the following updates: new events elevated ALT and elevated AST with all relevant information added.

Follow-up: 27-May-2020 and 28-May-2020 (processed together). The Investigator provided the following updates: events elevated ALT and elevated AST deleted, outcome updated, death information added and relevant lab information updated.

Follow-up: 05-Jun-2020. The Investigator provided the following updates: fatal event acute hypoxemic respiratory failure added, relevant laboratory results added.

Follow-up: 19-Jun-2020 The Investigator provided the following updates: concomitant medication added, details regarding autopsy added. Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Expectedness Assessment per current IB (version 14):
Acute hypoxemic respiratory failure: unexpected



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17810896

Elevated AST: unexpected
Elevated ALT: unexpected

(b) (6)

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Transthoracic echocardiogram	(b) (6)	(b) (6)	NO	
Type 2 diabetes mellitus			YES	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Aspartate aminotransferase	40	U/L	10	37	N
Aspartate aminotransferase	477	U/L	10	37	N
Aspartate aminotransferase	222	U/L	10	37	N
Aspartate aminotransferase	102	U/L	10	37	N
Blood pressure measurement	104/62	mmHg			N
Chest X-ray					Y
Heart rate	103	beats/min			N
Oxygen saturation	96	%			N
Alanine aminotransferase	217	U/L	9	50	N
Blood pressure measurement	104/67	mmHg			N
Blood pressure measurement	163/82	mmHg			N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17810896

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood pressure measurement	124/70	mmHg			N
Body temperature	98.8	degF			Y
Platelet count	359	10 ³ /uL	156	325	N
White blood cell count	14.04	10 ³ /uL	3.12	8.44	N
Aspartate aminotransferase	131	U/L	10	37	N
Heart rate	101	beats/min			N
Absolute neutrophil count	11.58	UNK			Y
Respiratory rate	28	breaths/min			N
Respiratory rate	13	breaths/min			N
Aspartate aminotransferase	99	U/L	10	37	N
Blood bilirubin	0.5	mg/dL	0.2	1.3	N
Body temperature	99.7	degF			Y
Body temperature	37.4	deg			N
Respiratory rate	16	breaths/min			N
Respiratory rate	32	breaths/min			N
Alanine aminotransferase	24	U/L	9	50	N
Heart rate	116	beats/min			N
Oxygen saturation	94	%			N
Oxygen saturation	94	%			N
White blood cell count	12.59	10 ³ /uL	3.12	8.44	N
Body temperature	36.6	deg			N
Body temperature	38	deg			N
Heart rate	72	beats/min			N
Heart rate	99	beats/min			N
Platelet count	350	10 ³ /uL	156	325	N
Alanine aminotransferase	634	U/L	9	50	N
Alanine aminotransferase	281	U/L	9	50	N
Blood pressure measurement	131/67	mmHg			N
Body temperature	37.5	deg			N
Heart rate	110	beats/min			N
Respiratory rate	23	breaths/min			N
Alanine aminotransferase	101	U/L	9	50	N
Alanine aminotransferase	138	U/L	9	50	N
Blood bilirubin	0.8	mg/dL	0.2	1.3	N
Oxygen saturation	91	%			N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17810896

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Oxygen saturation	100	%			N
Oxygen saturation	92	%			N
Respiratory rate	35	breaths/min			N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	HYDROXYCHLOROQUIN E	600 MG/		600 mg	COVID-19	07-Apr-2020	07-Apr-2020	60876 MIN
2	HYDROXYCHLOROQUIN E	400 MG/		400 mg		08-Apr-2020	12-Apr-2020	60876 MIN
3	REMDESIVIR	200 MG/	Intravenous (not otherwise specified)	200 mg, UNK	Accidental exposure to product	15-Apr-2020	15-Apr-2020	37745 MIN

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811201

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: BRA Event Date: Outcomes: DE,OT, Application Type: BLA
 FDA Rcvd Date: 21-May-2020 Mfr Rcvd Date: 12-May-2020 Mfr Control #:BR-ROCHE-2601755 Application #: 125276

Patient Information:

Age: 40 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19	May-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	NOT PROVIDED				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2601755 is a spontaneous case, received on 12/May/2020 from a hematologist in Brazil. It concerns a 40 year old male patient (age not reported) who died while administering tocilizumab (Actemra) for COVID-19 (intentionally used for unlabelled indication (off lable use)).

The patient's medical history, past drugs, concurrent conditions and concomitant medications were not reported.

Prior to receiving therapy with tocilizumab, the patient was hospitalized and was having extracorporeal membrane oxygenation (ECMO) with kidney failure and pulmonary thromboembolism (PTE), which occurred due to Covid-19. In May/2020, he started receiving tocilizumab (dosing regime not reported, lot number: not reported) for COVID-19 (intentional use for unlabelled indication (off lable use)). On (b) (6) he died due to unknown cause. Autopsy information was not reported.

The reporter did not provide the causality of unknown cause of death with tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811201

No further information was provided.

Relevant Medical History:

None

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811201

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811943

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Event Date:** 02-Apr-2020 **Outcomes:** DE,HO,LT, **Application Type:** BLA

FDA Rcvd Date: 25-May-2020 **Mfr Rcvd Date:** 22-May-2020 **Mfr Control #:** US-SA-2020SA102646 **Application #:** 761037

Patient Information:

Age: 46 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	REGN mAb1 200 mg, 1X	COVID-19	03-Apr-2020	03-Apr-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	6311 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Bacteraemia	NA
COVID-19	NA
Pneumothorax	NA
Thrombocytopenia	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811943

Event/Problem Narrative:

Initial information from the Company sponsored study (b) (6) was received on 11-Apr-2020.

Patient ID: (b) (6) Site: (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

A 46-year-old, Caucasian, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6) The patient experienced tension pneumothorax on (b) (6) before receiving study drug, non-serious AESI Bacteremia on (b) (6) SAE Thrombocytopenia on (b) (6) and Hypoxic respiratory failure due to Covid-19 on (b) (6) after receiving study drug.

No relevant medical history was reported.

Relevant concomitant medications included hydroxychloroquine, amlodipine besilate, plaquenil, vancomycin and piperacillin.

On (b) (6), nasopharyngeal swab was taken for SARS-CoV-2-PCR virus test and was positive. On the same day, the patient was admitted to hospital. ECG showed minimal voltage criteria for LVH (Left ventricular hypertrophy). Chest X-ray was also performed, which suggested subtle bibasilar opacities. the pulmonary vasculature was unremarkable.

On (b) (6) before the administration of IP, the patient experienced tension pneumothorax (Grade 3) leading to hospitalization and had thoracostomy tube placed as a corrective treatment for the event.

On (b) (6) patients peripheral oxygen saturation (SpO2) was 92%, blood pressure was 150/71 mmHg, pulse was 87 beats per minute (bpm), and respiratory rate was 26 respirations per minute (rpm). Platelet count was 220x10E9/L (ref range 160-383), white blood cell (WBC) count was 9.98x10E9/L (4.22 - 10.33) and neutrophils 8.81x10E3/uL (1.98-6.59). Chemistry results were alanine aminotransferase (ALT) 11 Units/L (10 - 50), aspartate aminotransferase (AST) 22 Units/L (10 - 50), carbon dioxide (bicarbonate) 17 mmol/L (22 - 31) and total bilirubin 0.2 mg/dL (0.2 - 1.3).

On (b) (6) the patient's white blood cell (WBC) count was 8.58.

On (b) (6) patient's platelet count was 182x10E9/L and WBC count was 8.44x10E9/L.

On (b) (6), (b) (6) days 9 hrs. 11 min after the first administration of IP, the patient developed bacteremia (Grade 4) and thrombocytopenia (Grade 4). Bacteremia was considered as non-serious adverse event of special interest and thrombocytopenia was considered as life



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811943

threatening. Blood culture tests were performed and moderate growth of Staphylococcus aureus, heavy growth of Pseudomonas aeruginosa and Haemophilus influenzae was noted in sample. White blood cells, Gram negative rods, gram positive cocci and rods were also present on test. Patient's WBC count increased to 12.21x 10E9/L. Patients platelet count was also low, 112x10E9/L (160-383). No corrective treatment was applied for thrombocytopenia. As a corrective treatment for bacteremia, the patient started receiving vancomycin, at a dose of 1000 mg daily, intravenously.

On (b) (6), the patient also started receiving piperacillin-tazobactam, at a dose of 3.375 g, every eight hours, intravenously, as a corrective treatment for bacteremia.

On (b) (6) the patient received vancomycin at a dose of 1500 mg, intravenously, after which vancomycin was stopped.

On (b) (6) piperacillin-tazobactam was stopped.

On (b) (6) blood pressure was 142/74 mmHg, pulse was 86 beats per minute (bpm), and respiratory rate was 32 respirations per minute (rpm).

On (b) (6) treatment assignment blind was broken for regulatory reporting purposes.

On (b) (6) at 03:46, platelet count of 170x10E9/L and the event thrombocytopenia was deemed resolved.

On (b) (6) patient's SpO2 was 96%, blood pressure 109/51 mmHg, pulse 85 beats per minute (bpm) and respiratory rate 25 respirations per minute (rpm). Bicarbonate value was 35 mmol/L.

On (b) (6) (b) (6) days 9 hrs. 11 min after administration of IP, patient's SpO2 was 93%, blood pressure 126/51 mmHg, pulse 81 beats per minute (bpm) and respiratory rate 25 respirations per minute (rpm). Bicarbonate value was 32 mmol/L. Platelet count was 250x10E9/L and WBC count 19.13x10E9/L. On the same day, patient experienced hypoxic respiratory failure due to Covid-19 (Grade 5) and died.

The patient died on (b) (6) Cause of death was hypoxic respiratory failure due to Covid-19. Autopsy was not performed.

At the time of patients death, bacteremia had not resolved and outcome of pneumothorax was unknown.

Action taken with study drug in response all the events was not applicable.

For COVID-19:

Relationship to investigational product according to Investigator: no reasonable possibility

Investigator causality rationale: No alternative explanation provided.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811943

Relationship to investigational product according to Company: not reportable

Company causality rationale: A 46-year-old, male patient enrolled in the trial, experienced hypoxic respiratory failure due to Covid-19 and died after administration of the blinded study drug. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug is the most plausible cause for hypoxic respiratory failure in this subject. Therefore, event is assessed as unrelated to the study drug or to any clinical trial procedure.

For Thrombocytopenia:

Relationship to investigational product according to Investigator: no reasonable possibility

Investigator causality rationale: No alternative explanation provided.

Relationship to investigational product according to Company: not reportable

Company causality rationale: A 46-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced thrombocytopenia, (b) (6) days after receiving the study drug. Reported event is confounded with the use of concomitant medications plaquenil, vancomycin and piperacillin. Therefore, thrombocytopenia is assessed as not related to study drug and not related to any study procedure.

For Pneumothorax:

Relationship to investigational product according to Investigator: no reasonable possibility

Investigator causality rationale: No alternative explanation provided.

Relationship to investigational product according to Company: not reportable

Company causality rationale: A 46-year-old, male patient enrolled in the trial, experienced tension pneumothorax one day before administration of the blinded study drug. Considering that the event occurred before receipt of study drug, severe or critical COVID-19 with pneumonia before initiation of the study drug is the most plausible cause for tension pneumothorax in this subject. Therefore, event is assessed as unrelated to the study drug or to any clinical trial procedure.

For Bacteraemia:

Relationship to investigational product according to Investigator: reasonable possibility

Investigator causality rationale: Bacteremia occurred on (b) (6) drug was given on (b) (6) which makes this adverse event potentially related to study drug (Sarilumab known to increase risk of infections). That said, patient does have central lines and is on renal replacement therapy (CRRT) so his Staphylococcus aureus bacteraemia could likely be from a line infection.

Relationship to investigational product according to Company: reportable

Company causality rationale: A 46-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced bacteraemia (b) (6) days after receiving the study drug. Blood culture was positive for Staphylococcus aureus, Pseudomonas aeruginosa and Haemophilus influenzae, as well as gram-positive cocci and gram-negative rods. Based on plausible temporal relationship between the event and study drug administration and a known fact that higher rate of bacterial infections was observed in patients treated with sarilumab,



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811943

causality for the event is assessed as related to study drug and not related to any clinical trial procedure.

Relationship to study conduct or study procedure: The Investigator assessed both events as not related to study conduct or study procedure.

Follow-up: 16-Apr-2020:

The Investigator provided the following updates: patient's age corrected, event bacteremia downgraded to non-serious AESI, outcome, dosing details, relevant tests, event course and resolution date updated.

Follow-up: 28-Apr-2020:

The Investigator provided the following updates: new event Hypoxic respiratory failure due to Covid-19 added and clinical course updated.

Follow-up: 28-Apr-2020:

The Investigator provided the following updates: intensity and seriousness criteria updated.

Follow-up: 12-May-2020, 13-May-2020 and 18-May-2020 (processed together):

The Investigator provided the following updates: outcome of the event Thrombocytopenia, clinical course, medical history and concomitant and corrective medication updated, event added (Tension pneumothorax). Upon internal review, the PT term was updated for event Hypoxic respiratory failure due to Covid-19.

Correction on 22-May-2020: The following was corrected based on internal review, company causality of Thrombocytopenia.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute kidney injury	(b) (6)		YES
Renal osteodystrophy	(b) (6)		YES
Chronic kidney disease			YES
Essential hypertension			YES
Renal osteodystrophy			YES
Type 2 diabetes mellitus			YES



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811943

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood pressure					Y
ECG					Y
Heart rate	86	beats/min			N
Platelet count	182	10 ⁹ /L	160	383	N
Platelet count	250	10 ⁹ /L	160	383	N
Respiratory rate	25	breaths/min			N
WBC	8.44	10 ⁹ /L	4.22	10.33	N
Carbon dioxide	17	mmol/L	22	31	N
Bilirubin	0.2	mg/dL	0.2	1.3	N
Blood culture					Y
Blood pressure	126/51	mmHg			N
Chest X-ray					Y
Heart rate	85	beats/min			N
Neutrophils	8.81	10 ³ /uL	1.98	6.59	Y
Respiratory rate	25	breaths/min			N
WBC	9.98	10 ⁹ /L	4.22	10.33	Y
WBC	8.58	10 ⁹ /L	4.22	10.33	N
WBC	12.21	10 ⁹ /L	4.22	10.33	N
Blood pressure					Y
Blood pressure	109/51	mmHg			N
Carbon dioxide	35	mmol/L	22	31	N
WBC	19.13	10 ⁹ /L	4.22	10.33	N
Oxygen saturation	92	%			Y
Platelet count	170	10 ⁹ /L	160	383	N
SARS-CoV-2 PCR test					Y
Blood culture					Y
Carbon dioxide	32	mmol/L	22	31	N
Heart rate	87	beats/min			Y
Oxygen saturation	96	%			N
Oxygen saturation	93	%			N
Platelet count	112	10 ⁹ /L	160	383	N
Respiratory rate	32	breaths/min			N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811943

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	11	U/L	10	50	N
Aspartate aminotransferase	22	U/L	10	50	N
Aspartate aminotransferase			10	50	Y
Heart rate	81	beats/min			N
Platelet count	220	10 ⁹ /L	160	383	N
Respiratory rate	26	breaths/min			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	BENZONATATE	100 MG/Q8H	Oral	100 mg, tid	Cough	03-Apr-2020	04-Apr-2020	5 DAY
2	COMPAZINE [PROCHLORPERAZINE EDISYLATE]				Vomiting			6 DAY
3	COMPAZINE [PROCHLORPERAZINE EDISYLATE]	10 MG/	Intravenous (not otherwise specified)	10 mg, PRN as necessary	Nausea	02-Apr-2020		6 DAY
4	NORVASC	5 MG/QD	Oral	5 mg, qd	Hypertension	02-Apr-2020	04-Apr-2020	6 DAY
5	PEPCID [ALUMINIUM HYDROXIDE GEL, DRIED;MAGNESIUM CARBONATE]	20 MG/Q12H	Intravenous (not otherwise specified)	20 mg, bid	Prophylaxis	04-Apr-2020	04-Apr-2020	4 DAY
6	PLAQUENIL [HYDROXYCHLOROQUI NE PHOSPHATE]	200 MG/Q12H	Oral	200 mg bid		03-Apr-2020	04-Apr-2020	8 DAY
7	PLAQUENIL [HYDROXYCHLOROQUI NE PHOSPHATE]	400 MG/Q12H	Oral	400 mg, bid		02-Apr-2020	07-Apr-2020	8 DAY
8	PLAQUENIL [HYDROXYCHLOROQUI NE PHOSPHATE]	400 MG/Q12H	Oral	400 mg bid	COVID-19	31-Mar-2020	03-Apr-2020	8 DAY
9	THORAZINE [CHLORPROMAZINE]	10 MG/1X	Oral	10 mg, 1x once	Drug use for unknown indication	01-Apr-2020	01-Apr-2020	7 DAY
10	TYLENOL	650 MG/	Oral	650 mg, as necessary	Drug use for unknown indication	31-Mar-2020		8 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811943

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
11	ZOFRAN [ONDANSETRON]				Vomiting			8 DAY
12	ZOFRAN [ONDANSETRON]	4 MG/	Intravenous (not otherwise specified)	4 mg, PRN (as necessary)	Nausea	31-Mar-2020		8 DAY

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811956

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 02-Apr-2020 Outcomes: DE,HO Application Type: ANDA

FDA Rcvd Date: 21-May-2020 Mfr Rcvd Date: 14-May-2020 Mfr Control #: ES-FRESENIUS KABI-FK202004819 Application #: 204764

Patient Information:

Age: 72 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LINEZOLID (MANUFACTURER UNKNOWN)		600 MG/Q12H	Intravenous (not otherwise specified)	600 mg every 12 hours	Drug use for unknown indication	28-Mar-2020	16-Apr-2020
2	HYDROXYCHLOROQUIN E		400 MG/QD	Oral	400 mg/day	COVID-19 pneumonia	26-Mar-2020	02-Apr-2020
3	MEROPENEM (MANUFACTURER UNKNOWN)		1 G/Q8H	Intravenous (not otherwise specified)	1 g every 8 hours	Drug use for unknown indication	04-Apr-2020	19-Apr-2020
4	METAMIZOLE		2 G/Q8H	Intravenous (not otherwise specified)	2 g every 8 hours	Drug use for unknown indication	13-Apr-2020	16-Apr-2020
5	PIPERACILLIN/TAZOBAC TAM 4G / 0.5G (MANUFACTURER UNKNOWN)		1 DF/Q8H	Intravenous (not otherwise specified)	1 DF every 8 hours	Drug use for unknown indication	04-Apr-2020	07-Apr-2020
6	TOCILIZUMAB		600 MG/1X			Adult respiratory stress syndrome	27-Mar-2020	27-Mar-2020
7	TOCILIZUMAB					COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	LINEZOLID (MANUFACTURER UNKNOWN)	20 Day	Yes	NA	UNK			FRESENIUS MEDICAL CARE	
2	HYDROXYCHLOROQUIN E	22 Day	Yes	NA	UNK				
3	MEROPENEM (MANUFACTURER UNKNOWN)	13 Day	Yes	NA	UNK				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811956

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
4 METAMIZOLE	4 Day	Yes	NA	UNK				
5 PIPERACILLIN/TAZOBAC TAM 4G / 0.5G (MANUFACTURER UNKNOWN)	13 Day	Yes	NA	UNK				
6 TOCILIZUMAB	21 Day	Yes	NA	UNK				
7 TOCILIZUMAB	21 Day	Yes	NA	UNK				

Event Information:

Preferred Term (MedDRA ® Version: 23.1)

ReC

Drug reaction with eosinophilia and systemic symptoms

NA

Hypofibrinogenaemia

NA

Upper gastrointestinal haemorrhage

NA

Event/Problem Narrative:

This case from SPAIN was received from the EMA with the worldwide case reference no. ES-AEMPS-627000.

A 72-year-old male patient received MEROPENEM (manufacturer and batch number unknown), 1 g every 8 hours intravenously from 04Apr2020 until 19Apr2020 and Piperacillin/Tazobactam 4 g/0.5 g (manufacturer and batch number unknown) 1 DF every 8 hours intravenously from 04Apr2020 until 07Apr2020 and LINEZOLID (manufacturer and batch number unknown) 600 mg every 12 hours intravenously from 28Mar2020 until 16Apr2020, all for an unknown indication.

As co-suspect medications, the patient received Roactemra 600 mg total on 27Mar2020 for coronavirus infection and adult respiratory stress syndrome, Metamizol 2 g every 8 hours intravenously from 13Apr2020 until 16Apr2020 for an unknown indication and Hydroxychloroquine from 26Mar2020 until 02Apr2020 400 mg/day orally for coronavirus infection and pneumonia.

On (b) (6) the patient experienced Hypofibrinogenemia and recovered on (b) (6) from this event. On (b) (6) the patient experienced DRESS syndrome and upper gastrointestinal hemorrhage. Outcome of upper gastrointestinal hemorrhage was reported as recovering and from DRESS syndrome as not recovered. All suspect drugs were discontinued. The case was considered to be serious (caused/prolonged hospitalisation). It was reported that the patient died on (b) (6) due to septic shock and COVID-19 pneumonia.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17811956

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Adult respiratory stress syndrome			
COVID-19 pneumonia			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: FRESENIUS KABI

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17812256

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 27-Mar-2020 Outcomes: DE,OT, Application Type: NDA
 FDA Rcvd Date: 21-May-2020 Mfr Rcvd Date: 19-May-2020 Mfr Control #: ES-PFIZER INC-2020200777 Application #: 050670

Patient Information:

Age: 62 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	AZITHROMYCIN		500 MG/	Oral	500 mg, daily	COVID-19 pneumonia	27-Mar-2020	01-Apr-2020
2	CEFTRIAZONE		2 G/	Intravenous (not otherwise specified)	2 g, daily		27-Mar-2020	01-Apr-2020
3	DEXAMETHASONE		20 MG/	Intravenous (not otherwise specified)	20 mg, daily	COVID-19	29-Mar-2020	01-Apr-2020
4	ENOXAPARINE		80 MG/	Subcutaneous	80 mg, unknown	Thromboembolism prophylaxis	01-Apr-2020	03-Apr-2020
5	HYDROXYCHLOROQUIN E		400 MG/	Oral	400 mg, daily	COVID-19 pneumonia	27-Mar-2020	02-Apr-2020
6	ROACTEMRA		600 MG/	Intravenous (not otherwise specified)	600 mg, single	COVID-19 pneumonia	27-Mar-2020	27-Mar-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	AZITHROMYCIN		NA	NA				PFIZER	
2	CEFTRIAZONE		NA	NA					
3	DEXAMETHASONE		NA	NA					
4	ENOXAPARINE		NA	NA					
5	HYDROXYCHLOROQUIN E		NA	NA					
6	ROACTEMRA		NA	NA					



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17812256

Event Information:

Preferred Term (MedDRA ® Version: 23.1)

ReC

Anaemia	NA
Hypocoagulable state	NA
Hypofibrinogenaemia	NA
Off label use	NA
Product use in unapproved indication	NA
Respiratory failure	NA
Thrombocytopenia	NA

Event/Problem Narrative:

This is a spontaneous report downloaded from the European Medicines Agency (EMA) EudraVigilance- WEB ES-AEMPS-628603.

A contactable physician reported that a 62-year-old male patient started to receive azithromycin (manufacturer unknown), oral from 27Mar2020 to 01Apr2020 at 500 mg, daily for covid-19 pneumonia; ceftriaxone (manufacturer unknown), intravenous from 27Mar2020 to 01Apr2020 at 2 g, daily for an unspecified indication; dexamethasone (manufacturer unknown), intravenous from 29Mar2020 to 01Apr2020 at 20 mg, daily for covid-19, hydroxychloroquine (manufacturer unknown), oral from 27Mar2020 to 02Apr2020 at 400 mg, daily for covid-19 pneumonia; low molecular weight heparin (ENOXAPARINE), subcutaneous from 01Apr2020 to 03Apr2020 at 80 mg, unknown for high risk of thromboembolic disease; tocilizumab (ROACTEMRA), intravenous from 27Mar2020 to 27Mar2020 at 600 mg, single for covid-19 pneumonia. The patient's medical history and concomitant medications were not reported. On 03Apr2020, the patient experienced hypofibrinogenemia with the outcome of recovered on 03Apr2020 and hypocoagulable state with the outcome of recovered on 10Apr2020. On 08Apr2020, the patient experienced thrombocytopenia with the outcome of not recovered. On 14Apr2020, the patient experienced anaemia with no clinical symptoms with the outcome of not recovered. The patient experienced respiratory insufficiency on an unspecified date and died. The patient died on (b) (6)

It was unknown whether autopsy was performed. The action taken in response to the events for all of the suspect drugs was post-therapy.

Pfizer is a marketing authorization holder of azithromycin in the country of incidence or the country where the product was purchased (if different). This may be a duplicate report if another marketing authorization holder of azithromycin has submitted the same report to the regulatory authorities.

No follow-up attempts are possible. No further information is expected.

Relevant Medical History:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17812256

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No	Sender Organization: PFIZER	503B Compounding Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17813329

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ESP
Event Date: 31-Mar-2020
Outcomes: DE,
Application Type: ANDA
FDA Rcvd Date: 21-May-2020
Mfr Rcvd Date: 11-May-2020
Mfr Control #: ES-TEVA-2020-ES-1236090
Application #: 065150

Patient Information:

Age: 26 YR
Sex: Female
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	AZITROMICINA (7019A)		500 MG/QD	Oral	500 Milligram Daily;	COVID-19 pneumonia	23-Mar-2020	24-Mar-2020
2	DEXAMETASONA (722A)		20 MG/QD	Intravenous (not otherwise specified)	20 Milligram Daily;		28-Mar-2020	01-Apr-2020
3	DEXKETOPROFENO (7312A)		25 MG/Q8H	Intravenous (not otherwise specified)	75 Milligram Daily;		27-Mar-2020	01-Apr-2020
4	ENOXAPARINA (2482A)		40 MG/QD	Subcutaneous	40 Milligram Daily;		27-Mar-2020	01-Apr-2020
5	HIDROXICLOROQUINA (2143A)		400 MG/QD	Oral	400 Milligram Daily;	COVID-19 pneumonia	23-Mar-2020	01-Apr-2020
6	TOCILIZUMAB (8289A)		600 MG/	Intravenous (not otherwise specified)		Severe acute respiratory syndrome	29-Mar-2020	29-Mar-2020
7	TOCILIZUMAB (8289A)					COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	AZITROMICINA (7019A)	9 Day	NA	NA	Unknown				
2	DEXAMETASONA (722A)	4 Day	NA	NA	Unknown				
3	DEXKETOPROFENO (7312A)	4 Day	NA	NA					
4	ENOXAPARINA (2482A)	5 Day	NA	NA	Unknown				
5	HIDROXICLOROQUINA (2143A)	9 Day	NA	NA	Unknown			TEVA	



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17813329

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
6 TOCILIZUMAB (8289A)	3 Day	NA	NA	Unknown				
7 TOCILIZUMAB (8289A)	3 Day	NA	NA	Unknown				

Event Information:

Preferred Term (MedDRA Version: 23.1)

ReC

Coagulopathy

NA

Event/Problem Narrative:

11-May-2020, Spontaneous, Health authority Serious report (Report duplicates - AGEMED: ES-AEMPS-628824)

A Physician reported the case of a 26-Years-old Female patient who received AZITROMICINA (7019A) (AZITHROMYCIN, Product cannot be excluded as a Teva product), HIDROXICLOROQUINA (2143A) (HYDROXYCHLOROQUINE, Product cannot be excluded as a Teva product), DEXAMETASONA (722A) (DEXAMETHASONE, not Teva's product), ENOXAPARINA (2482A) (ENOXAPARIN, not Teva's product), TOCILIZUMAB (8289A) (TOCILIZUMAB, not Teva's product), DEXKETOPROFENO (7312A) (DEXKETOPROFEN, not Teva's product).

The patient took AZITROMICINA (7019A) for COVID-19 PNEUMONIA (AZITHROMYCIN, Oral, from 23-Mar-2020, until 24-Mar-2020, 500Milligram per day) batch: Unknown, HIDROXICLOROQUINA (2143A) for COVID-19 PNEUMONIA (HYDROXYCHLOROQUINE, Oral, from 23-Mar-2020, until 01-Apr-2020, 400Milligram per day) batch: Unknown, DEXAMETASONA (722A) (DEXAMETHASONE, Intravenous (not otherwise specified), from 28-Mar-2020, until 01-Apr-2020, 20Milligram per day) batch: Unknown, ENOXAPARINA (2482A) (ENOXAPARIN, Subcutaneous, from 27-Mar-2020, until 01-Apr-2020, 40Milligram per day batch: Unknown, TOCILIZUMAB (8289A) for SEVERE ACUTE RESPIRATORY SYNDROME, SRAS COVID 19 (TOCILIZUMAB, Intravenous (not otherwise specified), from 29-Mar-2020, until 29-Mar-2020, 600 MG) batch: Unknown, DEXKETOPROFENO (7312A) (DEXKETOPROFEN, Intravenous (not otherwise specified), from 27-Mar-2020, until 01-Apr-2020, 75Milligram per day, 25 MG).

While on the suspect medications, the patient experienced COAGULOPATHY(Serious , since 31-Mar-2020) .

At the time of the report the outcome of the AEs was: COAGULOPATHY: Fatal.

Action taken with suspect drugs: AZITROMICINA (7019A) - Drug discontinued; HIDROXICLOROQUINA (2143A) - Drug discontinued; DEXAMETASONA (722A) - Drug discontinued; ENOXAPARINA (2482A) - Dosage maintained; TOCILIZUMAB (8289A) - Drug discontinued.

The patient had medical history of C-SECTION(since (b) (6) until (b) (6) not Continuing).

On (b) (6) the patient died. The patient died from MULTIORGAN FAILURE, COVID-19. It is unknown whether an autopsy was performed.

The patient's concomitant medication were unspecified.

The patient's past medication were unspecified.

Lab tests were not reported.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17813329

This case was considered serious based on the following criteria: (Death)
Because this is a spontaneous case, regulatory distribution will be handled as though it is a related case.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Caesarean section	(b) (6)	(b) (6)	NO

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17813329

Reporter Source:

Study Report?: No

Sender Organization: TEVA

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17814749

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: COL
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 22-May-2020
Mfr Rcvd Date: 18-May-2020
Mfr Control #: CO-ROCHE-2604743
Application #: 125276

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		800 MG/	Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2604743 is a spontaneous case, received on 18/May/2020 from a pharmacist in Colombia. It concerns a patient of unknown demographics who was treated intentionally for tocilizumab for an unapproved indication which is covid-19 (off-label use) and died whilst being treated with tocilizumab (Actemra).

The patient's medical history, past drugs, concurrent conditions and concomitant medications were not reported.

On an unknown date, the patient started therapy with tocilizumab (lot number: not reported) 800 mg for (route and frequency not reported) for covid-19 (off label use). On (b) (6) the patient died due to unknown cause. It was unknown if an autopsy was performed or not.

The pharmacist did not report a causality between unknown cause of death and tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17814749

At the time of the patient's death, it was not reported if tocilizumab was ongoing or not.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17814749

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17814753

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 02-May-2020
Outcomes: DE,HO,LT,
Application Type: BLA
FDA Rcvd Date: 22-May-2020
Mfr Rcvd Date: 19-May-2020
Mfr Control #: US-ROCHE-2605856
Application #: 125276

Patient Information:

Age: 71 YR
Sex: Male
Weight: 90 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		800 MG/1X	Intravenous drip	Ongoing: No	COVID-19 pneumonia	28-Apr-2020	28-Apr-2020
2	ACTEMRA		400 MG/1X	Intravenous drip	Ongoing: No		29-Apr-2020	29-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				
2	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Cerebrovascular accident	NA
Death	NA
Intentional product use issue	NA
Off label use	NA
Pneumothorax	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17814753

Event/Problem Narrative:

AER 2605856 is a spontaneous case, received on 19/May/2020 from a pharmacist in the USA. It concerns a 71 year old male patient who developed pneumothorax, life threatening stroke and died due to unknown cause whilst being treated intentionally with tocilizumab (Actemra) for COVID-19 pneumonia (off label use).

Concurrent conditions included atrial fibrillation, hypertension, hyperlipidemia, benign prostatic hyperplasia, psoriatic arthritis and gout. Concomitant medications included hydroxychloroquine, apixaban (Eliquis), dexamethasone, norepinephrine and methotrexate. No medical history or past drugs were reported.

On (b) (6) the patient was admitted to the hospital with symptoms of COVID-19. He already had two weeks of symptoms prior to admission and initially tested positive for COVID-19 in the outpatient setting before presenting to the hospital (date unknown). In addition, his wife and daughter had also tested positive. Blood cultures collected on the day of admission were negative and did not reveal any co-infection for him. On (b) (6) the patient started receiving hydroxychloroquine (HCQ) 400 mg by mouth twice daily for the treatment of COVID-19 infection. He received a total of two doses. Then he received HCQ 200 mg by mouth twice daily from (b) (6) to (b) (6). On (b) (6) chest X-ray (CXR) revealed a new bilateral finding suggestive of pneumonia. All laboratory measures were reported as of 04:00 (4:00 AM) each morning, and the reported values on (b) (6) were prior to the first dose of tocilizumab administered. The test utilized to diagnose COVID-19 was asked, but not provided. On same day, test was performed at: 04:00 and showed Interleukin-6 (IL-6) was at 255 pg/mL (normal range: 0-15 pg/mL), C-Reactive Protein (CRP) was at 182.7 mg/L (normal range: 0-10 mg/L), Ferritin was at 1150 ng/mL (normal range: 17.9-464 ng/mL) and Lactate Dehydrogenase (LDH) was at 1607 IU/L (normal range: 313-618 IU/L). All laboratory measures were reported as of 04:00 (4:00 AM) each morning, and the reported values on (b) (6) were prior to the first dose of tocilizumab administered. The test utilized to diagnose COVID-19 was asked, but not provided. On the same day, he later received his first dose of tocilizumab IV 800 mg (intentionally used for unlabeled indication, off label use). On (b) (6) A second dose of tocilizumab IV 400 mg was administered. On (b) (6) C-Reactive Protein (CRP) was at 166.8 mg/L, Ferritin was at 1430 ng/mL, LDH was 1817 IU/L. One day later, on (b) (6) he worsened and was subsequently intubated. At the time, a feeding tube was also placed and all oral medications were administered through the feeding tube. On same day, (Test time: 04:00) C-Reactive Protein (CRP) was at 57.7 mg/L, Ferritin was at 1170 ng/mL, LDH was at 1923 IU/L. On (b) (6) (Test time: 04:00) IL-6 was at 1500 pg/mL, Lactate Dehydrogenase was at 1565 IU/L. On (b) (6) another CXR revealed a large right-sided pneumothorax, which resolved after a chest tube was immediately placed on the very same day. On (b) (6) he once again tested positive for COVID-19, confirmed by a repeat test on (b) (6). On (b) (6) Ferritin was at 813 ng/mL. Additionally, a head CT (computed tomography) scan (CAT scan), also on (b) (6) revealed infarcts in the posterior parietal lobe and the front parietal region with no evidence of hemorrhagic infarcts-findings suggestive of a stroke. At the time of stroke, he was reported to be on full dose anticoagulation with Eliquis (apixaban) 5 mg twice daily while in the intensive care unit (ICU). He received dexamethasone every 8 hours at various doses throughout the course of his hospital stay. He was admitted to the ICU and did require vasopressors, further clarified as norepinephrine, at some point (time and dose not clarified). He did not require any dialysis during his hospital admission. He was reported to take methotrexate for psoriatic arthritis, but his dosing regimen and last known dose was not clarified. Unless otherwise indicated, it is unknown whether patient's listed health conditions and medications being used were ongoing at the time of death. Exact cause of death was not clarified. No other events were reported. He passed away on (b) (6) while still intubated until time of death. Cause of death was not reported. It was not reported if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17814753

At the time of the death, the outcome of the stroke was unknown.

The pharmacist did not report a causality of stroke, death and pneumothorax with tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Atrial fibrillation			UNKNOWN
Benign prostatic hyperplasia			UNKNOWN
Gout			UNKNOWN
Hyperlipidaemia			UNKNOWN
Hypertension			UNKNOWN
Psoriatic arthropathy			UNKNOWN

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
C-reactive protein	166.8	mg/L	0	10	N
Serum ferritin	1430	ng/mL	17.9	464	N
Blood lactate dehydrogenase	1817	IU/L	313	618	N
Interleukin level	1500	pg/mL	0	15.5	N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17814753

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Interleukin level	255	pg/mL	0	15.5	N
Serum ferritin	1150	ng/mL	17.9	464	N
C-reactive protein	182.7	mg/L	0	10	N
Blood lactate dehydrogenase	1607	IU/L	313	618	N
Blood lactate dehydrogenase	1923	IU/L	313	618	N
Blood lactate dehydrogenase	1565	IU/L	313	618	N
Serum ferritin	1170	ng/mL	17.9	464	N
C-reactive protein	57.7	mg/L	0	10	N
Serum ferritin	813	ng/mL	17.9	464	N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	DEXAMETHASONE	Q8H	Unknown	Various doses administered every 8 hours ;Ongoing: Unknown				
2	ELIQUIS	5 MG/Q12H	Oral		Atrial fibrillation			
3	HYDROXYCHLOROQUIN E	200 MG/Q12H	Oral			24-Apr-2020	27-Apr-2020	16 DAY
4	HYDROXYCHLOROQUIN E	400 MG/Q12H	Oral		COVID-19	23-Apr-2020	23-Apr-2020	16 DAY
5	METHOTREXATE				Psoriatic arthropathy			
6	NOREPINEPHRINE		Intravenous (not otherwise specified)					

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17815379

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: IRN
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 22-May-2020
Mfr Rcvd Date: 18-May-2020
Mfr Control #: IR-ROCHE-2604565
Application #: 125276

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2604565 is a spontaneous case, received on 18/May/2020 from a physician in Iran, Islamic Republic Of It concerns a patient of unknown demographics who was died and used tocilizumab (Actemra) for unapproved indication covid-19 (off label use).

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On an unknown date, the patient started therapy with tocilizumab (lot number and dosing regimen not reported) for covid-19 intentional use for unapproved indication (off label use). On an unknown date, the patient was died due to unknown cause. It was unknown if an autopsy was performed or not.

At the time of death, it was not reported if the therapy with tocilizumab was ongoing or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17815379

The physician did not report a causality of death with tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17815379

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17815826

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ROM **Event Date:** **Outcomes:** DE, **Application Type:** BLA

FDA Rcvd Date: 22-May-2020 **Mfr Rcvd Date:** 20-May-2020 **Mfr Control #:** RO-ROCHE-2605615 **Application #:** 125276

Patient Information:

Age: 77 YR **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		800 MG/	Unknown	2 vials of 400 mg	COVID-19	12-May-2020	
2	ROACTEMRA		800 MG/	Unknown	2 vials of 400 mg		13-May-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN,UNK NOWN				
2	ROACTEMRA		NA	NA	UNKNOWN,UNK NOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1)	ReC
Death	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17815826

Event/Problem Narrative:

AER 2605615 is a spontaneous case, received on 20/May/2020 from a pharmacist in Romania. It concerns a 77 year old patient (gender unspecified) who was died (captured as death nos) whilst being treated with tocilizumab (Roactemra).

Concurrent conditions included covid 19 infection, acute respiratory infection. No medical history, past drug and concomitant medications were reported.

On 12/May/2020, the patient started therapy with tocilizumab (lot number, route and frequency not reported) at 800 mg for covid-19 infection. On 13/May/2020, the patient started therapy with tocilizumab (lot number, route and frequency not reported) at 800 mg for covid-19 infection. On an unknown date in (b) (6) he was died. It was unknown if an autopsy was performed or not.

The reporter did not assess the causality of event death NOS.

The company assessed the causality of event death NOS as not related to tocilizumab in view of limited information about clinical course leading to death, cause of death, investigations and autopsy report which prevents reasonable assessment of causal association at this time. The causality will be reassessed upon receipt of relevant follow up information.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
COVID-19			
Respiratory tract infection			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17815826

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17816151

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: IRN
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 22-May-2020
Mfr Rcvd Date: 18-May-2020
Mfr Control #: IR-ROCHE-2604564
Application #: 125276

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2604564 is a spontaneous case, received on 18/May/2020 from a physician in Iran, Islamic Republic Of. It concerns a patient of unknown demographics who died and used Actemra intentional used for unapproved indication (off label use) whilst being treated with tocilizumab (Actemra).

No medical history, past drugs, concurrent conditions and concomitant medications were not reported.

On an unspecified date, the patient started therapy with tocilizumab (lot number and dosing regimen were not reported) for COVID-19 (off label use). On an unspecified date, the patient died. It was not reported if an autopsy was performed or not.

At the time of this report, therapy with tocilizumab was not reported.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17816151

The physician did not report a causality between death with tocilizumab.

No further information was reported.

This case is cross-referenced with AER 2604564, AER 2604564 and AER 2604564, as same reporter.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17816151

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17816709

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 28-Apr-2020 Outcomes: DE,HO,LT,OT, Application Type: BLA
 FDA Rcvd Date: 29-Jun-2020 Mfr Rcvd Date: 19-Jun-2020 Mfr Control #:US-SA-2020SA116331 Application #: 761037

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	1x, REGN mAb1 400 mg	COVID-19	23-Apr-2020	23-Apr-2020
2	SARILUMAB		1X	Intravenous (not otherwise specified)	1x, REGN88 or placebo 200 mg or 400 mg, single or multiple, 1X		04-May-2020	04-May-2020
3	SARILUMAB		1X	Intravenous (not otherwise specified)	1x, REGN88 or placebo 200 mg or 400 mg, single or multiple, 1X		24-Apr-2020	24-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	20718 MINUTES	NA	NA				SANOFI	
2	SARILUMAB	20718 MINUTES	NA	NA				SANOFI	
3	SARILUMAB	20718 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA Ⓜ Version: 23.1)	ReC
Acute kidney injury	NA
Alanine aminotransferase increased	NA
Anaemia	NA
Aspartate aminotransferase increased	NA
COVID-19	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17816709

Deep vein thrombosis	NA
Hypotension	NA
Pulmonary embolism	NA
Shock	NA

Event/Problem Narrative:

Based on additional information received on 13-May-2020 and 14-May-2020 (processed together), the overall reporter causality has been updated from not related to related and company causality has been updated from not reportable to reportable.

Initial information received on 01-May-2020 regarding a solicited valid serious case received from (lp) regeneron-usa gsa-ppc under reference number 2020-35298 on 01-May-2020 and transmitted to Sanofi on 04-May-2020, in the scope of company sponsored study (b) (6)

(b) (6)

Patient ID (b) (6) Site: (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

A 56-year-old, male patient, of unreported ethnicity, with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6)

(b) (6)

The patient experienced hypotension and shock on (b) (6) left lower extremity DVT on (b) (6) acute kidney injury on (b) (6), pulmonary embolus on (b) (6), symptomatic anemia or (b) (6) Death due to complications of Covid-19 on (b) (6) and elevated ALT and elevated AST on (b) (6) after receiving study drug.

The patient's medical history included coronary artery disease (CAD), peripheral artery disease (PAD), diabetes mellitus (DM) and hepatitis C virus (HCV).

Relevant concomitant medication included metoprolol, vancomycin, methylprednisolone, acetaminophen, ceftriaxone and aspirin.

On 06-Apr-2020, the patient started experiencing earliest symptoms of pneumonia.

On 19-Apr-2020, chest X-ray was performed and showed the presence of patchy bilateral infiltrates.

On 23-Apr-2020, rales/crackles were present on lung auscultation. The patient had fever, with the highest temperature recorded within 24 hours prior to dosing of 100.9 degrees Fahrenheit (degree F), measured orally. The patient was on high-flow nasal cannula, and his peripheral capillary oxygen saturation (SpO2) was 97%. Patients blood pressure was 141/64 mmHg, pulse 81 beats per minute (bpm), respiratory rate



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19 respirations per minute (rpm), temperature 97.6 degree F and the patient was alert. Patient's blood chemistry results were: alanine aminotransferase (ALT) 107 U/L (reference range: 1-45), aspartate aminotransferase (AST) 121 U/L (reference range: 1-40), sodium 140 mEq/L (reference range: 135-145), potassium 4.9 mEq/L (reference range: 3.5-5), carbon dioxide (bicarbonate) 21.2 mEq/L (reference range: 20-28), creatinine 1.9 mg/dL (reference range: 0.5-1), and total bilirubin 0.3 mg/dL (reference range: 0.1-1.2). Patients haematology results included: platelets 222/nL (reference range: 150-440), white blood cells (WBC) 4.94/nL (reference range: 3.9-10.6), neutrophils (absolute) 4.20/nL (reference range: 1.9-8.7), red blood cells (RBC) 3.98 x10E12/L (reference range: 4.5-5.3), haemoglobin 10.8 g/dL (reference range: 13-16) and haematocrit 33.1 % (reference range: 37-49).

On (b) (6) patients platelet count was 304/nL. Patient was intubated. Blood pressure decreased to 103/59 mmHg. On the same day, (b) (6) days 9 hrs. 18 min after the administration of the investigational product, the patient experienced shock (Grade 4) and hypotension (Grade 3). The event was hypotension was assessed to be medically significant and required hospitalization; shock was assessed to be life threatening leading to hospitalization. Echocardiogram was performed but the results were not provided. The patients hospitalization was prolonged due to shock. WBC count was 9.84, neutrophils were 8.43. Information regarding corrective treatment for shock was not provided.

On (b) (6) (b) (6) days 9 hrs. 18 min after the administration of the investigational product, the patient experienced Left lower extremity deep vein thrombosis (DVT) (Grade 4). This event was assessed to be medically significant, life threatening and required hospitalization. Lower extremity venous duplex bilateral was performed and patient started receiving continuous infusion of heparin, at a dose of 1050 units/hour, intravenously, as a corrective treatment for the event.

On (b) (6) (b) (6) days 9 hrs. 18 min after the administration of the investigational product, the patient experienced acute kidney injury (AKI) (Grade 3) assessed as medically significant. His sodium level was 140 mEq/L, potassium 4.9 mEq/L and bicarbonate 22.4 mEq/L. Platelet count decreased back to 239/nL. Nephrology was consulted, and the patient was recommended avoidance of nephrotoxins, renal diet and was to be monitored for need for continuous renal replacement therapy (CRRT). The patient's hospitalization was prolonged due to left lower extremity DVT. Treatment with heparin was stopped for DVT.

On (b) (6) patients creatinine value was 5.9 mg/dL. On the same day, the patient started corrective treatment for hypotension with norepinephrine 1-30 mcg/min, continuous infusion, intravenously.

On (b) (6) creatinine decreased to 3.3 mg/dL.

On (b) (6) blood pressure was 146/68 mmHg and event hypotension was deemed as resolved. Creatinine was 3.4 mg/dl. Patient started with continuous renal replacement therapy (CRRT) as a corrective treatment for the event acute kidney injury. On the same day (b) (6) days 9 hrs 18 min after the administration of study drug, the patient experienced pulmonary embolus (Grade 4). assessed to be life threatening. Information regarding corrective treatment was not provided.

On (b) (6) creatinine increased to 5.0 mg/dL. On the same day (b) (6) days 9 hrs. 18 min after the administration of the investigational product, the patient experienced symptomatic anemia (Grade 3) assessed to be medically significant. RBC decreased to 2.21 x10E12/L, haemoglobin decreased to 6.2 g/dL and haematocrit decreased to 20.2%. Patient received packed red blood cell (PRBC) transfusion as a



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corrective treatment for the event anemia and stopped on the same day.

On (b) (6) haemodialysis catheter was inserted for AKI.

On (b) (6) days 9 hrs. 18 min after the administration of study drug, the patient was diagnosed with elevated ALT and AST (Grade 3 for both). Both the events were assessed to be medically significant adverse events of special interest. On the same day, AST peak of 752 was noticed. Information regarding corrective treatment for both the events was not provided.

On (b) (6) a peak value of ALT 500 was observed.

On (b) (6) the patients ALT was 419 and AST 236. The event elevated AST was considered as recovered on the same day.

On (b) (6), computerized tomography (CT) angiogram showed filling defect consistent with pulmonary embolism that was unchanged compared to prior study.

On (b) (6), the patients WBC was 13.41, neutrophils absolute was 11.70.

On (b) (6) ALT increase was resolved with value 113 U/L.

On (b) (6) oxygen saturation decreased to 95%, blood pressure decreased to 101/62 mmHg, pulse increased to 98 bpm, respiratory rate increased to 30 rpm, body temperature increased to 99.3 degree F, ALT decreased to 86, AST decreased to 44, sodium decreased to 132, potassium decreased to 3.7, creatinine decreased to 1.4, RBC increased to 2.65, haemoglobin increased to 8.0, haematocrit increased to 25.9, WBC decreased to 12.56, neutrophils (absolute) decreased to 8.40 and platelets decreased to 141. On the same day at 13:55, 25 days 23 hrs. 13 min after the administration of IP, the patient died from shock due to complications of COVID-19 (Grade 5). On (b) (6) the patient died. The cause of death was reported as shock due to COVID-19. Autopsy was not performed.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

At the time of patients death, outcome of Left lower extremity DVT, Shock, Pulmonary embolus, Acute kidney injury and Symptomatic anemia was not recovered.

Action taken with study drug in response to Death due to complications of COVID-19 was not applicable, and in response to other events was dose not changed.

For COVID-19:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: Other suspected causes included COVID-19.

Relationship with IP according to company: not reportable.

Company causality rationale: A 56-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced death due to COVID 19 after receiving the study drug. The reported event is assessed as not related to the study drug or any clinical trial



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procedure since it is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's reported comorbidities such as coronary artery disease, peripheral artery disease, diabetes mellitus and hepatitis C virus.

For Deep vein thrombosis:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: Not applicable. Other suspected cause was reported as COVID-19 coagulopathy.

Relationship with IP according to company: not reportable.

Company causality rationale: A 56-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced left lower extremity DVT (b) (6) days after receiving the study drug. The reported event is assessed as not related to the study drug or any clinical trial procedure since it is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's reported comorbidities. It's been recently observed that patients with underlying COVID-19 disease are at a higher risk for thrombotic and thromboembolic events.

For Shock:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: Other suspected causes were COVID-19 infection, sepsis.

Relationship with IP according to company: not reportable.

For Pulmonary embolus:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: Other suspected cause was noted as COVID-19 coagulopathy.

Relationship with IP according to company: not reportable.

For shock and Pulmonary embolus:

Company causality rationale: A 56-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced shock and pulmonary embolism, after receiving the study drug. The events are assessed as not related to study drug or any clinical trial procedure since it is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's comorbidities. It has been reported recently that patients with COVID-19 are at higher risk for venous thrombosis and thromboembolism.

For Alanine aminotransferase increased and Aspartate aminotransferase increased:

Relationship with IP according to investigator: reasonable possibility.

Investigator causality rationale: AE of special interest but does not appear temporally related to study investigational product. Other suspected causes include critical illness.

Relationship with IP according to company: reportable.

Company causality rationale: A 56-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced elevated AST and ALT, (b) (6) days after receiving the (b) (6) dose of the study drug. Patient's baseline AST and ALT values were increased, however, they've further increased following study drug administration. Based on a plausible temporal association between study drug administration and the reported events and known potential effect of study drug on functional liver enzymes, causality for the events of



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elevated AST and ALT is assessed as related to study drug. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation. The events are not related to any clinical trial procedure. The events are confounded with concomitant use of methylprednisolone, acetaminophen, ceftriaxone and aspirin.

For Hypotension:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: Other suspected causes include COVID-19 infection, critical illness and sedation.

Relationship with IP according to company: not reportable.

Company causality rationale: A 56-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced hypotension, (b) (6) days after receiving the second dose of study drug. The reported event is assessed as not related to the study drug or any clinical trial procedure since it is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's reported comorbidities such as coronary artery disease (CAD), peripheral artery disease (PAD), diabetes mellitus (DM) and hepatitis C virus (HCV).

For acute kidney injury:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: Not applicable. Other suspected cause was reported as COVID-19 infection.

Relationship with IP according to company: not reportable.

Company causality rationale: A 56-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced acute kidney injury (b) (6) days after receiving the study drug. The reported event is assessed as not related to the study drug or any clinical trial procedure since it is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's reported comorbidities.

For Anaemia:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: Not related. Other suspected causes include critical illness.

Relationship with IP according to company: not reportable.

Company causality rationale: A 56-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced symptomatic anemia, (b) (6) after receiving (b) (6) dose of study drug. The reported event is assessed as not related to the study drug or any clinical trial procedure since the patient had decreased hemoglobin before onset of treatment with study drug and the event is likely due to progression of COVID-19 infection and pneumonia further aggravated by patient's reported comorbidities such as coronary artery disease (CAD), peripheral artery disease (PAD), diabetes mellitus (DM) and hepatitis C virus (HCV).

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow-up: 04-May-2020, 05-May-2020 and 07-May-2020 (process together):

The Investigator provided the following updates: study drug administration added, new events, corrective treatments added, clinical course updated.



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Follow-up: 13-May-2020 and 14-May-2020 (processed together):

The Investigator provided the following updates: new events pulmonary embolus, shock, elevated ALT, elevated AST, were added, causality added, outcome added, corrective treatments added, clinical course updated, labs added.

Follow-up: 20-May-2020:

The Investigator provided the following updates: new fatal event added, study status, clinical course and concomitant medication details updated.

Follow-up: 05-Jun-2020:

The Investigator provided the following updates: event hypotension outcome updated and clinical course updated.

Follow up: 19-Jun-2020

The Investigator provided the following updates: outcome of event Left lower extremity DVT, Acute kidney injury, Symptomatic anemia, Shock and Pulmonary embolus, outcome and resolution date for Elevated ALT, event term updated for event Pulmonary embolus.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Acute respiratory failure	(b) (6)		YES	
Coronary artery disease			YES	
Diabetes mellitus			YES	
GERD			YES	
Hepatitis C			YES	
Peripheral arterial disease			YES	
Medical History Product(s)	Start Date	End Date	Indications	Events



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Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	500	U/L	1	45	N
Aspartate aminotransferase	752	U/L	1	40	N
Blood pressure	141/64	mmHg			Y
Body temperature	100.9	degF			Y
Hematocrit	25.9	%	37	49	N
Hemoglobin	10.8	g/dL	13	16	N
Bilirubin	0.3	mg/dL	0.1	1.2	Y
Creatinine	5	mg/dL	0.5	1	N
Creatinine	1.4	mg/dL	0.5	1	N
Body temperature	97.6	degF			Y
Hematocrit	33.1	%	37	49	N
Pulse rate	81	beats/min			N
Platelet count	239	10 ⁹ /L	150	440	N
Platelet count	141	10 ⁹ /L	150	440	N
Alanine aminotransferase	419	U/L	1	45	N
Creatinine	5.9	mg/dL	0.5	1	N
Potassium	4.9	meq/L	3.5	5	Y
Body temperature	99.3	degF			Y
Neutrophil count	11.70	10 ⁹ /L	1.9	8.7	N
Red blood cell count	2.65	10 ¹² /L	4.5	5.3	N
White blood cell count	12.56	10 ⁹ /L	3.9	10.6	N
Aspartate aminotransferase	121	U/L	1	40	N
Sodium	140	meq/L	135	145	Y
Body temperature	100.9	degF			Y
Carbon dioxide	22.4	meq/L	20	28	Y
Hemoglobin	6.2	g/dL	13	16	N
White blood cell count	9.84	10 ⁹ /L	3.9	10.6	N
CT angiography					Y
Creatinine	3.3	mg/dL	0.5	1	N
Potassium	4.9	meq/L	3.5	5	Y
Potassium	3.7	meq/L	3.5	5	N
Blood pressure	101/62	mmHg			N
Sodium	132	meq/L	135	145	N
Pulse rate	98	beats/min			N
Oxygen saturation	95	%			N
Alanine aminotransferase	107	U/L	1	45	N
Creatinine	5	mg/dL	0.5	1	N
Creatinine	3.4	mg/dL	0.5	1	N
Blood pressure	103/59	mmHg			N
Carbon dioxide	21.2	meq/L	20	28	Y



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Chest X-ray					Y
Hematocrit	20.2	%	37	49	N
Hemoglobin	8	g/dL	13	16	N
Neutrophil count	4.20	10 ⁹ /L	1.9	8.7	N
Neutrophil count	8.40	10 ⁹ /L	1.9	8.7	N
Respiratory rate	30	breaths/min			N
White blood cell count	4.94	10 ⁹ /L	3.9	10.6	Y
White blood cell count	13.41	10 ⁹ /L	3.9	10.6	N
White blood cell count	13.41	10 ⁹ /L	3.9	10.6	Y
Alanine aminotransferase	86	U/L	1	45	N
Aspartate aminotransferase	236	U/L	1	40	N
Blood pressure	146/68	mmHg			N
Sodium	140	meq/L	135	145	Y
Echocardiogram					Y
Oxygen saturation	97	%			N
Platelet count	222	10 ⁹ /L	150	440	Y
Red blood cell count	3.98	10 ¹² /L	4.5	5.3	N
Red blood cell count	2.21	10 ¹² /L	4.5	5.3	N
Respiratory rate	19	breaths/min			Y
Alanine aminotransferase	113	U/L	1	45	N
Aspartate aminotransferase	44	U/L	1	40	N
Creatinine	1.9	mg/dL	0.5	1	N
Neutrophil count	8.43	10 ⁹ /L	1.9	8.7	N
Neutrophil count	11.70	10 ⁹ /L	1.9	8.7	N
Platelet count	304	10 ⁹ /L	150	440	N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN				Pain			19 DAY
2	ACETAMINOPHEN				Fever			19 DAY
3	ACETAMINOPHEN	650 MG/	Sublingual	650 mg, PRN	Fever	19-Apr-2020	19-May-2020	19 DAY
4	ACETAMINOPHEN-CODEINE	1X		300/60 mg, 1X	Pain	21-Apr-2020	21-Apr-2020	17 DAY



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	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
5	ASPIRIN [ACETYLSALICYLIC ACID]	81 MG/QD		81 mg, QD	Anticoagulant therapy	20-Apr-2020	27-Apr-2020	18 DAY
6	CEFTRIAXONE	1000 MG/1X	Intravenous (not otherwise specified)	1000 mg, 1X	Viral pneumonia	19-Apr-2020	19-Apr-2020	19 DAY
7	CEFTRIAXONE	1000 MG/QD	Intravenous (not otherwise specified)	1000 mg, QD		21-Apr-2020	23-Apr-2020	19 DAY
8	DOXYCYCLINE	100 MG/1X		100 mg, 1X	COVID-19 pneumonia	19-Apr-2020	19-Apr-2020	19 DAY
9	DOXYCYCLINE	100 MG/Q12H		100 mg, bid		20-Apr-2020	23-Apr-2020	19 DAY
10	METHYLPREDNISOLON E	60 MG/Q12H		60 mg, q12h	Inflammation	22-Apr-2020	27-Apr-2020	16 DAY
11	METOPROLOL	100 MG/QD	Oral	100 mg, qd	Hypertension	23-Apr-2020	28-Apr-2020	15 DAY
12	SOLU-CORTEF	100 MG/1X	Intravenous (not otherwise specified)	100 mg, 1X	Inflammation	28-Apr-2020	28-Apr-2020	10 DAY
13	VANCOMYCIN	1250 MG/Q12H	Intravenous (not otherwise specified)	1250 mg, q12h	COVID-19 pneumonia	28-Apr-2020	29-Apr-2020	10 DAY
14	VANCOMYCIN	1250 MG/1X		1250 mg, 1X		01-May-2020	01-May-2020	10 DAY
15	ZOSYN	3.375 G/Q6H	Intravenous (not otherwise specified)	3.375 g, q6h	COVID-19 pneumonia	28-Apr-2020	08-May-2020	10 DAY

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17816816

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Event Date:** **Outcomes:** DE,HO,OT, **Application Type:** BLA

FDA Rcvd Date: 11-Jun-2020 **Mfr Rcvd Date:** 04-Jun-2020 **Mfr Control #:** US-ROCHE-2604712 **Application #:** 125276

Patient Information:

Age: 62 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ACTEMRA		700 MG/	Intravenous (not otherwise specified)		COVID-19	06-May-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Blood pressure fluctuation	NA
Cardiac arrest	NA
Death	NA
Intentional product use issue	NA
Off label use	NA
Sepsis	NA



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FOIA Case Report Information

Case ID: 17816816

Event/Problem Narrative:

AER 2604712 is a spontaneous case, received on 18/May/2020 from a consumer in the USA and concerns a 62 year old male patient who intentionally used tocilizumab (Actemra) for unlabelled indication, off label use, developed cardiac arrest, fluctuating blood pressure, sepsis and deceased due to hypoxia.

The patient's concurrent conditions included cardiac stents placement and he was a smoker. Concomitant medication included acetylsalicylic acid (Asprin). Medical history include CAD, history of MA, high cholesterol and history of smoking, no past drugs were reported.

On (b) (6) he was diagnosed with COVID-19 (test was positive: unknown method and where was done) and was hospitalized with symptoms of SOB, cough and fever. He received azithromycin and hydroxychloroquine to treat COVID-19, but therapy was withdrawn on (b) (6) (azithromycin) and on (b) (6) (hydroxychloroquine) due to cardiac stent history. On the same day, he received convalescent plasma and was kept on ventilator. On an unknown date in (b) (6) after starting tocilizumab, he experienced varying blood pressures, further clarified as fluctuating. On (b) (6) the patient started therapy with intravenous tocilizumab (lot number: not reported) at a dose of 700 mg for COVID-19, off label use. On the same day, he was put on ventilator. On (b) (6) the patient experienced cardiac arrest, which has resolved. On an unknown date after receiving tocilizumab, he had sepsis for which vancomycin was given (stopped due to AKI), then cefepime and doxycycline given. On (b) (6) he was deceased due to hypoxia. It was not reported whether autopsy was performed or not.

At the time of death, fluctuating blood pressure was persisting.

The consumer did not report a causality between deceased, cardiac arrest, fluctuating blood pressure and sepsis with tocilizumab.

No further information was provided.

Additional information was received on 04/Jun/2020. The following information was added to the case: new event (sepsis), medical history updated and drugs used to treat AE added, cause of death updated.

Relevant Medical History:

CAD, history of MA, high cholesterol

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Coronary arterial stent insertion	2015		YES
Tobacco user			YES



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Case ID: 17816816

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ASPRIN							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



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FOIA Case Report Information

Case ID: 17816827

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 23-Mar-2020
Outcomes: DE,HO,LT,
Application Type: BLA
FDA Rcvd Date: 12-Nov-2020
Mfr Rcvd Date: 30-Oct-2020
Mfr Control #: US-SA-2020SA079483
Application #: 761037

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	200 mg, 1X	COVID-19	20-Mar-2020	20-Mar-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	8487 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Acidosis	NA
Acute kidney injury	NA
Acute respiratory failure	NA
Alanine aminotransferase increased	NA
Aspartate aminotransferase increased	NA
Multiple organ dysfunction syndrome	NA



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FOIA Case Report Information

Case ID: 17816827

Event/Problem Narrative:

Based on the information received on 10-Apr-2020, the company causality initially assessed as not reportable was updated to reportable.

Initial information received on 27-Mar-2020 and 30-Mar-2020 (processed together) regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference 2020-27314 on 27-Mar-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6)

Patient ID: (b) (6) Center ID: (b) (6) Country: United States.

Protocol: (b) (6)

(b) (6)

A 79-year-old, multiracial, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6) The patient experienced Acute respiratory failure with hypoxia [Acute respiratory failure] on (b) (6) Acute kidney injury (AKI) on (b) (6) Acidosis in the setting of AKI [Acidosis] on (b) (6) Elevated ALT (alanine aminotransferase) [Alanine aminotransferase increased], Elevated AST (aspartate aminotransferase) [Aspartate aminotransferase increased], and Acute respiratory failure with hypoxia and Multisystem organ failure [Multiple organ dysfunction syndrome] due to COVID 19 on (b) (6)

Relevant medical history included hypertension, hypoxemia, creatinine elevation, shortness of breath and abdominal pain.

Relevant concomitant medication included hydroxychloroquine and amiodarone.

On 16-Mar-2020, X-ray chest imaging was performed and showed left lower lung opacity which may represent infection.

On (b) (6) the patient was admitted to hospital and CT-scan was performed which showed diffuse bilateral groundglass and subsegmental opacities. Patchy opacities were prominent in the posterior aspects of the right upper and bilateral lower lobes with associated bronchiolectasis.

On (b) (6) the patient experienced earliest symptoms of pneumonia with highest body temperature reported within 24 hours prior to dosing of 98.8 degrees Fahrenheit (F), measured orally. Arterial blood pH was 7.49. Treatment was continued in intensive care unit with use of supplemental oxygen by face mask and by non-rebreather mask. Chest X-ray showed peripheral hazy opacities in the right lung and left lower lung and no pneumothorax or pleural effusion.

On (b) (6) the patient had ECG (electrocardiogram) performed which showed normal results. The patient was positive for SARS-CoV-2 Virus test on the same day. On the same day vitals reported: oxygen saturation (SpO2) 93-96 % blood pressure (BP) 145/76 mmHg, pulse 87 beats per minute (bpm), respiratory rate 18 respirations per minute (rpm), body temperature 98.1 F measured orally. Patient was alert. Blood



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chemistry and haematology tests were also performed and results reported: alanine aminotransferase (ALT) 38 U/l (4-33), aspartate aminotransferase (AST) 86 U/L (4-40), creatinine 1.53 mg/dl (0.5 - 1.3), urea 24 mg/dl (7-23); platelets 316 K/uL (150-400), white blood cells (WBC) 9.41 K/uL (3.8 - 10.5).

On (b) (6) at 12:44 (b) (6) days 18 hours 56 minutes after the first administration of study drug, the patient experienced acute respiratory failure with hypoxia (intensity: grade 4) and was put on an invasive mechanical ventilation with FiO2 50%. The event was assessed as life-threatening and led to hospitalization. Patient was unresponsive and was admitted to intensive care unit (ICU). On the same day, the patient was intubated, and chest X-ray scan was performed, and showed increased hazy and linear opacities more in the lung bases consistent with COVID 19 positive infection. Endotracheal tube and enteric tube are both in place. Lungs show no focal consolidations although groundglass opacifications were consistent with known COVID infection. SpO2 decreased to 87, BP decreased to 117/66.

On (b) (6) at 10:18 (b) (6) days 16 hours 30 minutes the first administration of study drug, the patient experienced acute kidney injury (intensity: grade 4). The event was assessed as life-threatening and led to hospitalization. Creatinine increased to 3.13 and urea increased to 35. Patient was on continuous renal replacement therapy and was given bumetanide injection at dose of 20 mg, once, intravenous as a treatment for acute kidney injury. Chest X-ray was performed, and right central venous catheter was placed with unchanged appearance of patchy bilateral diffuse infiltrates. SpO2 increased to 94 and respiratory rate to 25.

On (b) (6) at 09:05 (b) (6) days 15 hours 17 minutes after the first administration of study drug, the patient experienced acidosis, in setting of acute kidney injury (intensity: grade 4). The event was assessed as life-threatening and led to hospitalization. Arterial blood pH decreased to 7.19, WBC increased to 21.14. Continuous renal replacement therapy (CRRT) was continued as corrective treatment. On the same day, the patient received treatment for acute kidney injury with lactated Ringers bolus at a dose of 500 ml, infuse once over 30 minutes, intravenous.

On (b) (6) at 01:56 (b) (6) days 8 hours 8 minutes after the first administration of study drug, the patient experienced elevated AST (intensity: grade 4), with level of 6525 and elevated ALT (intensity: grade 4), with level of 2390. Both the events were assessed as life-threatening and AESIs (ALT or AST increase). No corrective treatment was given in response to the events. SpO2 increased to 100, BP decreased to 54/36, body temperature increased to 100.3, arterial blood pH decreased to 7.08, WBC decreased to 19.01 and platelets decreased to 139. On the same day at 15:15 (b) (6) days 21 hours 27 minutes after the first administration of study drug, the patient developed multisystem organ failure (intensity: grade 5) due to COVID-19, no corrective treatment was given in response to the event and the patient died. Autopsy was not performed.

The patient had not recovered from the events Acute respiratory failure with hypoxia, Acute kidney injury, Acidosis in the setting of AKI, Elevated ALT and Elevated AST at time of death.

Action taken with study drug in response to the events was not applicable.



FDA - Adverse Event Reporting System (FAERS)

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Causality assessment is as follows:

(b) (6)

Multiple organ dysfunction syndrome: Severity = Grade 5; Investigator Causality = Not Related; Company Causality = Not Related
Investigator causality rationale: Event occurred 6 days after one time IP administration.

Acute respiratory failure: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Not Related
Investigator causality rationale: Event occurred 3 days after one time IP administration.

Acute kidney injury: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Not Related
Investigator causality rationale: Event occurred 4 days after one time IP administration.

Acidosis: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Not Related
Investigator causality rationale: Event occurred 5 days after one time IP administration.

Company causality rationale: A 79-year-old male patient with severe or critical COVID-19 experienced acute respiratory failure with hypoxia, acute kidney injury, acidosis and multisystem organ failure which subsequently led to death . The patient had chronic conditions such as hypertension and hyperlipidaemia. The patient was already hypoxic and had creatinine elevation before study drug administration. Although there is a temporal relationship between study drug administration and adverse events, based on patient's underlying chronic conditions along with serious COVID -19 pneumonia and advanced age, there is a reasonable possibility that the reported events acute respiratory failure with hypoxia, acute kidney injury, acidosis and multisystem organ failure are not related to study drug or any study drug procedure.

Alanine aminotransferase increased: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Related
Aspartate aminotransferase increased: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Related
Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 79-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced alanine aminotransferase increased and aspartate aminotransferase increased, (b) (6) days after receiving study drug. Based on a plausible temporal relationship between study drug administration and the reported event and known potential effect of study drug on functional liver enzymes, causality for both events is assessed as related to study drug. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation. The event is not related to any clinical trial procedure. Since the increase of ALT as AST was significant, other possible confounders are concomitant medications and multi organ system failure secondary to COVID-19 infection.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up received date: 31-Mar-2020

The Investigator provided the following updates: event term, clinical course, dosing section, outcomes updated, laboratory tests, severity added.

Follow up received date: 06-Apr-2020



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

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The Investigator provided the following updates: seriousness criterion for Acidosis in the setting of AKI and relevant concomitant medications updated.

Upon internal review, unblinding was performed

Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up: 10-Apr-2020, 13-Apr-2020 and 16-Apr-2020 (processed together)

The Investigator provided the following updates: two event added - Elevated AST and Elevated AST, clinical course updated, causality confirmed for Acute respiratory failure with hypoxia.

Follow up: 18-Apr-2020

The Investigator provided the following updates: event course and rationale for multiple events updated, concomitant medications and some dosing details added.

Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up: 13-May-2020

The Investigator provided the following updates: treatment medication added and outcomes of events updated.

Follow-up: 14-Aug-2020

The Investigator provided the following updates: event outcomes, event stop dates, laboratory test results, corrective treatment and clinical course updated.

Follow up: 25-Aug-2020

The Investigator provided the following updates: outcomes of the events and clinical course updated.

Expectedness Assessment per current IB (version 14):

Multisystem organ failure due to COVID 19: unexpected

Acute respiratory failure with hypoxia : unexpected

Acute kidney injury: unexpected

Acidosis in the setting of AKI: unexpected

Elevated ALT: unexpected

Elevated AST: unexpected



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17816827

(b) (6)

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension	02-Feb-2016	(b) (6)	NO
Hypoxemia	16-Mar-2020	(b) (6)	NO
Abdominal pain	(b) (6)	(b) (6)	NO
Creatinine increased	(b) (6)	(b) (6)	NO
Fever			
Hyperlipidemia			YES
Pain			
Shortness of breath			

Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17816827

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Aspartate aminotransferase	6525	U/L	4	40	N
Creatinine	3.13	mg/dL	0.5	1.3	Y
Urea	24	mg/dL	7	23	Y
Chest X-ray					Y
Chest X-ray					Y
pH	7.19	UNK			Y
Platelet count	139	10 ³ /uL	150	400	Y
Blood pressure	117/66	mmHg			N
Body temperature	98.1	degF			Y
CT scan					Y
Alanine aminotransferase	38	U/L	4	33	N
Aspartate aminotransferase	86	U/L	4	40	N
Blood pressure	145/76	mmHg			Y
pH	7.49	UNK			Y
White blood cell count	19.01	10 ³ /uL	3.8	10.5	Y
Blood pressure	54/36	mmHg			N
Body temperature	100.3	degF			Y
Chest X-ray					Y
ECG					Y
Oxygen saturation	100	%			Y
SARS-CoV-2 test					N
Alanine aminotransferase	2390	U/L	4	33	Y
Platelet count	316	10 ³ /uL	150	400	Y
Respiratory rate	25	breaths/min			Y
Chest X-ray					Y
Respiratory rate	18	breaths/min			Y
White blood cell count	21.14	10 ³ /uL	3.8	10.5	Y
Pulse rate	87	beats/min			N
Oxygen saturation					Y
Oxygen saturation	87	%			Y
Oxygen saturation	94	%			N
White blood cell count	9.41	10 ³ /uL	3.8	10.5	Y
Creatinine	1.53	mg/dL	0.5	1.3	Y
Urea	35	mg/dL	7	23	Y
pH	7.08	UNK			Y



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17816827

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/Q6H	Oral	650 mg, q6h		17-Mar-2020	Mar-2020	9 DAY
2	ACETAMINOPHEN	1000 MG/	Intravenous (not otherwise specified)	1000 mg, PRN	Pain	21-Mar-2020	26-Mar-2020	9 DAY
3	ACETAMINOPHEN	1000 MG/	Intravenous (not otherwise specified)	1000 mg, PRN	Fever	21-Mar-2020	26-Mar-2020	9 DAY
4	ACETAMINOPHEN				Fever			9 DAY
5	ALBUTEROL [SALBUTAMOL]	90 UG/Q6H	Respiratory (inhalation)	90 ug, Q6H	Shortness of breath	21-Mar-2020	23-Mar-2020	5 DAY
6	AMIODARONE [AMIODARONE HYDROCHLORIDE]		Intravenous (not otherwise specified)	150 mg in excel bag dextrose 5% 100 ml, once infuse over 10 mins	Arrhythmia	25-Mar-2020	26-Mar-2020	2355 MIN
7	ASPIRIN [ACETYLSALICYLIC ACID]	325 MG/QD	Oral	325 mg, QD	Prophylaxis	24-Mar-2020	26-Mar-2020	3795 MIN
8	CHLORHEXIDINE	4 PCT/QD	Topical	4 %, qd		24-Mar-2020	26-Mar-2020	3 DAY
9	CHLORHEXIDINE	15 ML/Q12H		15 ml, q12h, swab mouth and throat	Prophylaxis	23-Mar-2020	Mar-2020	3 DAY
10	FAMOTIDINE	20 MG/QD	Intravenous (not otherwise specified)	20 mg, qd	COVID-19	23-Mar-2020	26-Mar-2020	5235 MIN
11	FENTANYL	100 UG/1X	Intravenous (not otherwise specified)	100 ug, 1X	Sedation	23-Mar-2020	23-Mar-2020	5235 MIN
12	HEPARIN	Q6H	Subcutaneous	5000 ut, Q6h	DVT prophylaxis	17-Mar-2020	24-Mar-2020	9 DAY
13	HEPARIN		Intravenous (not otherwise specified)	25000 units in dextrose 5% 250 ml, infuse at 12 ml/hrdose rate 1200 units/hr	DVT prophylaxis	24-Mar-2020	26-Mar-2020	9 DAY
14	HYDROXYCHLOROQUIN E	200 MG/Q12H	Oral	200 mg, Q12H		20-Mar-2020	23-Mar-2020	7 DAY
15	HYDROXYCHLOROQUIN E	400 MG/Q12H	Oral	400 mg, q12h	COVID-19	19-Mar-2020	19-Mar-2020	7 DAY
16	HYDROXYCHLOROQUIN E	200 MG/Q12H	Oral	200 mg, bid		24-Mar-2020	24-Mar-2020	7 DAY



FDA - Adverse Event Reporting System (FAERS)

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Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
17 MIDAZOLAM		Intravenous (not otherwise specified)	100 mg in sodium chloride 0.9% 100 ml, infuse at 1.38 ml/hr dose rate 0.02 mg/kg/hr	Sedation	23-Mar-2020	25-Mar-2020	5235 MIN
18 NOREPINEPHRINE [NOREPINEPHRINE HYDROCHLORIDE]		Intravenous (not otherwise specified)	8 mg in sodium chloride 0.9% 250 ml, infuse at 25.9 ml/hr dose rate 0.2 mcg/kg/min	Drug use for unknown indication	23-Mar-2020	23-Mar-2020	5235 MIN
19 NOREPINEPHRINE [NOREPINEPHRINE HYDROCHLORIDE]		Intravenous (not otherwise specified)	16 mg in sodium chloride 0.9% 250 ml, infuse at 3.24 ml/hr dose rate 0.05 mcg/kg/min		24-Mar-2020	26-Mar-2020	5235 MIN
20 POTASSIUM CHLORIDE		Intravenous (not otherwise specified)	10 meq/100ml, intermittent		22-Mar-2020	22-Mar-2020	4 DAY
21 POTASSIUM CHLORIDE	40 MEQ/1X	Oral	40 meq, 1X	Hypokalemia	21-Mar-2020	21-Mar-2020	4 DAY
22 PROPOFOL		Intravenous (not otherwise specified)	1000 mg in IV solution 100 ml, infuse at 0.21 ml/hr dose rate 0.5 mcg/kg/min	Drug use for unknown indication	23-Mar-2020	26-Mar-2020	5235 MIN
23 PROPOFOL				Drug use for unknown indication			5235 MIN
24 RINGERS LACTATE	500 ML/	Intravenous (not otherwise specified)	500 ml total	Fluid replacement	23-Mar-2020	23-Mar-2020	5235 MIN

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17817430

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 31-Mar-2020 Outcomes: DE, Application Type: ANDA

FDA Rcvd Date: 22-May-2020 Mfr Rcvd Date: 13-May-2020 Mfr Control #: ES-CADILA HEALTHCARE LIMITED-ES-ZYDUS-051273 Application #: 211147

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Azithromycin		500 MG/	Oral	500 milligram	COVID-19 pneumonia	23-Mar-2020	24-Mar-2020
2	DEXAMETHASONE		20 MG/	Intravenous (not otherwise specified)	20 milligram	Product used for unknown indication	28-Mar-2020	01-Apr-2020
3	DEXKETOPROFEN		25 MG/	Intravenous (not otherwise specified)	25 milligram every 8 hours	Product used for unknown indication	27-Mar-2020	01-Apr-2020
4	ENOXAPARIN		40 MG/	Subcutaneous	40 milligram	Product used for unknown indication	27-Mar-2020	01-Apr-2020
5	HYDROXYCHLOROQUIN E		400 MG/	Oral	400 milligram	COVID-19 pneumonia	23-Mar-2020	01-Apr-2020
6	TOCILIZUMAB		600 MG/	Intravenous (not otherwise specified)	600 MG	Severe acute respiratory syndrome	29-Mar-2020	29-Mar-2020
7	TOCILIZUMAB					COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Azithromycin	9 Day	NA	NA				ZYDUS PHARM	
2	DEXAMETHASONE	4 Day	NA	NA					
3	DEXKETOPROFEN	5 Day	NA	NA					
4	ENOXAPARIN	5 Day	NA	NA					
5	HYDROXYCHLOROQUIN E	9 Day	NA	NA					



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17817430

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC	
6 TOCILIZUMAB	3 Day	NA	NA						
7 TOCILIZUMAB	3 Day	NA	NA						

Event Information:

Preferred Term (MedDRA Version: 23.1)

ReC

Coagulopathy

NA

Event/Problem Narrative:

This regulatory report received on 13-May-2020 via Spain regulatory authority (ES-AEMPS-628824) from a physician concerns a 26 year old adult female patient who developed Coagulopathy while receiving Azithromycin, Hydroxychloroquine, dexamethasone, enoxaparin, tocilizumab and dexametopfen.

Patient's medical condition included Severe acute respiratory syndrome and COVID-19 pneumonia. Medical history and concomitant medication was not reported.

The patient received Azithromycin 500 mg orally from 23-Mar-2020 to 24-Mar-2020, Hydroxychloroquine 400 mg orally from 23-Mar-2020 to 01-Apr-2020 for COVID-19 pneumonia, dexamethasone 20 mg intravenously from 28-Mar-2020 to 01-Apr-2020, enoxaparin 40mg subcutaneously and dexametopfen 25 mg every 8 hours intravenously from 27-Mar-2020 to 01-Apr-2020 for unknown indication, tocilizumab 600 mg intravenously on 29-Mar-2020 for Severe acute respiratory syndrome and COVID-19 pneumonia.

On 31-Mar-2020, the patient developed Coagulopathy. On (b) (6) the patient died.

Action taken with suspect drugs was not applicable.

Outcome of Coagulopathy was fatal. Cause of death was reported as multiorgan failure and Covid-19 pneumonia.

The case was considered to be serious as the patient died.

Reporter did not provide causality assessment between the adverse event and suspect drug.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17817430

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Caesarean section	(b) (6)	(b) (6)	NO

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ZYDUS PHARM

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17819799

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: IRN
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 24-May-2020
Mfr Rcvd Date: 18-May-2020
Mfr Control #: IR-ROCHE-2604563
Application #: 125276

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2604563 is a spontaneous case, received on 18/May/2020 from a physician in Iran, Islamic Republic Of. It concerns a patient of unknown demographics who intentionally used Actemra for unlabeled indication (off label use) and died whilst being treated with tocilizumab (Actemra).

No medical history, past drug, concurrent condition and concomitant medications were reported.

On an unknown date, the patient started therapy with tocilizumab (lot number and therapy details not provided) for covid-19 infection [intentionally used for unlabeled indication (off label use)]. It was reported by the intensivist that one patient received off label use of tocilizumab as a treatment for COVID-19. However, the patient died. The patient died on an unknown date. It was unknown if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17819799

The physician did not report a causality between death and tocilizumab.

No further information was provided.

This case is cross-referenced with AER 2604563, same reporter, AER 2604563, same reporter, AER 2604563, same reporter.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17819799

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17819809

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: COL
Event Date: 10-May-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 24-May-2020
Mfr Rcvd Date: 12-May-2020
Mfr Control #: CO-ROCHE-2599964
Application #: 125276

Patient Information:

Age: 65 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ACTEMRA		600 MG/	Intravenous (not otherwise specified)		COVID-19	08-May-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA	2 Day	NA	NA	B2082B14,B2086 B04,B2082B24				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Blood pressure decreased	NA
COVID-19	NA
Ill-defined disorder	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17819809

Event/Problem Narrative:

AER 2599964 is a spontaneous case received on 12/May/2020 from a pharmacist via company representative in Colombia. It concerns a 65 year old male patient who used actemra intentionally for unapproved indication which is coronavirus infection (COVID-19) (off label use) and died due to decrease in blood pressure, respiratory infection associated with SARS COV2 positive and oxygenation disorders (unk diagnosis) while being treated with tocilizumab (Actemra).

Concurrent conditions included hypertension. No medical history, past drugs and concomitant medications were reported.

On 08/May/2020, the patient started therapy with intravenous tocilizumab (lot number : B2082B14 , B2086B04, B2082B24, expiry date: 30/Aug/2021, 30/Nov/2021,30/Aug/2021) 600 mg (frequency not reported) for COVID-19 (off label use). On (b) (6) he was hospitalized. It was reported that there was no change in CT or X-ray. On (b) (6) he died due to decrease in blood pressure, respiratory infection associated with SARS COV2 positive and severe oxygenation disorders. It was not reported if an autopsy was performed or not.

At the time of death, it was not reported if therapy with tocilizumab was ongoing or not.

The pharmacist did not report a causality between decrease in blood pressure, oxygenation disorders and respiratory infection associated with sars cov2 positive and tocilizumab.

No further information was available.

Additional information was received on 16/May/2020. The following information was added to the case: No adverse event removed, new events (decrease in blood pressure, respiratory infection associated with sars cov2 positive and oxygenation disorders) and event description.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension			UNKNOWN

Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17819809

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17820249

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 21-Apr-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 25-May-2020 Mfr Rcvd Date: 14-May-2020 Mfr Control #: IT-ROCHE-2601569 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		8 MG/KG/Q12H	Intravenous (not otherwise specified)	On 17/Apr/2020, received last dose of tocilizumab	COVID-19 pneumonia			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC
 Cardiac arrest NA

Event/Problem Narrative:

AER 2601569 is a clinical study case, received on 14/May/2020 from a physician in Italy. It concerns a patient of unknown demographics (patient number: (b) (6)) who developed cardiac arrest whilst enrolled in (b) (6) (b) (6)

The patient's concomitant medications included linezolid (Linezolid). No medical history, Past drug and concurrent condition were reported.

On an unknown date, (b) (6) (b) (6) . On (b) (6) the patient developed cardiac arrest (severity: grade 5) and patient died. It was unknown if an autopsy was performed or not.

The physician assessed the cardiac arrest as related to tocilizumab.

The company assessed cardiac arrest as not related to tocilizumab and related to underlying COVID-19 pneumonia. Inflammatory response of



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

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cytokines, overwhelming the immune system response to the infection, which can lead to damage of organs, including lungs, heart, and kidneys. Signs of myocardial injury are present in at least one quarter of severe cases. Also COVID-19 pneumonia can aggravate underlying co-morbidities leading to severe complications of underlying heart disease.

No further information was provided.

Relevant Medical History:

BPCO (Bronchopneumopathie chronique obstructive)

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	LINEZOLIDE		Unknown					

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17820249

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17820893

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: MEX Event Date: Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 25-May-2020 Mfr Rcvd Date: 08-May-2020 Mfr Control #: MX-ROCHE-2599126 Application #: 125276

Patient Information:

Age: Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ROACTEMRA		800 MG/hr	Intravenous (not otherwise specified)	single dose	COVID-19			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2599126 is a spontaneous case, received on 08/May/2020 from a consumer via company representative in Mexico. It concerns a male patient (age not reported) who intentionally use Roactemra for an unapproved indication (off label use) and died due to unknown cause while being treated with tocilizumab (Roactemra).

No medical history, concomitant medication, concurrent condition and past drugs were reported.

The patient's health status was unknown. On an unknown date, the patient was given therapy with intravenous tocilizumab 800 mg single dose for one hour in 100 ml of 0.9% saline (sodium chloride) (lot number: not reported) for COVID-19 (Off label use for unapproved indication). Likewise, the patient's family member does not want to be contacted at the moment to provide more information. He died on (b) (6) His family member reported that the disease complicated in at older age. His family member does not currently want to be



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contacted to provide more information. The cause of death was unknown. It was unknown if the autopsy was performed or not.

At the time of death, reporter did not provide the causality of unknown cause of death.

No further information was provided. It will not be possible to perform a follow up since the patient does not want to be contacted.

Additional information was received on 19/May/2020 and the following information was added to the case: secondary reporter, event added (unknown cause of death), event description.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	SALINE [SODIUM CHLORIDE]							

Reporter Source:

Reporter Source:
Sender Report?: No **Sender Organization:** ROCHE **503B Compounding Outsourcing Facility?:**



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Case ID: 17820893

Literature Text:



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FOIA Case Report Information

Case ID: 17820959

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 06-May-2020 Outcomes: DE,HO, Application Type: BLA

FDA Rcvd Date: 25-May-2020 Mfr Rcvd Date: 20-May-2020 Mfr Control #:US-ROCHE-2606772 Application #: 125276

Patient Information:

Age: 63 YR Sex: Male Weight: 61.6 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		400 MG/	Intravenous (not otherwise specified)		COVID-19	20-Apr-2020	20-Apr-2020
2	ACTIVASE		50 MG/Q2H	Intravenous (not otherwise specified)		COVID-19	09-May-2020	09-May-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA	22 Day	Unk	NA	UNKNOWN				
2	ACTIVASE	3 Day	Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Bacterial infection	NA
COVID-19	NA
Enterobacter infection	NA
Intentional product use issue	NA
Off label use	NA



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FOIA Case Report Information

Case ID: 17820959

Event/Problem Narrative:

AER 2606772 is a spontaneous case, received on 20/May/2020 from a pharmacist in the USA. It concerns a 63 year old male patient who was treated intentionally for unlabeled indication (off label use) and developed covid complications leading to death (covid-19 infection), carbapenem resistant enterobacteriaceae (unk diagnosis) and carbapenemase producing enterobacteriaceae (unk diagnosis) whilst being treated with tocilizumab (Actemra) and alteplase (Activase).

Concomitant medications included hydroxychloroquine, azithromycin, vasopressin and norepinephrine. No medical history, past drugs and concurrent conditions were reported.

On 20/Apr/2020, the patient started therapy with intravenous tocilizumab (lot number: not reported) 400 mg (frequency not reported) for covid-19 (off label use). On 06/May/2020, he developed carbapenem resistant enterobacteriaceae (unk diagnosis) and carbapenemase producing enterobacteriaceae (unk diagnosis). On 09/May/2020, he started therapy with intravenous alteplase (lot number: not reported) 50 mg every 2 hours for covid-19 (off label use). On ^{(b) (6)} he developed covid complications (covid-19 infection) and he patient was hospitalised which lead to death. On an unknown date, he died. It was unknown if an autopsy was performed or not.

At the time of death, the outcome of carbapenem resistant enterobacteriaceae (unk diagnosis) and carbapenemase producing enterobacteriaceae (unk diagnosis) was not reported. It was not reported if therapy with alteplase and tocilizumab was altered or not in response to the covid complications leading to death (covid-19 infection), carbapenem resistant enterobacteriaceae (unk diagnosis) and carbapenemase producing enterobacteriaceae (unk diagnosis).

The pharmacist did not report the causality between covid complications leading to death (covid-19 infection) with tocilizumab and alteplase while did not report the causality of carbapenem resistant enterobacteriaceae (unk diagnosis) and carbapenemase producing enterobacteriaceae (unk diagnosis) with tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events



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Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Platelet count					N
Haematocrit					N
Haemoglobin					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	AZITHROMYCIN				COVID-19			
2	HYDROXYCHLOROQUIN E				COVID-19			
3	NOREPINEPHRINE	12 UG/	Unknown					
4	VASOPRESSIN	.4 MG/	Unknown					

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



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FOIA Case Report Information

Case ID: 17820998

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: HUN
Event Date: 08-May-2020
Outcomes: DE,OT,
Application Type: BLA
FDA Rcvd Date: 25-May-2020
Mfr Rcvd Date: 11-May-2020
Mfr Control #: HU-ROCHE-2599797
Application #: 125276

Patient Information:

Age: 65 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		400 MG/	Intravenous (not otherwise specified)	1 dose	COVID-19	07-May-2020	07-May-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	1 Day	Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Bradycardia	NA
Cardiac arrest	NA
Death	NA
Hypotension	NA
Off label use	NA



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Case ID: 17820998

Event/Problem Narrative:

AER 2599797 is a spontaneous case, received on 11/May/2020 from a physician via company representative in Hungary. It concerns a 65 year old male patient who developed bradycardia, hypotension, asystole, used tocilizumab for unlabeled frequency and died whilst being treated with tocilizumab (Tocilizumab).

No medical history past drugs concurrent conditions or concomitant medications were reported.

On 07/May/2020, the patient started therapy with intravenous tocilizumab (lot number: UNKNOWN) 400 mg, 1 dose for COVID infection, (off label for COVID infection) . On ^{(b) (6)} he experienced Bradycardia, hypotension, asystole and died. It was also stated that he was ventilated and was in critical condition when he received Tocilizumab. It was not reported if an autopsy was performed or not and there was no clear cause of death reported.

At the time of this report It was not reported if therapy with tocilizumab was altered or not.

The physician assessed the causality between bradycardia, hypotension, asystole and death with tocilizumab as unrelated.

The company assessed bradycardia, hypotension, asystole as medically significant event.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



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Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



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FOIA Case Report Information

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Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 19-Apr-2020
Outcomes: DE,HO,LT,OT,
Application Type: BLA
FDA Rcvd Date: 29-Jun-2020
Mfr Rcvd Date: 17-Jun-2020
Mfr Control #: US-SA-2020SA112586
Application #: 761037

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	REGN mAb1 400 mg, single	COVID-19	13-Apr-2020	13-Apr-2020
2	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	REGN mAb1 400 mg, single		21-Apr-2020	21-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	42373 MINUTES	NA	NA				SANOFI	
2	SARILUMAB	42373 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Acute respiratory failure	NA
Acute respiratory failure	NA
Atrial flutter	NA
Bacteraemia	NA
Bradycardia	NA
Myocardial infarction	NA
Oesophageal ulcer haemorrhage	NA
Pulmonary alveolar haemorrhage	NA
Renal tubular necrosis	NA



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Respiratory failure	NA
Septic shock	NA
Transaminases increased	NA

Event/Problem Narrative:

Based on the additional information received on 06-Jun-2020, the case has been upgraded to SUSAR (seriousness criteria for the event of Transaminases increased added).

Initial information received on 21-Apr-2020 regarding a solicited valid serious case received from (Ip) regeneron-usa gsa-pcp under reference number 2020-33890 on 21-Apr-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6)
Patient ID: (b) (6) Site: (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

A 62-year-old, male PT(patient), unreported ethnicity, with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

Pt experienced Acute worsened respiratory failure [Acute respiratory failure] Onset date: (b) (6) Acute worsened respiratory failure [Acute respiratory failure] Onset date: (b) (6) Septic shock serious AESI Onset date: (b) (6) Atrial flutter with rapid ventricular response [Atrial flutter] Onset date: (b) (6) ; Worsened hypoxic respiratory failure [Respiratory failure] Onset date: (b) (6) Elevated ALT/AST [Transaminases increased] serious AESI (ALT or AST increase); Ischemic acute tubular necrosis [Renal tubular necrosis] Onset date: (b) (6) ; Possible myocardial infarction [Myocardial infarction] Onset date: (b) (6) GI bleed related to a superficial esophageal ulcer [Oesophageal ulcer haemorrhage] Onset date: (b) (6) Symptomatic bradycardia [Bradycardia] Onset date: (b) (6) ; Possible bacteremia [Bacteraemia] serious AESI Onset date: (b) (6) Possible diffuse alveolar hemorrhage [Pulmonary alveolar haemorrhage] Onset date: (b) (6) after receiving study drug. Pt died on (u) (v) The cause of death was reported as acute worsened respiratory failure. Autopsy was not performed.

Relevant medical history: hypoxic respiratory failure and obesity.

No relevant concomitants.

(b) (6) :hospitalized, SARS-CoV-2 positive



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(b) (6) :alanine aminotransferase (ALT) was 23 U/L (0-44), aspartate aminotransferase (AST) 16 U/L (0-34), total bilirubin 0.3mg/dl (0-1), neutrophils $3.6 \times 10^9/L$ (1.8-7.8), white blood cells $5.2 \times 10^9/L$ (4-11), platelets $194 \times 10^9/L$ (150-450), blood pressure 132/ 95 mmHg, oxygen saturation (SpO2) 95 %, temperature 98.8degree F, pulse 100 bpm and respiratory rate 20 rpm.

(b) (6) :worsening shortness of breath. DVT, PE: negative. CT: worsening of ground glass opacities. Pt transferred to step-down unit, started on HFNC.

(b) (6) :furosemide, 20mg, daily, IV, for respiratory failure

Worsened hypoxic respiratory failure [Respiratory failure]: Medically significant, Hospitalization; Onset date: (b) (6) Severity: Grade 3; Outcome: Not Recovered / Not Resolved; Event resolved on: Ongoing

(b) (6) : (b) (6) days 8 hrs 48 min after administration of study drug , worsening hypoxemic failure (intensity: grade 3), transferred to ICU, therapy via BiPAP, SpO2 90

(b) (6) :weaned to HFNC and non-rebreather mask

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

(b) (6) :linezolid, 600mg, BID, cefepime, 2g, TID, IV

(b) (6) :furosemide, 40mg, daily, IV for respiratory failure

(b) (6) :pulse 137, atrial fibrillation with rapid ventricular response, adenosine, 6mg, once, IV, and metoprolol, 2.5mg, BID, orally, for atrial flutter

Atrial flutter with rapid ventricular response [Atrial flutter]: Hospitalization; Onset date: (b) (6) ; Severity: Grade 2; Outcome: Recovered / Resolved with sequelae; Event resolved on: (b) (6)

(b) (6) :narrow complex tachycardia (170s), (b) (6) days 3 hrs after administration of study drug atrial flutter with rapid ventricular response (intensity: grade 2), adenosine 6-12-12mg, cardioversion performed. Atrial flutter converted to sinus rhythm. Versed, 4mg and 2mg, and fentanyl, 100mcg, both once, IV, and synchronized cardioversion at 100 joules with transition to sinus tachycardia (120-130s). BIPAP discontinued and pt was put on HFNC 60L 100. Pt afebrile, fluid balance negative.

(b) (6) :furosemide, 40mg, TID, IV, for respiratory failure



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Acute worsened respiratory failure [Acute respiratory failure]: Life threatening; Onset date: (b) (6) Severity: Grade 4; Outcome: Unk; Event resolved on: Ongoing

Possible myocardial infarction [Myocardial infarction]: Medically significant; Onset date: (b) (6) Severity: Grade 1; Outcome: Unk; Event resolved on: Ongoing

(b) (6) :chest pain, pt unresponsive, intubated and sedated, troponins elevated. Head CT: negative. ECG: ST segment with 60 seconds of coronary balloon occlusion premature ventricular contractions, possible left atrial abnormality, septal infarct (age undetermined), inferior infarct (possibly acute), and non-specific ST wave abnormality (b) (6) days 17 hrs 37 min after administration of study drug pt had acute worsened respiratory failure (intensity: grade 4) and (b) (6) days 17 hrs 30 min after administration of study drug a possible myocardial infarction (intensity: grade 1). Nimbec (cisatracurium besilate), Diprivan (propofol), titrated, IV, and Veletri (epoprostenol), 1.5mg, continuous, inhalation, due to desaturations on 100 of FIO2 and PEEP of 10, for worsened respiratory failure. Fentanyl, 25 mcg and 50 mcg, midazolam, 2mg, every 2 hours as needed (PRN), IV, vecuronium, 10mg, once, IV, and norepinephrine, titrated, continuous infusion, for respiratory failure. Acetylsalicylic acid, 325 mg, once, orally, for possible myocardial infarction, and metoprolol, 5mg, once, IV, for atrial flutter. Pt placed back on BIPAP 18/10 rate of 12.

Elevated ALT/AST [Transaminases increased]: Medically significant, serious AESI (ALT or AST increase); Onset date: (b) (6) Severity: Grade 1; Outcome: Unk; Event resolved on: Unk

(b) (6) (b) (6) days 4 hrs 2 min after administration of study drug ALT 196 and AST 134 (intensity: grade 1), sepsis. Blood culture and stool: negative for C.difficile. Vancomycin, 1250mg, every 4h, and piperacillin, 3.375 g, TID, both IV, for septic shock, and metoprolol, 5mg, qid, iv, for atrial flutter.

GI bleed related to a superficial esophageal ulcer [Oesophageal ulcer haemorrhage] (initially reported as GI bleed [initially coded as Gastrointestinal haemorrhage]): Medically significant; Onset date: (b) (6) Severity: Grade 2; Outcome: Unk; Event resolved on: Ongoing

(b) (6) (b) (6) days after administration of study drug GI bleed related to superficial esophageal ulcer (intensity: grade 2). Hb 15.6 to 12.6 g/dl (14-17.5). Dark stools positive for occult blood, type and screen obtained. Dexmedetomidine, titrated, for respiratory failure.

Symptomatic bradycardia [Bradycardia]: Medically significant; Onset date: (b) (6) Severity: Grade 1; Outcome: Recovered / Resolved; Event resolved on: (b) (6)

Septic shock [Septic shock]: Life-threatening, serious AESI (Clinically significant invasive bacterial or fungal infections); Onset date: (b) (6) Severity: Grade 4; Outcome: Recovered/Resolved with sequelae; Event resolved on: (b) (6)

(b) (6) (b) (6) days 2 hrs 20 min after administration of study drug, patient developed symptomatic bradycardia (intensity: grade 1) and (b) (6) days



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after administration of study drug, patient developed septic shock (grade 4), became hypotensive and required vasopressors. Pulse 46, SpO2 82, respiratory rate 32, BP 66/46 and 77/62. Leukocytosis and fever. Lactate 2.2. Etiology was possibly septic given leukocytosis and fever or cardiogenic in setting of arrhythmia. Antibiotics, and 500 ml bolus of normal saline, and adenosine, 6mg, daily, IV, and metoprolol, 12.5mg, qid, orally, for atrial flutter. Recovered from bradycardia.

(b) (6) :supraventricular tachycardia (150 bpm) which was found to be atrial flutter with VSS. Metoprolol, 5mg, once, diltiazem, 10mg, PRN, adenosine, 12mg, once, 10mg, once, all IV, diltiazem, 30mg, qid, orally, and heparin, 5000 unit, TID, subcutaneous, for atrial flutter. Recovered from the event. Ceftriaxone 1 g, daily, IV, and phenylephrine, titrated, for septic shock.

(b) (6) :atrial flutter, resolved with cardioversion, heparin and esmolol, both titrated, and diltiazem, 60mg, qid, orally. Paroxysmal atrial flutter was predominant, although paroxysmal atrial fibrillation was also seen. Fentanyl and cisatracurium, titrated, and vecuronium, 10mg, once, iv, for respiratory failure. Urine output decreased to nearly anuria, did not improve with multiple boluses of IV fluids. IV diuresis overnight, without urine output. O2 needs increased with FiO2 100. Pt paralyzed and proned.

Ischemic acute tubular necrosis [Renal tubular necrosis] (initially reported as Anuric acute kidney injury secondary to ischemic acute tubular necrosis [initially coded as Acute kidney injury]): Medically significant; Onset date: (b) (6) Severity: Grade 2; Outcome: Recovered/Resolved with sequelae; Event resolved on: (b) (6)

(b) (6) (b) (6) days after administration of suspect drug, patient developed anuric acute kidney injury secondary to ischemic acute tubular necrosis (intensity: grade 2), furosemide.

(b) (6) :creatinine 3.87, Hb 9.3, platelets 139. CRRT with SCUF mode 100-200ml/hour ultrafiltration as tolerated.

(b) (6) :two length melanotic stools. Hb 8.3 to 7.6. SCUF machine clotted.

(b) (6) :GI endoscopy

(b) (6) :bumetanide instead of RRT

(b) (6) :urine output >2L

(b) (6) :BCx: positive for S.epidermis

Possible bacteremia [Bacteraemia]: Medically significant, serious AESI (Clinically significant invasive bacterial or fungal infections); Onset date: (b) (6) Severity: Grade 2; Outcome: Unk; Event resolved on: Ongoing



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(b) (6) : (b) (6) days 2 hrs 48 min after administration of suspect drug, patient developed possible bacteremia (intensity: grade 2). BCx positive for aerobic cultures. Bronchoalveolar lavage performed. Arterial line removed. H/H 6.9/21.2. Received PRBCs.

Possible diffuse alveolar hemorrhage [Pulmonary alveolar haemorrhage]: Medically significant; Onset date: (b) (6) Severity: Grade 3; Outcome: Unk; Event resolved on: Ongoing

(b) (6) :anticoagulant therapy stopped. Bronchoscopy. Blood in lungs and Hb decreased, (b) (6) days 6 hrs 11 min after administration of suspect drug, patient developed possible diffuse alveolar haemorrhage (intensity: grade 3), SpO2 86. Mahurkar/central line, midline central venous catheters, catheter for renal replacement therapy removed. Blood cultures, bronchoalveolar lavage, COVID-19 cultures: negative.

(b) (6) :BCx: negative. Pt afebrile, without leucocytosis, vancomycin.

(b) (6) :BCx: positive for anaerobic cultures

(b) (6) :H/H 6.2/18.6. PRBCs for possible diffuse alveolar haemorrhage, pulse steroids and supportive therapy.

Acute worsened respiratory failure [Acute respiratory failure]: Death; Onset date: (b) (6) ; Severity: Grade 5; Outcome: Fatal; Event resolved on (b) (6)

(b) (6) :atrial flutter, (b) (6) days 6 hrs 11 min after administration of suspect drug, patient developed atrial fibrillation (intensity: grade 5). Diltiazem, 30mg, qid. Pulse 150's. WBC 13.9. lactate 5.3, bicarb boluses and drip; vasopressin, levophed and epinephrine drips. Steroids held, vancomycin, cefepime and micafungin. On (b) (6) (b) (6) days 6 hrs 11 min, after administration of study drug, patient developed Worsening acute renal failure (Intensity: Grade 5) with oliguria; CTCAE Grade 3. Creatinine 3.13, potassium 5.9, HCO3 22, BUN 157. Bumex 2mg/4mg IV, insulin regular 10U/ D50, albuterol nebs for management of acute hyperkalemia.

(b) (6) :multisystem organ failure due to COVID-19. DNR was made and the Pt died.

Action taken with study drug in response to the events was not applicable.

Causality assessment is as follows:

For acute respiratory failure and acute respiratory failure:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: No alternative explanation was provided

Relationship with IP according to company: not reportable.

Company causality rationale: A 62-year-old male PT of unreported ethnicity, with severe or critical COVID-19 experienced acute worsened



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respiratory failure on two occasions after receipt of study drug. First one, after coming off from BIPAP and than (b) (6) days later the PT again experienced acute worsened respiratory failure but with fatal outcome. Based on the information provided, severe or critical COVID-19 before initiation of the study drug is cause for both events of worsened hypoxic respiratory failure in this PT. Therefore, the events are assessed as unrelated to the study drug or to any clinical trial procedure.

For Septic shock and Atrial flutter:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: Other suspected causes included cardiogenic shock.

Relationship with IP according to company: not reportable.

Company causality rationale: A 62-year-old male PT with severe or critical COVID-19 experienced septic shock and atrial flutter (b) (6) and (b) (6) days after receiving the last dose of the study drug. PT's baseline WBC and neutrophil count were within reference ranges and started increasing after study drug administration. Infections are common in hospital setting, in intubated and catheterized PTs, especially in a setting of pre-existing worsening infection where the PT had already been compromised such as PT's COVID-19 pneumonia. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug is the most plausible cause for the development of both events in this PT. Therefore, the events are assessed as unrelated to the study drug or to any clinical trial procedure.

For Respiratory failure

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: Not related. Other suspected cause included COVID-19.

Relationship with IP according to company: not reportable.

Company causality rationale: A 62-year-old male PT of unreported ethnicity, with severe or critical COVID-19 experienced worsened hypoxic respiratory failure, after receiving study drug. Based on the information provided, severe or critical COVID-19 before initiation of the study drug is cause for worsened hypoxic respiratory failure in this PT. Therefore, the event is assessed as unrelated to the study drug or to any clinical trial procedure.

For Transaminases increased:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: Decision is pending.

Relationship with IP according to company: reportable.

Sanofi company comment dated 25-May-2020: Patient's baseline AST and ALT values within reference ranges however, they've further increased following study drug administration. Based on a plausible temporal association between study drug administration and the event of increased transaminases and known potential effect of study drug on functional liver enzymes, causality for the event of increased transaminases is assessed as related to the study drug. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation.

For Myocardial infarction and Bradycardia:



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Relationship with IP according to investigator: no reasonable possibility.
Investigator causality rationale: No alternative explanation was provided
Relationship with IP according to company: not reportable.

For Oesophageal ulcer haemorrhage:

Relationship with IP according to investigator: no reasonable possibility.
Investigator causality rationale: Not stated, but the PT had been on anticoagulants.
Relationship with IP according to company: not reportable.

Company causality rationale: A 62-year-old male PT with severe or critical COVID-19 experienced increased transaminases, acute kidney injury, myocardial infarction, GI bleed related to a superficial esophageal ulcer and bradycardia, (b) (6) (b) (6) and (b) (6) (6) days after receiving the study drug, respectively. PT's baseline AST and ALT values within reference ranges however, they've further increased following study drug administration. Based on a plausible temporal association between study drug administration and the event of increased transaminases and known potential effect of study drug on functional liver enzymes, causality for the event of increased transaminases is assessed as related to the study drug. It was observed that higher rate of PTs treated with sarilumab experience transaminase elevation. Reportedly, the PT started receiving anticoagulant therapy which is significant confounding factor for the development of gastrointestinal haemorrhage. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug is the most plausible cause for the development of acute kidney injury, myocardial infarction, GI bleed related to a superficial esophageal ulcer and bradycardia in this PT. Considering above mentioned, the events of acute kidney injury, myocardial infarction, oesophageal ulcer haemorrhage and bradycardia are assessed as unrelated to the study drug or to any clinical trial procedure.

Renal tubular necrosis:

Relationship with IP according to investigator: no reasonable possibility.
Investigator causality rationale: Other suspected causes included ischemic acute tubular necrosis.
Relationship with IP according to company: not reportable.

Company causality rationale: A 62-year-old male PT of unreported ethnicity, with severe or critical COVID-19 experienced ischemic acute tubular necrosis (b) (6) days after study drug administration. Based on the information provided, severe or critical COVID-19 before initiation of the study drug is likely cause for this event. Therefore, the event is assessed as unrelated to the study drug or to any clinical trial procedure.

Bacteraemia:

Relationship with IP according to investigator: no reasonable possibility.
Investigator causality rationale: Other suspected causes included contaminant or being related to lines
Relationship with IP according to company: not reportable.

Company causality rationale: A 62-year-old male PT of unreported ethnicity, with severe or critical COVID-19 experienced bacteremia (b) (6) days after study drug administration. Blood cultures were positive for S.epidermidis and also aerobic and anaerobic cultures were positive. PT's arterial line was removed. Based on the information provided, severe or critical COVID-19 before initiation of the study drug compromising the PT, along with use of catheters is likely cause for this event. Therefore, the event is assessed as unrelated to the study drug or to any clinical



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17821297

trial procedure

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Hypoxic respiratory failure	(b) (6)		YES	
Obesity			YES	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Lactate					Y
Blood pressure	77/62	mmHg			N
Body temperature	98.2	degF			Y
Chest CT					Y
Hemoglobin	6.2	UNK			Y
Pulse rate	100	beats/min			N
Pulse rate	104	beats/min			N
Pulse rate					Y
Respiratory rate	20	breaths/min			N
White blood cells	5.2	10 ⁹ /L	4	11	N
Aspartate aminotransferase	125	U/L	0	34	N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17821297

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood culture					Y
Blood pressure	127/110	mmHg			N
Stool culture					Y
X-ray					Y
Alanine aminotransferase	196	U/L	0	44	N
Aspartate aminotransferase	134	U/L	0	34	N
Creatinine	2.30	mg/dL	0.8	1.4	N
Body temperature	98.8	degF			Y
Body temperature	101.3	degF			Y
CT scan					Y
Stool culture					Y
Pulse rate	137	beats/min			N
Pulse rate	46	beats/min			N
Screening test					Y
Oxygen saturation	90	%			N
Oxygen saturation	87	%			N
Alanine aminotransferase	23	U/L	0	44	N
Bilirubin	0.3	mg/dL	0	1	N
Blood pressure	108/80	mmHg			N
BUN	157	UNK			Y
Chest X-ray					Y
Hemoglobin	15.6	g/dL	14	17.5	N
Hemoglobin	6.9	UNK			Y
Platelet count	194	10 ⁹ /L	150	450	N
Respiratory rate	35	breaths/min			N
Respiratory rate	32	breaths/min			N
Blood culture					Y
LDH	2.2	U/L	100	190	N
Potassium					Y
Blood pressure	132/95	mmHg			N
CT scan					Y
Chest CT					Y
Hemoglobin	9.3	g/dL	14	17.5	N
Oxygen saturation	95	%			N
Troponin	0.529	UNK			Y
Creatinine	3.87	mg/dL	0.8	1.4	N
Lactate	2.2	UNK			Y
Blood pressure	66/46	mmHg			N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17821297

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Bronchoalveolar lavage					Y
Oxygen saturation	91	%			N
Alanine aminotransferase	268	U/L	0	44	N
Bicarbonate	22	UNK			Y
Creatinine	3.13	mg/dL	0.8	1.4	N
Blood culture					Y
Chest X-ray					Y
Head CT					N
ECG					Y
Hematocrit	21.2	UNK			Y
Hematocrit	18.6	UNK			Y
Pulse rate	170	beats/min			Y
Pulse rate	40	beats/min			N
Pulse rate	150	beats/min			Y
Oxygen saturation	82	%			N
Oxygen saturation	86	%			N
Platelet count	139	10 ⁹ /L	150	450	N
Aspartate aminotransferase	16	U/L	0	34	N
Blood culture					Y
Blood culture					Y
Blood culture					Y
Chest CT					Y
COVID-19					Y
Pulse rate	150	beats/min			Y
Neutrophil count	3.6	10 ⁹ /L	1.8	7.8	N
Respiratory rate	22	breaths/min			N
SARS-CoV-2 test					N
Troponin	2.920	UNK			Y
White blood cells	13.9	10 ⁹ /L	4	11	N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/	Oral	650 mg, (Once PRN)		30-Apr-2020	30-Apr-2020	18337 MIN
2	ACETAMINOPHEN	650 MG/	Oral	650 mg; (Once PRN)	COVID-19	04-May-2020	04-May-2020	18337 MIN



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17821297

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
3 ACETAMINOPHEN	650 MG/	Intravenous (not otherwise specified)	650 mg, (Once PRN)		02-May-2020	02-May-2020	18337 MIN
4 ACETAMINOPHEN	650 MG/	Oral	650 mg, Q6H PRN		13-May-2020	20-May-2020	18337 MIN
5 ANGIOMAX			titrated continus infusion		15-May-2020	16-May-2020	25537 MIN
6 ANGIOMAX	250 MG/	Intravenous (not otherwise specified)	250 mg, UNK	COVID-19	25-Apr-2020	06-May-2020	25537 MIN
7 ARIXTRA	2.5 MG/QD	Subcutaneous	2.5 mg, QD		24-Apr-2020	25-Apr-2020	9697 MIN
8 ARIXTRA	10 MG/QD	Subcutaneous	10 mg, QD	COVID-19	06-May-2020	12-May-2020	9697 MIN
9 AZITHROMYCIN	500 MG/QD	Oral	500 mg, qd	COVID-19	11-Apr-2020	15-Apr-2020	45697 MIN
10 CEFTRIAZONE	1 G/QD	Intravenous (not otherwise specified)	1 g, qd	COVID-19	11-Apr-2020	15-Apr-2020	45697 MIN
11 EPOPROSTENOL				Hypoxic respiratory failure			31297 MIN
12 EPOPROSTENOL	1.5 MG/		1.5 mg, CONT	Hypoxic respiratory failure	21-Apr-2020	06-May-2020	31297 MIN
13 IMMUNOGLOBULIN 5 TRCS	35 G/QD	Intravenous (not otherwise specified)	35 g, QD	COVID-19	25-Apr-2020	27-Apr-2020	25537 MIN
14 LOVENOX [ENOXAPARIN SODIUM]	40 MG/Q12H	Subcutaneous	40 mg, BID		17-Apr-2020	22-Apr-2020	44257 MIN
15 LOVENOX [ENOXAPARIN SODIUM]	40 MG/QD	Subcutaneous	40 mg, QD		17-Apr-2020	17-Apr-2020	44257 MIN
16 LOVENOX [ENOXAPARIN SODIUM]	40 MG/QD	Subcutaneous	40 mg, QD		23-Apr-2020	24-Apr-2020	44257 MIN
17 LOVENOX [ENOXAPARIN SODIUM]	120 MG/Q12H	Subcutaneous	120 mg, Q12H		22-Apr-2020	23-Apr-2020	44257 MIN
18 LOVENOX [ENOXAPARIN SODIUM]	40 MG/Q12H	Subcutaneous	40 mg, Q12H	COVID-19	12-Apr-2020	17-Apr-2020	44257 MIN
19 METHYLPREDNISOLON E	250 MG/QD	Intravenous (not otherwise specified)	250 mg, qd		03-May-2020	05-May-2020	38497 MIN



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17821297

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
20	METHYLPREDNISOLON E	500 MG/QD	Intravenous (not otherwise specified)	500 mg, qd		18-Apr-2020	18-Apr-2020	38497 MIN
21	METHYLPREDNISOLON E	60 MG/QD	Intravenous (not otherwise specified)	60 mg, qd		28-Apr-2020	02-May-2020	38497 MIN
22	METHYLPREDNISOLON E	200 MG/1X	Intravenous (not otherwise specified)	200 mg, 1X		02-May-2020	02-May-2020	38497 MIN
23	METHYLPREDNISOLON E	40 MG/QD	Intravenous (not otherwise specified)	40 mg, qd		22-Apr-2020	26-Apr-2020	38497 MIN
24	METHYLPREDNISOLON E	250 MG/1X	Intravenous (not otherwise specified)	250 mg, 1X		17-Apr-2020	17-Apr-2020	38497 MIN
25	METHYLPREDNISOLON E	125 MG/1X	Intravenous (not otherwise specified)	125 mg, 1X	COVID-19	16-Apr-2020	16-Apr-2020	38497 MIN
26	METHYLPREDNISOLON E	40 MG/Q12H	Intravenous (not otherwise specified)	40 mg, q12h		19-Apr-2020	21-Apr-2020	38497 MIN
27	METHYLPREDNISOLON E	500 MG/QD	Intravenous (not otherwise specified)	500 mg, qd		27-May-2020	29-May-2020	38497 MIN
28	METHYLPREDNISOLON E		Intravenous (not otherwise specified)	250, unk		30-May-2020	01-Jun-2020	38497 MIN
29	METHYLPREDNISOLON E	250 MG/QD	Intravenous (not otherwise specified)	250 mg, qd		26-Apr-2020	27-Apr-2020	38497 MIN
30	METHYLPREDNISOLON E	250 MG/QD	Intravenous (not otherwise specified)	250 mg, QD		17-Apr-2020	17-Apr-2020	38497 MIN
31	PHYTONADIONE	5 MG/QD	Oral	5 mg, qd	International normalized ratio	17-Apr-2020	19-Apr-2020	37057 MIN
32	PREDNISONE	60 MG/QD	Oral	60 mg, qd	COVID-19	11-Apr-2020	16-Apr-2020	45697 MIN
33	TOCILIZUMAB	800 MG/1X	Intravenous (not otherwise specified)	800 mg, 1X		02-May-2020	02-May-2020	19777 MIN



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17821297

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
34 TOCILIZUMAB	944 MG/1X	specified) Intravenous (not otherwise specified)	944 mg, 1X		02-May-2020	02-May-2020	19777 MIN
35 TOCILIZUMAB	800 MG/QD	Intravenous (not otherwise specified)	800 mg, qd	COVID-19	29-Apr-2020	30-Apr-2020	19777 MIN

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822236

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: BGR
Event Date: 23-Apr-2020
Outcomes: DE,OT,
Application Type: BLA
FDA Rcvd Date: 11-Jun-2020
Mfr Rcvd Date: 04-Jun-2020
Mfr Control #: BG-ROCHE-2594856
Application #: 125276

Patient Information:

Age: 71 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		600 MG/	Intravenous (not otherwise specified)		COVID-19	04-Apr-2020	
2	ROACTEMRA					Pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	19 Day	Unk	NA	UNKNOWN				
2	ROACTEMRA	19 Day	Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Acute kidney injury	NA
Embolism	NA
Intentional product use issue	NA
Multiple organ dysfunction syndrome	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822236

Event/Problem Narrative:

AER 2594856 is a spontaneous case, received on 29/Apr/2020 from a physician via company representative in Bulgaria. It concerns a 71 year old male patient who reported drug intentional use for unapproved indication (off label use) and suspicion of thromboembolism, acute renal failure and multiple organ failure whilst being treated with tocilizumab (Roactemra).

Concomitant medications included nadroparin calcium (Fraxiparine), clexane (Enoxaparin sodium) and heparin, concurrent conditions included possible viral infection, acute respiratory failure, COVID-19 infection, severe hypoxemia and neurological symptoms, characteristic of myasthenic syndrome. No medical history and past drugs was reported.

On an unspecified date, it was reported that, his doctor reported that the he fell ill on 22/FEB/2020 but was treated for a viral infection at home. On ^{(b) (6)} he was admitted to a site for acute respiratory failure due to respiratory failure, with proven COVID-19 and severe hypoxemia and neurological symptoms, characteristic of myasthenic syndrome. The neurological status shows that he felt weakness in the legs and had difficulty moving the diaphragm - peripheral respiratory failure, and had ptosis of both eyelids. On ^{(b) (6)} the patient started therapy with intravenous tocilizumab (lot number: not reported) 600 mg (frequency not reported) for covid-19 infection with pneumonia which was an intentional use for unapproved indication (off label use). On an unknown date, according to the physician, the patient was fully recovered. The attending physician reported that he had been intubated and received tocilizumab 600 mg on ^{(b) (6)} after which he improved. He rolled over from deep sedation and relaxation to synchronised mode and spontaneous ventilation. Subsequently, he improved and was extubated. A few days later his condition worsened, he developed acute renal failure, during which he was treated on haemodialysis, and subsequently developed multiple organ failure. On ^{(b) (6)} he passed away, there was a suspicion of thromboembolism. Because of COVID-19, he had prophylaxis with clexane one 0.6 ampoule subcutaneously and then Heparin 30,000 IU for 24 hours intravenously. According to information provided by the attending physician, he had neurological symptoms since last year, after an untreated viral infection. No autopsy was performed as it is not allowed to have such on patients with COVID-19.

At the time of death, outcome of acute renal failure and multiple organ failure was not reported. Therapy status of intravenous tocilizumab was not reported.

The physician assessed causality of fatal suspicion of thromboembolism as not related with tocilizumab, while did not report the causality of acute renal failure and multiple organ failure with tocilizumab.

No further information was reported.

Additional information received on 20/May/2020. The following information was added to the case: Patients details (patients initial, gender, age at the time of event), event fatal pulmonary embolism, concomitant medications (nadroparin calcium (Fraxiparine), heparin) added.

Additional information was received on 04/Jun/2020. Following information was added to the case: New primary reporter added, concurrent conditions added (possible viral infection, acute respiratory failure, COVID-19 infection, severe hypoxemia and neurological symptoms, characteristic of myasthenic syndrome), therapy start date added for suspect drug (^{(b) (6)}), new events added (acute renal failure and



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822236

multiple organ failure), event pulmonary embolism updated to suspicion of thromboembolism, concomitant drug added (clexane), additional details added and event description updated accordingly

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Viral infection	22-Feb-2020		
Acute respiratory failure	(b) (6)		
COVID-19			
Hypoxia			
Neurological symptom			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822236

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	CLEXANE		Subcutaneous	one 0.6 ampoule				
2	FRAXIPARINE		Intravenous (not otherwise specified)	2x0.6	Prophylaxis			
3	HEPARIN	30000 IU/	Intravenous (not otherwise specified)					
4	HEPARIN	20000 IU/	Intravenous (not otherwise specified)					

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822237

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ROM Event Date: Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 26-May-2020 Mfr Rcvd Date: 24-Apr-2020 Mfr Control #:RO-ROCHE-2592926 Application #: 125276

Patient Information:

Age: 67 YR Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		800 MG/	Unknown	2 vials of 400 mg 25/Apr/2020	COVID-19	24-Apr-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2592926 is a spontaneous case, received on 24/Apr/2020 from a pharmacist in Romania. It concerns a 67 year old patient (gender unspecified) who was treated with tocilizumab (Roactemra) intentionally for unlabeled indication (off label use) and the patient had passed way (death NOS).

The patient's medical history, past drugs, concurrent conditions or concomitant medications were not reported.

On an unspecified date, the patient was diagnosed with covid-19 infection and was admitted to intensive care unit. On (b) (6) the patient started therapy with tocilizumab (lot number: unknown) (route, frequency: not reported) 400 mg 2 vials (total 800 mg) for treatment of covid-19 infection (off label use). On (b) (6) patient had a new administration of tocilizumab 400 mg 2 vials (total 800 mg). Later on, it was reported that, the patient had passed away and the cause of death was not provided. It was reported whether an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822237

At the time of death, therapy ongoing status of tocilizumab was not reported.

The reporter did not report the causality between death and tocilizumab.

No further information was provided.

Additional information was received on 05/May/2020. Following information was added to the case: primary reporter details updated, tocilizumab dose updated to 400 mg, 2 vials (800 mg), the reporting pharmacist does not agree to complete Tocilizumab AE form for Covid-19.

Additional information was received on 20/May/2020. Following information was added to the case: new event (death) and event description was updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822237

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822402

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ROM
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 26-May-2020
Mfr Rcvd Date: 16-Apr-2020
Mfr Control #: RO-ROCHE-2585924
Application #: 125276

Patient Information:

Age: 65 YR
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		400 MG/	Unknown		COVID-19	16-Apr-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	ASKED BUT UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2585924 is a spontaneous case received on 16/Apr/2020, from a pharmacist in Romania. It concerns a 65 year old patient (gender unspecified) who died whilst being treated with tocilizumab (Roactemra) for an off label use.

The patient's medical history, past drugs, concurrent conditions and concomitant medications were not reported.

On an unknown date, the patient started therapy with tocilizumab 400 mg (route, frequency not reported and lot number: unknown) for SARS-CoV-2 infection. The patient used drug intentionally for unapproved indication as an off label use. On an unspecified date, the patient died. The cause of death was not provided. It was not stated if autopsy was performed or not. The reporting pharmacist does not agree to provided additional information regarding this case.

At the time of the death, the therapy with tocilizumab was not reported.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822402

The reporter did not report the causality of death NOS with tocilizumab.

No further information was provided.

Additional information was received on 20/May/2020. The following information was added to the case: Event (death NOS).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822402

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822482

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ROM Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 26-May-2020 Mfr Rcvd Date: 05-May-2020 Mfr Control #:RO-ROCHE-2598127 Application #: 125276

Patient Information:

Age: 57 YR Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		400 MG/	Unknown	Therapy start date 04/May/2020. 1 vial of 400mg	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	NOT REPORTED				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2598127 is a spontaneous case, received on 05/May/2020 from a pharmacist via company representative in Romania. It concerns a 57 year old patient (gender: not specified) who was being treated with tocilizumab (Roactemra) as an off label use.

The patient's medical history, past drug, concurrent condition and concomitant medication were not reported.

On unknown date, the patient was admitted to hospital due Covid-19 infection. On (b) (6) the patient started therapy with tocilizumab (lot number: not reported) 400 mg (one vial of 400mg) (route and frequency: not reported) for covid-19 infection (intentional use for unlabeled indication). on an unknown date in (b) (6) the patient died. It was unknown if an autopsy was performed or not.

The pharmacist did not report the causality of death nos with tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822482

No further information was provided.

Additional information received on 20/May/2020. The following information was added to the case: Reporter details added. New event death was added.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
 Sender Organization: ROCHE
 503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17822482

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17823846

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ROM
Event Date: 24-Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 26-May-2020
Mfr Rcvd Date: 24-Apr-2020
Mfr Control #: RO-ROCHE-2592524
Application #: 125276

Patient Information:

Age: 51 YR
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		800 MG/	Unknown	2 vials of 400 mg.	COVID-19	24-Apr-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	ASKED BUT UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2592524 is a spontaneous case, received on 24/Apr/2020, from a pharmacist in Romania. It concerns a 51 year old patient (gender unspecified) who was intentionally treated with tocilizumab (Roactemra) for an unlabeled indication and later, the patient died.

The patient's medical history, past drug, concurrent condition and concomitant medication were not reported.

On an unknown date, the patient was diagnosed with Covid-19 and as admitted to intensive care unit. On (b) (6) the patient started therapy with tocilizumab (lot number: asked but unknown, route and frequency: not reported) 800 mg, 2 vials of 400 mg, for Covid-19 infection, as intentional use for unlabeled indication; off label use. On (b) (6) the patient had a new tocilizumab administration of 800 mg (2 vials of 400 mg). On unknown date, the patient died. The cause of death was not provided. It was not stated if autopsy was performed or not. The reporting pharmacist did not agree to complete tocilizumab AE form for Covid-19 and did not agree to provide additional information.



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At the time of this death, it was not reported if therapy with tocilizumab was ongoing or not.

The pharmacist did not report the causality of the event death NOS with tocilizumab.

No further information was provided.

Additional information was received on 05/May/2020. The following information was added to the case: Reporter details were updated (pharmacist last and first name); dosage was updated (400 mg 1 vials to 800 mg 2 vials of 400 mg) and event description was updated.

Additional information was received on 20/May/2020. The following information was added to the case: Event : death NOS with associated event description.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No Sender Organization: ROCHE 503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17823846

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17824668

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: FRA
Event Date: 11-Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 15-Sep-2020
Mfr Rcvd Date: 11-Sep-2020
Mfr Control #: FR-ROCHE-2591147
Application #: 125276

Patient Information:

Age: 59 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Tocilizumab		400 MG/QD	Intravenous (not otherwise specified)	dose 20 mg/ml 8 mg/kg Concentrate for solution for infusion	COVID-19	03-Apr-2020	03-Apr-2020
2	Tocilizumab		800 MG/QD	Intravenous (not otherwise specified)	dose 20 mg/ml 8 mg/kg Concentrate for solution for infusion		03-Apr-2020	03-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Tocilizumab		NA	NA	UNKNOWN,UNK NOWN				
2	Tocilizumab		NA	NA	UNKNOWN,UNK NOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Candida infection	NA
Enterococcal infection	NA
Hypoxia	NA
Ischaemic stroke	NA
Pneumonia	NA
Pneumonia bacterial	NA
Septic shock	NA
Serratia bacteraemia	NA
Serratia infection	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17824668

Event/Problem Narrative:

AER 2591147 is a clinical study case, received on 24/Apr/2020 from a physician in France. It concerns a 59 year old male patient (patient number (b) (6)) who experienced ventilator associated pneumonia, right temporo-parietal ischemic stroke, serratia infection, refractory hypoxia, ventilator associated bacterial pneumonia, serratia bacteremia, enterococcus faecalis infection and candida albicans infection and died due to episode of septic shock whilst enrolled in (b) (6)

Concurrent conditions included arterial hypertension, rectal cancer, COPD, testicular infection, pneumoconiosis, hepatic steatosis, carcinoma in situ of rectum, chronic thrombopenia, organizing pneumonia and chronic thrombocytopenia. Concomitant medications included cefepime, propofol, norepinephrine, irbesartan, cefotaxime sodium (Claforan), spiramycin (Rovamycine), oseltamivir phosphate (Tamiflu), cefepime hydrochloride (Cefepime), piperacillin sodium; tazobactam sodium (Tazocilline), cefepime (Cefepime), meropenem (Meropenem), vancomycin (Vancomycine) and caspofungin acetate (Cancidas). The patient's medical history, past drug were not reported.

The patient was hospitalized on (b) (6) :
(b) (6)
(u) (o) . On (b) (6) he experienced ventilator associated pneumonia, serratia infection and candidemia (D19 in intensive care). On the same day, antibiotherapy with tazocilline in front of purulent secretion. Adaptation of the antibiotherapy on (b) (6) with cefepime. On (b) (6), lab test of brain CT (computerized tomography) was performed which resulted into fortuitous evidence of an extended ischemic stroke in the right temporoparietal sylvian associated with moderate ventricular dilation and he experienced a right temporo-parietal ischemic stroke. On the same day, lab test of brain CT (computerized tomography) was performed which resulted into fortuitous evidence of an extended ischemic stroke in the right temporoparietal sylvian associated with moderate ventricular dilation. On (b) (6) he experienced a septic shock, ventilator associated bacterial pneumonia, serratia bacteremia, enterococcus faecalis infection and candida albicans infection. On the same day, a hemodynamic aggravation occurred leading to new septic shock. On (b) (6) cefepime replaced by meropenem. From (b) (6) to (b) (6) the different blood culture was found to be positive. On (b) (6) he experienced second episode of septic shock and later refractory hypoxia. On (b) (6) he experienced septic shock (third episode). It was not reported if therapy with tocilizumab was altered or not in response to the septic shock. Despite targeted antibiotic therapy, he died on (b) (6) at 3:05 am. from a shock septic and refractory hypoxia. It was not reported if an autopsy was performed or not. Further information was expected.

The physician assessed the causality of events ventilator associated pneumonia, serratia infection, episode of septic shock, ventilator associated bacterial pneumonia, serratia bacteremia, enterococcus faecalis infection, candida albicans infection and refractory hypoxia as related and right temporo-parietal ischemic stroke as no reasonable possibility (not related) with tocilizumab but related to disease progression or intercurrent disease.

The company assessed the ventilator associated pneumonia and right temporo-parietal ischemic stroke as medically significant.

No further information was provided.



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Additional information was received on 20/May/2020, following information was added to the case: Reporter (Physician), concurrent condition, suspect dose and frequency, events (Ventilator associated pneumonia, right temporo-parietal ischemic stroke), concomitant drugs.

Additional information was received on 29/May/2020. The following information was added to the case: new events, concomitant medications, medical history was added and event description was updated.

Additional information was received on 05/Jun/2020. The following information was added to the case: lab test was added and event description (It was reported that, according to the hospitalization report from (b) (6) to (b) (6) On (b) (6) antibiotherapy with tazocilline in front of purulent secretion. Adaptation of the antibiotherapy on (b) (6) with cefepime. On (b) (6) cefepime replaced by meropenem) was updated.

Additional information was received on 08/Jun/2020, following information was added to the case: (FR-DRCDAPHPP-202000514, 2020-001246-18), event onset date of septic shock, ventilator associated bacterial pneumonia (previous (b) (6)) updated to (b) (6) and end date added as (b) (6) (date of death). Causality Septic shock, Ventilator associated bacterial pneumonia and serratia bacteremia updated to no reasonable possibility (not related) (previous related). causality of ventilator associated pneumonia, serratia infection updated to reasonable possibility (previous not related), and ischaemic stroke (b) (6)), no reasonable possibility (not related).

Additional information was received on 16/Jun/2020, following information was added to the case: primary reporter, therapy detail, Concurrent conditions (Carcinoma in situ of rectum, chronic thrombopenia, organizing pneumonia), cause of death (shock septic and refractory hypoxia), causality of septic shock, ventilator associated bacterial pneumonia, serratia bacteremia, enterococcus faecalis infection, candida albicans infection updated to related (previously: not related), event description updated accordingly.

AER 2605566 was identified as a duplicate of AER 2591147. All information from AER 2605566 was added to AER 2591147, which remains the active case.

Additional information was received on 11/Sep/2020. The following information was added to the case. The cessation date of ventilator associated pneumonia, serrantia infection and ischemic stroke (b) (6)) and outcome(fatal) updated and event description updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Rectal cancer stage 0	Jan-2020		
Chronic obstructive pulmonary disease			



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Hepatic steatosis
 Hypertension
 Orchitis
 Organising pneumonia
 Pneumoconiosis
 Rectal cancer
 Thrombocytopenia

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Computerised tomogram head					N
Chest scan					N
Blood culture					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	CANCIDAS							
2	CEFEPIME							
3	CEFEPIME							
4	CEFEPIME							
5	CLAFORAN							
6	IRBESARTAN							
7	MEROPENEM							
8	NORADRENALINE							



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Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
9 PROPOFOL							
10 ROVAMYCINE							
11 TAMIFLU							
12 TAZOCILLINE							
13 VANCOMYCINE							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17826266

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 30-Mar-2020
Outcomes: DE,LT,OT,
Application Type: BLA
FDA Rcvd Date: 04-Aug-2020
Mfr Rcvd Date: 30-Jul-2020
Mfr Control #: US-SA-2020SA095180
Application #: 761037

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	REGN mAb1 200 mg, 1X	COVID-19	29-Mar-2020	29-Mar-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	438 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Acute kidney injury	NA
Alanine aminotransferase increased	NA
Aspartate aminotransferase increased	NA
Cholecystitis	NA
Encephalopathy	NA
Septic shock	NA



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FOIA Case Report Information

Case ID: 17826266

Event/Problem Narrative:

Based upon additional information received on 14-Apr-2020, the reporter causality for increase in ALT and AST was updated from not reported to Related.

Initial information received on 02-Apr-2020 regarding a solicited valid serious case received from (lp) regeneron-usa gsa-pcp under reference RGN MCN: 2020-28191 on 02-Apr-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6) Patient ID (b) (6) Site: (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

A 55-year-old, Hispanic or Latino, female patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

The patient experienced SAEs Septic shock, Encephalopathy and Acute kidney injury on (b) (6) Cholecystitis on (b) (6) and Death due to multi-organ failure resulting from COVID-19 on (b) (6) and serious AEs/Is Increase in ALT and Increase in AST on 30-Mar-2020, after receiving study drug.

Relevant medical history included transaminitis and type 2 diabetes mellitus

Relevant concomitant medications include hydroxychloroquine.

On an unspecified date in Mar-2020 the patient started experiencing shortness of breath, fatigue, non productive cough, myalgias and headache, and developed hypoxemia and fever. C-reactive protein (CRP) was increased.

On 20-Mar-2020 hemolysis index was elevated.

On 21-Mar-2020 the patient experienced earliest symptoms of pneumonia.

On (b) (6) the patient was admitted to hospital, and was transferred to intensive care unit (ICU) on the same day. Erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), red blood cells count (RBC) and ferritin were elevated. Electrocardiogram (ECG) was done, results were not provided. Nasopharyngeal swab was taken, along with blood for polymerase chain reaction (PCR) SARS-CoV-2 test, and the patient was positive for SARS-CoV-2 virus. The highest temperature recorded within 24 hours prior to study drug dosing was 102 degrees Fahrenheit (degF), measured axillary. Chest X-ray scans were performed and diffuse infiltrates on right side were noted.

On (b) (6) the patient was on invasive mechanical ventilation, and her peripheral capillary oxygen saturation (SpO2) was 95%, at the fraction of inspired oxygen (FiO2) set to 40%. The highest measured temperature was 38.9 degrees Celsius (degC), blood pressure was 113/64 mmHg, pulse was 74 beats per minute (bpm), while the respiratory rate was 30 respirations per minute (rpm). Results of the



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biochemistry were the following: alanine aminotransferase (ALT) 146, aspartate aminotransferase (AST) 145, creatinine - 0.7, total bilirubin - 0.3. Haematology results were: platelets 236, white blood cells (WBC) - 8.11, lymphocytes (absolute) - 0.77.

On (b) (6) at 03:37, i.e. (b) (6) hours and 18 minutes after the first investigational product (IP) administration, the patient was diagnosed with increase in ALT and AST (grade 4 for both), with values of 1797 and 4273, respectively. Both the events were assessed as life threatening, medically significant and adverse event of special interest (AESI). No corrective treatment was applied for both the events. The patient's SpO2 varied from 95 to 97%, temperature was 99.3 degF, blood pressure was 111/73 mmHg, pulse was 69 bpm, and respiratory rate remained 30 rpm. Results of biochemistry tests showed that lactate dehydrogenase (LDH) was 8438, and total bilirubin was 0.7. Platelets were 215 and WBC was 6.78.

On (b) (6) SpO2 was 97%, temperature was 99.5 degF, blood pressure was 122/62 mmHg, pulse increased to 90 bpm, and respiratory rate remained 30 rpm. ALT was 2186, AST was 3519, creatinine increased to 2, and LDH decreased to 5505. Platelets were 228, and WBC was 8.46.

On (b) (6) SpO2 was 98-99%, she experienced fever with body temperature of 101.7 degF, blood pressure increased to 135/96 mmHg, pulse increased to 99 bpm, and respiratory rate to 31 rpm. ALT decreased to 1730, AST to 1114, creatinine to 1.5, and LDH to 1656. Platelets were 249, and WBC was 11.37. Chest X-ray showed increase in bibasilar infiltrates.

On (b) (6) SpO2 was 95-97%, temperature was 100.8 degF, blood pressure dropped to 92/61 mmHg, pulse decreased to 80 bpm, and respiratory rate to 30 rpm. Creatinine decreased to 1.2, and LDH to 924. Platelets were 244, and WBC was 16.58. Chest X-ray indicated improved inspiratory effort with decreased pulmonary opacities most apparent on the right side of the lungs.

On (b) (6) SpO2 was 97%, temperature was 99.9 degF, blood pressure increased to 122/79 mmHg, pulse decreased to 72 bpm, and respiratory rate to 16 rpm. ALT decreased to 702, AST to 122, and creatinine remained 1.2. Platelets were 239, while WBC increased to 18.1. Chest X-ray indicated progressive bilateral pulmonary infiltrates.

On (b) (6) SpO2 was 95-97%, temperature was 99.3 degF, blood pressure was 127/71 mmHg, pulse increased to 75 bpm, and respiratory rate to 29 rpm. Platelets were 242, and WBC was 18.92. Chest X-ray indicated bilateral infiltrates most predominant at left side.

On (b) (6) SpO2 was 94-97%, temperature was 95.9 degF, blood pressure increased to 146/74 mmHg, pulse increased to 98 bpm, and respiratory rate to 37 rpm. ALT decreased to 407, while AST increased to 178, creatinine increased to 1.6, and LDH decreased to 850. Platelets were 268, and WBC was 19.19. Chest X-ray indicated vascular congestion with left side greater than right basilar opacities, that were slightly diminished. On the same day, Candida albicans was found in patient's sputum. The patient received unspecified medication as a corrective treatment.

On (b) (6) SpO2 was 92-96%, temperature was 102 degF, blood pressure decreased to 106/66 mmHg, and pulse was 96 bpm. ALT further decreased to 328, while AST continued to increase (193), as well as creatinine (2.4), while total bilirubin was 2.1. Platelets were 258,



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and WBC further increased to 21.61. Chest X-ray indicated interval progression of pulmonary edema and pneumonia with small bilateral pleural effusion. On the same day, (b) (6) days after administration of study drug, the patient experienced septic shock (Intensity: Grade 5), acute kidney injury (Intensity: Grade 4) and encephalopathy (Grade 4). The events acute kidney injury and encephalopathy were assessed as life threatening. The event acute kidney injury was also assessed as medical significant.

On (b) (6) SpO2 was 92-95%, temperature was 100 degF, blood pressure decreased to 104/54 mmHg, pulse increased to 107 bpm, and respiratory rate was 34 rpm. ALT dropped to 295 and AST to 159, while creatinine increased to 2.9, and total bilirubin to 3.5. Platelets were 234, WBC was 24.88. Chest X-ray indicated persistent mild diffuse bilateral pulmonary opacities. On the same day, (b) (6) days 19 hours 45 min after administration of study drug, the patient started experiencing cholecystitis (Intensity: Grade 3) and percutaneous transhepatic biliary drainage was performed. The event was assessed as life threatening and medically significant.

On (b) (6) SpO2 was 89-94%, temperature was 102 degF, blood pressure further decreased to 69/48 mmHg, and pulse increased to 111 bpm. Creatinine was 3.7. On the same day, at 16:47, the patient died due septic shock. Chest X-ray indicated interval progression of bilateral airspace opacities suggestive of worsening pulmonary edema and/or pneumonia with increase in bilateral pleural effusions, no pneumothorax. It was not reported whether any corrective treatment was administered for the event. The cause of death was Septic shock. Autopsy was not performed.

Event outcome: unknown for increase in ALT, increase in AST, not recovered for Encephalopathy, Acute kidney injury and Cholecystitis and Fatal for septic shock.

Action taken with study drug in response to the events was not applicable.

On 17-Apr-2020 the event Death due to multi-organ failure resulting from COVID-19 was downgraded from SAE to non-serious non-AESI and inactivated, with no rationale provided.

On (b) (6) treatment assignment blind was broken for regulatory reporting purposes.

On 05-May-2020, the Investigator downgraded the event Candida albicans in sputum from serious AESI to non-serious AESI as it was confirmed the event did not meet seriousness criteria of life threatening.

On 27-May-2020 the event Candida albicans in sputum was downgraded from Non-serious AESI to non-serious non-AESI and inactivated, as the event did not meet AESI criteria.

For the event, Septic shock, Acute kidney injury, Encephalopathy and Cholecystitis:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: No alternative explanation was provided.

Relationship with IP according to company: not reportable.

Company causality rationale: A 55-year-old, female patient with severe or critical COVID-19 infection and worsening pneumonia experienced



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cholecystitis, encephalopathy, acute kidney injury, septic shock and subsequent death, after receiving the study drug. The events are assessed as not related to study drug or any clinical trial procedure since they are secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and comorbidities like type 2 diabetes. The clinical course is commonly observed in terminal COVID19 infection.

For events increased in ALT and increase in AST:

Relationship with IP according to investigator: reasonable possibility

Investigator causality rationale: No alternative explanation was provided.

Relationship with IP according to company: reportable.

Company causality rationale: A 55-year-old, female patient with severe or critical COVID-19 infection and worsening pneumonia experienced increase in ALT and AST, one day after receiving study drug. The patient has pre existing and ongoing history of transaminitis , however the condition worsened after study drug administration. Therefore, based on a plausible temporal association between study drug administration and the reported events and known potential effect of study drug on functional liver enzymes, causality for the events Increase in ALT and AST is assessed as related to study drug. The events Increase in ALT and AST are not related to any clinical trial procedure.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 09-Apr-2020 and 12-Apr-2020 (processed together)

The Investigator provided the following updates: new event added, initially reported event term splitted to two events, clinical course updated.

Additional information received on 14-Apr-2020 and 16-Apr-2020 (processed together) from investigator:

New events septic shock, acute kidney injury and encephalopathy added, concomitant drugs added, lab tests added, reporter causality for Alanine aminotransferase increased and Aspartate aminotransferase increased updated, clinical course updated. Text amended accordingly.

Additional information received on 17-Apr-2020

The Investigator provided the following updates: new event Candida albicans in sputum added, clinical course updated.

Follow up: 05-May-2020 The Investigator provided the following updates: event downgraded from serious AESI to non-serious AESI (Candida albicans in sputum): Upon internal review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up: 27-May-2020 the event Candida albicans in sputum was downgraded from Non-serious AESI to non-serous non-AESI and inactivated, as the event did not meet AESI criteria.

Correction on 30-Jul-2020: The following was corrected based on internal review - Outcome of the events increase in AST and increase in ALT updated.



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Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
CRP increased	Mar-2020	(b) (6)	NO	
Cough	Mar-2020	(b) (6)	NO	
Fatigue	Mar-2020	(b) (6)	NO	
Fever	Mar-2020	(b) (6)	NO	
Headache	Mar-2020	(b) (6)	NO	
Myalgia	Mar-2020	(b) (6)	NO	
Shortness of breath	Mar-2020	(b) (6)	NO	
Bilateral pulmonary infiltrates	(b) (6)	(b) (6)	NO	
ESR increased	(b) (6)	(b) (6)	NO	
Ferritin increased	(b) (6)	(b) (6)	NO	
Hypoxemia	(b) (6)	(b) (6)	NO	
LDH increased	(b) (6)	(b) (6)	NO	
RBC count increased	(b) (6)	(b) (6)	NO	
Bilateral pulmonary infiltrates				
Calculus of kidney				
Transaminitis				
Type 2 diabetes mellitus				
Medical History Product(s)	Start Date	End Date	Indications	Events



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Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	1797	UNK			Y
Alanine aminotransferase	1730	UNK			Y
Creatinine	2	UNK			Y
Creatinine	1.2	UNK			Y
Diastolic blood pressure	73	mmHg			N
Diastolic blood pressure	62	mmHg			N
Diastolic blood pressure	74	mmHg			N
Diastolic blood pressure	66	mmHg			N
Diastolic blood pressure	54	mmHg			N
Systolic blood pressure	135	mmHg			N
Systolic blood pressure	106	mmHg			N
Body temperature	100	degF			Y
Chest X-ray					Y
Heart rate	74	beats/min			N
Heart rate	80	beats/min			N
Oxygen saturation					Y
Respiratory rate	30	breaths/min			N
Respiratory rate	31	breaths/min			N
Aspartate aminotransferase	4273	UNK			Y
Aspartate aminotransferase	178	UNK			Y
Creatinine	0.7	UNK			Y
LDH	5505	UNK			Y
Diastolic blood pressure	61	mmHg			N
Diastolic blood pressure	48	mmHg			N
Body temperature	102	degF			Y
Body temperature	102	degF			Y
Platelet count	215	UNK			Y
Platelet count	242	UNK			Y
White blood cells	16.58	UNK			Y
White blood cells	18.1	UNK			Y
White blood cells	19.19	UNK			Y
Alanine aminotransferase	702	UNK			Y
Creatinine	1.2	UNK			Y
Creatinine	2.4	UNK			Y
Creatinine	3.7	UNK			Y
LDH	1656	UNK			Y
Diastolic blood pressure	79	mmHg			N
Systolic blood pressure	122	mmHg			N



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FOIA Case Report Information

Case ID: 17826266

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Systolic blood pressure	146	mmHg			N
Systolic blood pressure	104	mmHg			N
Body temperature	99.3	degF			Y
Body temperature	101.7	degF			Y
Body temperature	95.9	degF			Y
Chest X-ray					Y
Chest X-ray					Y
Heart rate	90	beats/min			N
Heart rate	98	beats/min			N
Heart rate	96	beats/min			N
Platelet count	249	UNK			Y
Platelet count	244	UNK			Y
Platelet count	268	UNK			Y
Respiratory rate	29	breaths/min			N
White blood cells	6.78	UNK			Y
Aspartate aminotransferase	145	UNK			Y
Aspartate aminotransferase	3519	UNK			Y
Creatinine	2.9	UNK			Y
Diastolic blood pressure	96	mmHg			N
Diastolic blood pressure	71	mmHg			N
Body temperature	100.8	degF			Y
Body temperature	99.9	degF			Y
Body temperature	99.3	degF			Y
Heart rate	72	beats/min			N
Heart rate	75	beats/min			N
Heart rate	111	beats/min			N
Platelet count	234	UNK			Y
Respiratory rate	30	breaths/min			N
Respiratory rate	34	breaths/min			N
White blood cells	8.46	UNK			Y
White blood cells	21.61	UNK			Y
Alanine aminotransferase	295	UNK			Y
Bilirubin total	0.3	UNK			Y
Bilirubin total	3.5	UNK			Y
Systolic blood pressure	122	mmHg			N
Chest X-ray					Y
Oxygen saturation	95	%			N



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FOIA Case Report Information

Case ID: 17826266

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Platelet count	236	UNK			Y
Platelet count	228	UNK			Y
Respiratory rate	30	breaths/ min			N
White blood cells	18.92	UNK			Y
Alanine aminotransferase	2186	UNK			Y
Aspartate aminotransferase	122	UNK			Y
Bilirubin total	0.7	UNK			Y
Creatinine	1.6	UNK			Y
LDH	850	UNK			Y
Systolic blood pressure	111	mmHg			N
Systolic blood pressure	92	mmHg			N
Systolic blood pressure	127	mmHg			N
Body temperature	99.5	degF			Y
Chest X-ray					Y
Heart rate	99	beats/min			N
Heart rate	107	beats/min			N
Platelet count	258	UNK			Y
Respiratory rate	37	breaths/ min			N
White blood cells	8.11	UNK			Y
Alanine aminotransferase	146	UNK			Y
Alanine aminotransferase	328	UNK			Y
Aspartate aminotransferase	193	UNK			Y
Aspartate aminotransferase	159	UNK			Y
Creatinine	1.5	UNK			Y
LDH	8438	UNK			Y
Diastolic blood pressure	64	mmHg			N
Body temperature	102	degF			Y
Chest X-ray					Y
Oxygen saturation					Y
Oxygen saturation					Y
Respiratory rate	30	breaths/ min			N
Respiratory rate	16	breaths/ min			N
White blood cells	11.37	UNK			Y
Alanine aminotransferase	407	UNK			Y
Aspartate aminotransferase	3519	UNK			Y
Bilirubin total	2.1	UNK			Y



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
LDH	924	UNK			Y
Systolic blood pressure	113	mmHg			N
Systolic blood pressure	69	mmHg			N
Body temperature	99.3	degF			Y
Body temperature	38.9	Cel			N
Chest X-ray					Y
Chest X-ray					Y
Chest X-ray					Y
Heart rate	69	beats/min			N
Oxygen saturation					Y
Oxygen saturation	97	%			N
Oxygen saturation					Y
Oxygen saturation	97	%			N
Oxygen saturation					Y
Oxygen saturation					Y
Oxygen saturation					Y
Platelet count	239	UNK			Y
White blood cells	24.88	UNK			Y

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	AZITHROMYCIN	500 MG/QD	Intravenous (not otherwise specified)	500 mg, qd	Lung infiltration	29-Mar-2020	30-Mar-2020	15407 MIN
2	CEFEPIME	2 G/Q12H	Intravenous (not otherwise specified)	2 g, bid	Lung infiltration	01-Apr-2020	03-Apr-2020	11087 MIN
3	CEFTRIAZONE ALPHAPHARM	1 G/QD	Intravenous (not otherwise specified)	1 g, qd	Pneumonia	29-Mar-2020	01-Apr-2020	15407 MIN
4	HYDROXYCHLOROQUIN E	600 MG/Q12H	Oral	600 mg, bid	Corona virus infection	28-Mar-2020	30-Mar-2020	16847 MIN
5	LINEZOLID	600 MG/Q12H	Intravenous (not otherwise specified)	600 mg, bid	Lung infiltration	06-Apr-2020	08-Apr-2020	3887 MIN
6	MEROPENEM	500 MG/Q12H	Intravenous (not otherwise specified)	500 mg, bid	Drug use for unknown indication	03-Apr-2020	08-Apr-2020	8207 MIN



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	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
7	MICAFUNGIN	100 MG/QD	Intravenous (not otherwise specified)	100 mg, qd	Lung infiltration	06-Apr-2020	08-Apr-2020	
8	VANCOMYCIN	1000 MG/1X	Intravenous (not otherwise specified)	1000 mg, 1X		06-Apr-2020	06-Apr-2020	11087 MIN
9	VANCOMYCIN	1500 MG/QD	Intravenous (not otherwise specified)	1500 mg, qd	Sepsis	01-Apr-2020	03-Apr-2020	11087 MIN

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17826274

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 23-Apr-2020 Outcomes: DE,HO,LT, Application Type: BLA

FDA Rcvd Date: 28-Aug-2020 Mfr Rcvd Date: 24-Aug-2020 Mfr Control #:US-SA-2020SA111365 Application #: 761037

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	SARILUMAB		400 MG/1X	Intravenous (not otherwise specified)	400 mg, 1X	COVID-19	21-Apr-2020	21-Apr-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	3407 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Alanine aminotransferase increased	NA
Aspartate aminotransferase increased	NA
Hypotension	NA
Intestinal ischaemia	NA
Multiple organ dysfunction syndrome	NA
Pyrexia	NA



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Event/Problem Narrative:

Initial information received on 25-Apr-2020 regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference 2020-34286 on 25-Apr-2020 and transmitted to Sanofi on 28-Apr-2020, in the scope of company sponsored study (b) (6)

Center ID (b) (6) Patient ID: (b) (6) Country: United States

Study Title: (b) (6)

A 56-year-old, Black, female patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)
(b) (6)
(b) (6) The patient experienced Fever [Pyrexia]: Hospitalization, (Severity: Grade 2) on (b) (6)
Increase in AST [Aspartate aminotransferase increased]: Life threatening, Serious AESI (ALT or AST increase), (Severity: Grade 2) on (b) (6)
(b) (6) and Multisystem organ failure [Multiple organ dysfunction syndrome]: Death, (Severity: Grade 5) (b) (6) and Increase in ALT [Alanine aminotransferase increased]: Life threatening, Serious adverse event of special interest (AESI) (ALT or AST increase), (Severity: Grade 2) and Ischemia of right colon [Intestinal ischaemia]: Life threatening, (Severity: Grade 3) on (b) (6) after receiving study drug. Action taken with study drug in response to the events was not applicable. The patient died on (b) (6) The cause of death was reported as multisystem organ failure. Autopsy was not performed.

Relevant medical history included smoking, precordial chest pain, elevated ferritin, decreased albumin, increased fibrinogen, increased d-dimer and elevated troponin.

Relevant concomitant medications included acetaminophen and Zithromax (azithromycin).

On 24-Feb-2020, the patient experienced earliest symptoms of pneumonia. Evidence of pneumonia present were based on historical chest X-Ray or CT scan. The highest temperature recorded within 24 hours prior to dosing was 102 degrees Fahrenheit (degree F), measured oesophageal. The fever was documented in medical record. On 07-Mar-2020 the patient underwent a computerized tomography (CT) scan and X-ray for precordial chest pain and shortness of breath. Results were not provided.

On 08-Mar-2020 the patient underwent nebulizer treatments for precordial chest pain and shortness of breath and an electrocardiogram was taken for precordial chest pain and shortness of breath prolong QT wave abnormality.



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On 09-Mar-2020 the patient underwent a stress myocardial perfusion image ray for precordial chest pain and shortness of breath.

On 14-Apr-2020, the patient was positive on COVID-19.

On 19-Apr-2020 chest X-ray showed diffuse infiltrates.

On 20-Apr-2020, chest X-ray scan showed relatively diffuse interstitial and airspace opacities with some improved aeration of the lung bases compared to prior.

On (b) (6) the patients vitals included blood pressure 103/59mmHg, body temperature 96.8 degrees Fahrenheit (degree F), pulse 72 beats per minute (bpm), oxygen saturation (SpO2) 98% and respiratory rate 20 respirations per minute (rpm). Biochemistry and hematology showed alanine aminotransferase (ALT) 91 U/L (0-55), aspartate aminotransferase (AST) 117 U/L (5-34), total bilirubin 0.6 mg/dl (0.2-1.2), platelet count $204 \times 10^3/\text{uL}$ (142- 346), white blood cell count (WBC) $11.44 \times 10^3/\text{uL}$ (3.1- 9.5) and absolute neutrophil count (ANC) $9.18 \times 10^9/\text{L}$ (1.1-6.33). On the same day, patient's chest X-ray revealed slight interval increase in diffuse infiltrates, multifocal. The patient received supplementary oxygen via non-rebreather mask, high-flow nasal cannula, and mechanical ventilation. The patient required treatment in the intensive care unit (ICU) and was given vasopressors. Rales/crackles were not present on lung auscultation.

On (b) (6) (b) (6) days 19 hours after the administration of study drug, the patient developed a fever with temperature of 99 degree F. The patient started receiving Zosyn (piperacillin and tazobactam), 4.5 g, three times a day, intravenously, and vancomycin 15 mg/kg, continuous infusion, intravenously, both as a corrective treatment for fever. Fever resolved on the same day. Chest X-ray scan showed stable bilateral interstitial and ground glass opacity allowing for differences in radiographic technique. Blood pressure was 99/56, and the patient started receiving vasopressin at dose of 0.04 units/minute, intravenously, continuous infusion.

On (b) (6) (b) (6) days 8 hours after the administration of study drug, the patient experienced a life-threatening increase in ALT and AST, measuring 206 and 366, respectively. On the same day, the patient experienced life threatening ischaemia of right colon. Unspecified procedure was performed as a corrective treatment. Blood pressure was 91/63 mmHg and the patient was diagnosed with hypotension. Chest X-ray showed persistent opacities.

On (b) (6) (b) (6) days 3 hours 27 minutes after the administration of study drug, the patient experienced multisystem organ failure, and passed away at 19:12.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.
Causality assessment is as follows:



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Multiple organ dysfunction syndrome: Severity = Grade 5; Investigator Causality = Not related; Company Causality = Not Related
Hypotension: Severity = Grade 3; Investigator Causality = Not Related; Company Causality = Not Related

Alanine aminotransferase increased: Severity = Grade 2; Investigator Causality = Not related; Company Causality = Related

Aspartate

aminotransferase increased: Severity = Grade 2; Investigator Causality = Not related; Company Causality = Related

Ischemia of right colon: Severity = Grade 3; Investigator Causality = Not related; Company Causality = Not Related

Pyrexia: Severity = Grade 2; Investigator Causality = Not Related; Company Causality = Not Related
Investigator causality rationale for events: No alternative explanation was provided.

Company causality rationale: A 56-year-old female patient with severe or critical COVID-19 and worsening pneumonia died due to multisystem organ failure, (b) (6) days after receiving study drug. The patient also experienced alanine aminotransferase increased, aspartate aminotransferase increased, ischemia of right colon, hypotension and fever after receiving study drug. Based on the information provided, severe or critical COVID-19 with pneumonia is the most plausible cause for the development of multisystem organ failure, ischemia of right colon, hypotension and fever in this patient. Therefore, these events are assessed as unrelated to the study drug or to any clinical trial procedure. Based on a plausible temporal association between study drug administration and the reported events and known potential effect of study drug on functional liver enzymes, causality for the events of alanine aminotransferase increased and aspartate aminotransferase increased is assessed as related to study drug. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation. The events are not related to any clinical trial procedure.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 28-Apr-2020 and 30-Apr-2020 (processed together) Investigator provided the following updates: Medical history updated, ischemia of right colon stop date updated, Hypotension intensity grade updated, Fever stop date and intensity updated.

Follow up: 28-May-2020 Investigator provided the following updates: clinical course updated, performed procedures added, event outcome updated for hypotension.

Follow up: 09-Jun-2020 Investigator provided the following updates: outcome of event 'Increase in ALT' and 'Increase in AST' updated. Follow up: 15-Jun-2020 Investigator provided the following updates: outcome of the event Increase in AST updated. Follow up: 06-Aug-2020 Investigator provided the following updates: clinical course updated Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.



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Follow up: 11-Aug-2020 Investigator provided the following updates: seriousness criteria (event: Hypotension) updated; clinical course updated. Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up: 19-Aug-2020 Investigator provided the following updates: resolution date and clinical course updated. Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up: 24-Aug-2020 The Investigator provided the following updates: outcome of the event Increase in ALT updated.

Expectedness Assessment per current IB (version 14): Multisystem organ failure: unexpected Hypotension: unexpected Increase in ALT: unexpected Increase in AST: unexpected Ischemia of right colon: unexpected Fever: unexpected

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Smoker	1995	2020	NO
Shortness of breath	24-Feb-2020		YES
Wheezing	24-Feb-2020		YES
Chest pain precordial	09-Mar-2020		YES
ALP increased	19-Apr-2020		YES
ALT increased	19-Apr-2020		YES
AST increased	19-Apr-2020		YES
Albumin decreased	19-Apr-2020		YES
CRP increased	19-Apr-2020		YES
Ferritin increased	19-Apr-2020		YES
Fibrin D dimer increased	19-Apr-2020		YES
Fibrinogen increased	19-Apr-2020		YES



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Procalcitonin increased	19-Apr-2020	YES
Triglycerides high	19-Apr-2020	YES
Calcium decreased	20-Apr-2020	YES
Decreased RBC count	20-Apr-2020	YES
Glucose increased	20-Apr-2020	YES
LDH increased	20-Apr-2020	YES
Troponin increased	20-Apr-2020	YES
BUN increased	(b) (6)	YES
Creatinine increased	(b) (6)	YES
GFR decreased	(b) (6)	YES
GERD		YES
Hiatal hernia		YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	91	U/L	0	55	N
Bilirubin	0.6	mg/dL	0.2	1.2	N
Chest X-ray					Y
Oxygen saturation	98	%			N
Platelet count	204	10 ³ /uL	142	346	N
WBC	11.44	10 ³ /uL	3.1	9.5	N
Alanine aminotransferase	206	U/L	0	55	N
Chest X-ray					Y
Platelet count	206	10 ³ /uL	142	346	N
Aspartate aminotransferase	117	U/L	5	34	N
Aspartate aminotransferase	366	U/L	5	34	N
Blood pressure	103/59	mmHg			N
Blood pressure	99/56	mmHg			N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Body temperature	96.8	degF			Y
Chest X-ray					Y
Absolute neutrophil count	13.22	10*9/L	1.1	6.3	N
Pulse rate	72	beats/min			N
SARS-CoV-2 test					N
WBC	18.17	10*3/uL	3.1	9.5	N
Respiratory rate	20	breaths/min			N
Chest X-ray					Y
Chest X-ray					Y
Absolute neutrophil count	9.18	10*9/L	1.1	6.3	N
Bilirubin	2	mg/dL	0.2	1.2	N
Blood pressure	91/63	mmHg			N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN				Pain			8352 MIN
2	ACETAMINOPHEN	650 MG/	Oral	650 mg, as necessary	Fever	20-Apr-2020	25-Apr-2020	8352 MIN
3	ROCEPHIN [CEFTRIAXONE SODIUM]	1 G/QD	Intravenous (not otherwise specified)	1 g, QD	Ant biotic therapy	21-Apr-2020	25-Apr-2020	6912 MIN
4	ZITHROMAX	250 MG/QD	Oral	250 mg, qd	Ant biotic therapy	09-Mar-2018	18-Apr-2020	68832 MIN
5	ZITHROMAX	500 MG/QD	Oral	500 mg, qd		19-Apr-2020	25-Apr-2020	68832 MIN

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding Outsourcing Facility?:

Literature Text:



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FOIA Case Report Information

Case ID: 17826277

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 14-Apr-2020 Outcomes: DE,HO,OT, Application Type: BLA

FDA Rcvd Date: 01-Jun-2020 Mfr Rcvd Date: 20-May-2020 Mfr Control #:US-SA-2020SA112508 Application #: 761037

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	200 mg, single, 1X	COVID-19	30-Mar-2020	30-Mar-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	20736 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
Acute kidney injury	NA
Cardiac arrest	NA
Transaminases increased	NA

Event/Problem Narrative:

Initial information from the Company sponsored study ^{(b) (6)} was received on 21-Apr-2020
 Patient ID: ^{(b) (6)} Site: ^{(b) (6)} Country: United States.

Study title: ^{(b) (6)}

A 66-year-old, male patient of unreported ethnicity with severe or critical COVID-19 was enrolled in study ^{(b) (6)}
^{(b) (6)}
^{(b) (6)}
^{(b) (6)} The patient experienced Elevated transaminases on ^{(b) (6)} and Asystole on ^{(b) (6)} and Acute



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kidney injury on (b) (6) after receiving study drug.

No relevant medical history was reported.

Relevant concomitant medications included hydroxychloroquine, acetaminophen, azithromycin, methylprednisolone, meropenem and cefepime.

On 20-Mar-2020 the patient experienced earliest symptoms of pneumonia with rales/crackles on lung auscultation present.

On (b) (6) the patient was admitted to the hospital and transferred to intensive care unit (ICU).

On (b) (6), ECG was normal.

On (b) (6) the highest temperature that was recorded within 24 hours prior to dosing was 101.2 F (Fahrenheit), measured orally. The patient was treated with invasive mechanical ventilation and vasopressors. The following parameters were measured: SpO2 98%; blood pressure 131/87 mmHg; pulse 157 beats per minute (bpm); respiratory rate 26 respirations per minute (rpm); temperature 98.2 F (Fahrenheit), measured orally, and the patient was unresponsive. The following laboratory results were reported: alanine aminotransferase (ALT) 24 U/L (reference range 10-45), aspartate aminotransferase (AST) 33 U/L (reference range 10-40), creatinine 0.86 mg/dL (0.5 - 1.3) and total bilirubin 1.8 mg/dl (reference range 0.2-1.2). The following haematology results were provided: platelets 278x10E9/L (reference range 150-400) and white blood cells (WBC) 17.68x10E9/L (reference range 3.8-10.5). The patients pH was 7.32, PaCO2 49 mmHg, PaO2 127 mmHg and SaO2 was 98%. Chest X-ray showed diffuse airspace opacities throughout both lungs compatible with pneumonia.

On (b) (6) creatinine elevated to 2.18 and was trending down.

On (b) (6) chest X-ray showed bilateral patchy infiltrates with new retrocardiac consolidation or pleural effusion. Potassium increased to 7.0 mmol/L (3.5 - 5.3) and was trending down.

On (b) (6) chest X-ray was showed opacity in the right lower lung has decreased while opacity in the left lower lung was unchanged when compared to previous exam.

By (b) (6) ALT varied between 30 and 424, AST varied between 34 and 160.

On (b) (6) at 00:46, (b) (6) days 9 hrs 36 min after the first administration of IP, the patient experienced elevated transaminases (Grade 2). The event was assessed as medically significant adverse event of special interest. ALT was 372 and AST 138. No corrective treatment was applied.

On (b) (6) ALT was 283 and AST 88.

On (b) (6) at 02:59, the event of elevated transaminases was considered resolved. ALT was 90 and AST 21. Creatinine started raising from 1.44. On previous days creatinine was in reference range.

On (b) (6) and (b) (6) Chest X - ray showed left lower lobe pneumonia is present and diffuse airspace opacities in part post lungs which appear to be slightly worsening. Patchy opacities are once again noted within both lungs.

On (b) (6) blood pressure increased to 153/73mmHg. Creatinine level was 2.53.



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On (b) (6) days 8 hrs 50 min after the first administration of IP, patient experienced acute kidney injury (Grade 3) due to worsening of serum creatinine 3.02. The event led to hospitalization.

On (b) (6) continuous renal replacement therapy (CRRT) was initiated. Creatinine started decreasing.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

On (b) (6) chest X-ray showed bilateral small pleural effusion. Diffuse airspace opacities were seen throughout both lungs which remain unchanged when compared to previous study.

On (b) (6) X - ray showed bilateral pleural effusion and diffuse airspace opacity seen throughout both lungs. Potassium level was 4.0.

On (b) (6) SpO2 decreased to 72 %. Blood pressure was 63/31 mmHg, pulse 38 bpm and respiratory rate was 30 rpm. The patient was unresponsive. On the same day, (b) (6) days 9 hrs after the administration of the IP, the patient experienced asystole at 00:10 and died (Grade 5). No corrective treatment was used in response to the event. Details regarding autopsy were not provided. At the time of patients death, outcome of acute kidney injury was not resolved.

Action taken with study drug in response to the events was not applicable.

For Asystole:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: No alternative explanation provided.

Relationship with IP according to company: not reportable.

Company causality rationale: A 66-year-old male patient with severe or critical COVID-19 infection and worsening pneumonia experienced asystole and subsequent death, 35 days after receiving study drug. The event asystole is assessed as not related to study drug or any clinical trial procedure. The event is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age.

For Transaminases increased:

Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: No alternative explanation provided.

Relationship with IP according to company: reportable.

Company causality rationale: A 66-year-old male patient with severe or critical COVID-19 and worsening pneumonia experienced elevated transaminases, 15 days after receiving study drug. Baseline values of AST and ALT were within reference ranges. Concomitant medications hydroxychloroquine, acetaminophen, azithromycin, methylprednisolone, meropenem and cefepime may provide alternative aetiology for the reported event. Based on a plausible temporal association between study drug administration and the reported event and known potential effect of study drug on functional liver enzymes, causality is assessed as related to study drug. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation. The event is not related to any clinical trial procedure.

For Acute kidney injury:



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Relationship with IP according to investigator: no reasonable possibility.

Investigator causality rationale: No alternative explanation provided.

Relationship with IP according to company: not reportable.

Company causality rationale: A 66-year-old male patient with severe or critical COVID-19 and worsening pneumonia experienced acute kidney injury, (b) (6) days after receiving study drug. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug is the most plausible cause for the development of acute kidney injury in this patient. Therefore, the event is assessed as unrelated to the study drug or to any clinical trial procedure. Concomitant medications cefepime, meropenem and azithromycin may provide alternative aetiology for the event of acute kidney injury.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up received on 06-May-2020 and 07-May-2020 (processed together):

New event Asystole added; concomitant medications, relevant tests and clinical course updated; resolution date for Elevated transaminases updated.

Follow up: 20-May-2020:

The Investigator provided following updates: event Acute kidney injury added, clinical course update

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	60	U/L	10	45	N
Alanine aminotransferase	103	U/L	10	45	N
Bilirubin	1.8	mg/dL	0.2	1.2	N
Diastolic blood pressure	73	mmHg			N
Systolic blood pressure	131	mmHg			N
Electrocardiogram					Y
White blood cell count	17.68	10 ⁹ /L	3.8	10.5	N
X-ray					Y



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
X-ray					Y
Alanine aminotransferase	56	U/L	10	45	N
Alanine aminotransferase	133	U/L	10	45	N
Alanine aminotransferase	424	U/L	10	45	N
Alanine aminotransferase	372	U/L	10	45	N
Aspartate aminotransferase	160	U/L	10	40	N
Aspartate aminotransferase	21	U/L	10	40	N
Creatinine	0.86	mg/dL	0.5	1.3	N
Blood pH					Y
Alanine aminotransferase	283	U/L	10	45	N
Aspartate aminotransferase	49	U/L	10	40	N
Aspartate aminotransferase	88	U/L	10	40	N
Potassium	7	mmol/L	3.5	5.3	N
Diastolic blood pressure	87	mmHg			N
Heart rate	157	beats/min			N
X-ray					Y
X-ray					Y
Oxygen saturation	72	%			N
X-ray					Y
Alanine aminotransferase	30	U/L	10	45	N
Aspartate aminotransferase	138	U/L	10	40	N
Creatinine	2.53	mg/dL	0.5	1.3	N
Platelet count	278	10 ⁹ /L	150	400	N
PaO2	127	mmHg			N
Alanine aminotransferase	24	U/L	10	45	N
Alanine aminotransferase	47	U/L	10	45	N
Alanine aminotransferase	90	U/L	10	45	N
Aspartate aminotransferase	76	U/L	10	40	N
Heart rate	38	beats/min			N
Oxygen saturation	98	%			N
X-ray					Y
Aspartate aminotransferase	33	U/L	10	40	N
Aspartate aminotransferase	51	U/L	10	40	N
Aspartate aminotransferase	80	U/L	10	40	N
Aspartate aminotransferase	83	U/L	10	40	N
Potassium	4	mmol/L	3.5	5.3	N
Systolic blood pressure	153	mmHg			N
Body temperature	98.2	degF			Y
Respiratory rate	26	breaths/min			N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Aspartate aminotransferase	34	U/L	10	40	N
Creatinine	3.02	mg/dL	0.5	1.3	N
Diastolic blood pressure	37	mmHg			N
Systolic blood pressure	63	mmHg			N
PCO2	49	mmHg			N
Respiratory rate	30	breaths/min			N
X-ray					Y
X-ray					Y

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/QD	Oral	650 mg, QD	Fever	30-Mar-2020	30-Mar-2020	21646 MIN
2	ALBUTEROL [SALBUTAMOL SULFATE]	90 UG/	Respiratory (inhalation)	90 mcg PRN inhaled	Pneumonia	17-Apr-2020		24490 MIN
3	ALBUTEROL [SALBUTAMOL SULFATE]				COVID-19			24490 MIN
4	ASCORBIC ACID	500 MG/QD	Oral	500 mg, QD	Corona virus infection	30-Mar-2020	02-Apr-2020	21646 MIN
5	AZITHROMYCIN				Corona virus infection			24526 MIN
6	AZITHROMYCIN	500 MG/QD	Intravenous (not otherwise specified)	500 mg, QD	Pneumonia	28-Mar-2020	30-Mar-2020	24526 MIN
7	BENZONATATE	100 MG/	Oral	100 mg, PRN	Cough	28-Mar-2020	30-Mar-2020	24526 MIN
8	CEFEPIME	2000 MG/Q8H	Intravenous (not otherwise specified)	2000 mg, q8h	Pneumonia	10-Apr-2020	14-Apr-2020	5806 MIN
9	CEFEPIME				Corona virus infection			5806 MIN
10	FAMOTIDINE	20 MG/Q12H	Intravenous (not otherwise specified)	20 mg, bid	Corona virus infection	30-Mar-2020		21646 MIN



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17826277

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
11	HYDROXYCHLOROQUIN E	200 MG/Q12H	Oral	200 mg, BID	Corona virus infection	26-Mar-2020	31-Mar-2020	27406 MIN
12	MEROPENEM	1000 MG/Q12H	Intravenous (not otherwise specified)	1000 mg, BID	Pneumonia	07-Apr-2020	10-Apr-2020	10126 MIN
13	MEROPENEM				Corona virus infection			10126 MIN
14	METHYLPREDNISOLON E SODIUM SUCCINATE	40 MG/Q8H	Intravenous (not otherwise specified)	40 mg, q8h	Pneumonia	29-Mar-2020	11-Apr-2020	23086 MIN
15	METHYLPREDNISOLON E SODIUM SUCCINATE				Corona virus infection			23086 MIN
16	VANCOMYCIN				Corona virus infection			8686 MIN
17	VANCOMYCIN	1000 MG/Q12H	Intravenous (not otherwise specified)	1000 mg, bid	Pneumonia	08-Apr-2020	10-Apr-2020	8686 MIN

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17826772

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Event Date:** **Outcomes:** DE,OT, **Application Type:** NDA

FDA Rcvd Date: 27-May-2020 **Mfr Rcvd Date:** 18-May-2020 **Mfr Control #:** US-ADVANZ PHARMA-202005005590 **Application #:** 009768

Patient Information:

Age: **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	HYDROXYCHLOROQUIN E [HYDROXYCHLOROQUIN E SULFATE]		400 MG/		400 mg, bid (day 0)	COVID-19		
2	HYDROXYCHLOROQUIN E [HYDROXYCHLOROQUIN E SULFATE]		200 MG/		400 mg, bid (days 1-4)			
3	Heparin							
4	Linezolid				UNK	Leukocytosis		
5	Lopinavir/ritonavir		400 MG/		400 mg, bid (for 5 days)	Antiviral treatment		
6	Micafungin		100 MG/		100 mg, qd	Antifungal treatment		
7	Mycophenolic acid		360 MG/		360 mg, bid	Immunosuppression		
8	SULFAMETHOXAZOLE-TRIMETHOPRIM-DS				UNK	Pneumocystis jirovecii pneumonia		
9	Tacrolimus		6 MG/	Unknown	6 mg, bid	Immunosuppression		
10	Tobramycin				UNK	Leukocytosis		
11	Tocilizumab		400 MG/	Intravenous (not otherwise specified)	400 mg			

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17826772

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1 HYDROXYCHLOROQUIN E [HYDROXYCHLOROQUIN E SULFATE]		NA	NA				CONCORDIA	
2 HYDROXYCHLOROQUIN E [HYDROXYCHLOROQUIN E SULFATE]		NA	NA				CONCORDIA	
3 Heparin		NA	NA					
4 Linezolid		NA	NA					
5 Lopinavir/ritonavir		NA	NA					
6 Micafungin		NA	NA					
7 Mycophenolic acid		NA	NA					
8 SULFAMETHOXAZOLE- TRIMETHOPRIM-DS		NA	NA					
9 Tacrolimus		NA	NA					
10 Tobramycin		NA	NA					
11 Tocilizumab		NA	NA					

Event Information:

Preferred Term (MedDRA ® Version: 23.1)

ReC

Acute respiratory distress syndrome

NA

Multiple organ dysfunction syndrome

NA

Off label use

NA

Renal failure

NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17826772

Event/Problem Narrative:

Case number 202005005590 is a literature report (reference ID: 32378314) sent by physician on 18/May/2020.

The case refers to a 59-year-old female patient who experienced multiple organ dysfunction, acute respiratory distress syndrome, renal failure following treatment with Hydroxychloroquine for SARS-CoV-2 Off label use, Tacrolimus, Tocilizumab, Lopinavir/ritonavir, Micafungin, Sulfamethoxazole-trimethoprim-DS, Heparin, Tobramycin, Mycophenolic acid, Linezolid.

The patient's medical history included, heart transplant, Ventricular assist device insertion, Cardiac procedure complication, haemodialysis, Lung assist device therapy and the historical medications were not reported.

The patient's concurrent conditions cardiomyopathy, Chronic kidney disease, Diabetes mellitus.

The patient's concomitant medications included Cefepime, Vancomycin, Oseltamavir, IVIG.

The patient laboratory test included D-Dimer > 1000 ug/mL (1.29, 1.19, 1.22, 3.88, 1.06, 2.1, 1.68, 4.78, 12.65, 8.27), CPK, creatine phosphokinase (9-185 U/L) (86, 194, 1505, 2714, 2396, 1975, 2038, 1273), C-reactive protein (82, 110, 86, 44, 42, 56, 46, 46, 50, 63), high sensitivity troponin (55, 52, 52, 51, 5, 37, 33, 34, Absolute Lymphocyte count (1.49, 1.36 1.52, 1.85, 2.18, 4.05), Ferritin (281, 889, 927 1411, 3991, 4342, 3593 3299 2732), aspartate aminotransferase (8-37 U/L) (39, 34, 322, 265, 197, 160), alanine aminotransferase (8-35 U/L) (25, 22, 143, 129, 129, 125).

Author reported that the patient was 59-year-old African-American female with history of non-ischemic cardiomyopathy and left ventricular assist device prior to HT in 2012. Her post-transplant course was complicated by cardiac allograft vasculopathy (CAV, Stanford class II, ISHLT 0), diabetes mellitus (DM), hypertension (HTN), and chronic kidney disease (CKD) G3b-4/A3, with no graft dysfunction. Immunosuppression regimen consisted of tacrolimus 6mg twice daily with goal trough level of 4-6 ng/mL and mycophenolic acid (MPA) 360 mg twice daily. She had no recent hospitalizations, travel history, or sick contacts. She presented on 20/Mar/2020 with fever, myalgia, fatigue, diarrhea, productive cough and shortness of breath for 3 days. Temperature was 38.8C, heart rate 108 bpm, blood pressure 120/90mmHg, respiratory rate 25, oxygen saturation 92% on 3L nasal cannula (NC). Notable laboratory values include IL-6 62.7 pg/mL, immunoglobulin G (IgG) 1426 mg/dL, tacrolimus trough 8.5 ng/mL, and creatinine (Cr) 2.6 mg/dL (baseline 1.8-2.0 mg/dL). Additional laboratory values indicating severe disease in COVID-19 are shown in Table 1 4-6. Chest X-ray showed consolidative opacity in the left upper lobe perihilar region and diffuse bronchial wall thickening with patchy peribronchial ground-glass opacities bilaterally While awaiting testing for respiratory viruses and SARS-CoV-2, the patient was started on empiric cefepime, vancomycin, and oseltamavir. Given high suspicion for SARS-CoV-2, MPA was stopped and tacrolimus was held to achieve a goal of 4-6 ng/mL. Within hours of presentation on day 0, worsening respiratory failure developed, requiring high flow NC (HFNC). Arterial blood gas (ABG) at time of decompensation was pH 7.3, pCO₂ 32mmHg, pO₂ 64mmHg on 0.8 FiO₂. SARS-CoV-2 resulted positive. Hydroxychloroquine (400mg twice daily on day 0, followed by 200mg twice daily for days 1-4) and tocilizumab 400mg intravenous (1 dose) were initiated. Antibiotic coverage was broadened to include doxycycline. A single dose of intravenous immunoglobulin (IVIG) 10g was given, but not continued after a normal IgG level returned. Underlying CKD precluded enrollment into a remdesivir trial (excluded if CrCl<50 mL/min). As a second option, antiviral therapy with lopinavir/ritonavir 400mg twice daily for 5 days was added.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17826772

Consideration was given to drug-drug interactions with tacrolimus.

She initially improved on day 1 and was transitioned to NC. However, she subsequently developed worsening renal failure and acute respiratory distress syndrome. She was intubated on day 2 and started on continuous veno-venous hemodialysis (CVVHD). ABG at this time showed pH 7.25, pCO₂ 30mmHg, pO₂ 59mmHg on FiO₂ 0.8, and tacrolimus trough was 7.0 ng/mL. She required norepinephrine for vasoplegic shock and antifungal coverage with micafungin 100mg daily was added. Despite decreasing CRP, other inflammatory markers including ferritin, d-dimer and creatinine kinase continued to uptrend. High sensitivity troponin (Hs-Tn) remained stable and bedside echocardiogram showed preserved graft function. On days 3 and 4, low tidal volume ventilation was continued with FiO₂ 0.6 and PEEP 18mmHg, and on day 5, the patient was prone positioned. Given tacrolimus trough of 6.7 ng/mL, one dose of tacrolimus with 60% dose reduction was given, however because of rapidly rising levels, it was held thereafter. On day 7, given rising WBC and markedly elevated fungitell assay (259 pg/mL, <60 pg/mL), sulfamethoxazole-trimethoprim-DS was started for presumed pneumocystis jirovecii pneumonia. At this point, veno-venous extracorporeal membrane oxygenation (VV-ECMO) was considered for progressive ARDS, however the difficult decision was made not to offer VV-ECMO due to age, comorbidities, and poor prognosis. Heparin drip was started as the CVVHD line was clotting with rising d-dimer levels. Tobramycin and linezolid were given for worsening leukocytosis. On day 10, the patient's family was notified of her grave prognosis and care was withdrawn.

At the time of this report, the outcome of the events, multiple organ dysfunction, acute respiratory distress syndrome, renal failure was fatal.

The action taken with Hydroxychloroquine, Tacrolimus, Tocilizumab, Lopinavir/ritonavir, Micafungin, Sulfamethoxazole-trimethoprim-DS, Heparin, Tobramycin, Mycophenolic acid, Linezolid was not applicable.

De-challenge and re-challenge result was not applicable for the events multiple organ dysfunction, acute respiratory distress syndrome, renal failure with respect to Hydroxychloroquine Tacrolimus, Tocilizumab, Lopinavir/ritonavir, Micafungin, Sulfamethoxazole-trimethoprim-DS, Heparin, Tobramycin, Mycophenolic acid, Linezolid.

This case is considered to be serious due to seriousness criteria death.

The reporter considered the events of multiple organ dysfunction, acute respiratory distress syndrome, renal failure to be possibly related to Hydroxychloroquine.

Follow-up information was received on 19/May/2020 in the form of FTA. Version (1.0) was created.

Additional information added: Reporter's complete name, occupation and address line were updated in general tab. Laboratory details added. Concomitant drug drugs added. Narrative updated accordingly.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17826772

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Heart transplant	2012		
Ventricular assist device insertion	2012		
Cardiac procedure complication			
Cardiomyopathy			
Chronic kidney disease			
Diabetes mellitus			
Haemodialysis			
Lung assist device therapy			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
C-reactive protein	110	mg/L			N
Oxygen saturation	92	%			Y
Serum ferritin	281	ng/mL			N
Serum ferritin	2732	ng/mL			N
C-reactive protein	50	mg/L			N
Lymphocyte count	1.49	10 ³ /uL			N
C-reactive protein	46	mg/L			N
C-reactive protein	63	mg/L			N
Heart rate	108 bpm	per minute			N
PCO2	30	millimetre of mercury			N
Blood immunoglobulin G	1426	mg/dL			N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17826772

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
C-reactive protein	82	mg/L			N
C-reactive protein	42	mg/L			N
Lymphocyte count	1.36	10 ³ /uL			N
PO2	59	millimetre of mercury			N
Serum ferritin	3593	ng/mL			N
C-reactive protein	44	mg/L			N
PO2	64	millimetre of mercury			Y
Serum ferritin	889	ng/mL			N
C-reactive protein	56	mg/L			N
Lymphocyte count	1.85	10 ³ /uL			N
Serum ferritin	1417	ng/mL			N
Serum ferritin	4342	ng/mL			N
Blood pressure measurement	120/90	millimetre of mercury			N
Lymphocyte count	2.18	10 ³ /uL			N
Lymphocyte count	4.05	10 ³ /uL			N
Serum ferritin	3991	ng/mL			N
Blood creatinine	2.6	mg/dL	1.8	2.0	N
Body temperature	38.8C	degree Celsius			N
C-reactive protein	86	mg/L			N
Interleukin level	62.7	pg/mL			N
Lymphocyte count	1.52	10 ³ /uL			N
PCO2	32	millimetre of mercury			N
Serum ferritin	927	ng/mL			N
Serum ferritin	3299	ng/mL			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	Cefepime			UNK				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17826772

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
2	IVIG	10 G/	Intravenous (not otherwise specified)	10 g				
3	Oseltamavir			UNK				
4	Vancomycin							

Reporter Source:

Study Report?: No

Sender Organization: ADVANZ PHARMA

503B Compounding
Outsourcing Facility?:

Literature Text: Holzhauser L., Lourenco L., Sarswat N., Kim G., Chung B., Nguyen A.B.. Early Experience of COVID-19 in Two Heart Transplant Recipients: Case Reports and Review of Treatment Options. American journal of transplantation. 2020



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17829521

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 19-Mar-2020 Outcomes: DE,OT, Application Type: BLA

FDA Rcvd Date: 27-May-2020 Mfr Rcvd Date: 22-May-2020 Mfr Control #: ES-ROCHE-2607349 Application #: 125276

Patient Information:

Age: 21 YR Sex: Female Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB			Intravenous (not otherwise specified)	DESCONOCIDA	COVID-19	18-Mar-2020	
2	AMBISOME			Intravenous (not otherwise specified)		Acute respiratory failure	18-Mar-2020	21-Mar-2020
3	HIDROXICLOROQUINA SULFATO		400 MG/QD	Oral	400MG/24H	COVID-19	18-Mar-2020	21-Mar-2020
4	HIDROXICLOROQUINA SULFATO					Pneumonia		
5	LINEZOLID			Intravenous (not otherwise specified)		Acute respiratory failure	18-Mar-2020	21-Mar-2020
6	TOCILIZUMAB					Pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	2 Day	NA	NA	UNKNOWN				
2	AMBISOME	2 Day	No	NA	UNKNOWN				
3	HIDROXICLOROQUINA SULFATO	2 Day	No	NA	UNKNOWN				
4	HIDROXICLOROQUINA SULFATO	2 Day	No	NA	UNKNOWN				
5	LINEZOLID	2 Day	No	NA	UNKNOWN				
6	TOCILIZUMAB	2 Day	NA	NA	UNKNOWN				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17829521

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
Acute kidney injury	NA
Hepatitis	NA
Hypocoagulable state	NA
Pancreatitis acute	NA

Event/Problem Narrative:

AER 2607349 is a spontaneous case, received on 22/May/2020 from a physician in Spain via European Medicines Agency (EMA). It concerns a 21 year old female patient who developed acute pancreatitis, hepatitis, hypocoagulable state and failure kidney acute whilst being treated with amphotericin B, liposome (Ambisome), hydroxychloroquine sulfate (Hidroxicloroquina Sulfato), tocilizumab and linezolid.

The patient's medical history included blood stem cell transplant. Concurrent conditions included fanconis anaemia. No past drugs and concomitant medications were reported.

On 18/Mar/2020, the patient started receiving intravenous amphotericin B, liposome (lot number: unknown, dose and frequency not reported) for acute respiratory insufficiency, oral hydroxychloroquine sulfate (lot number: unknown) 400 mg once per day for COVID-19 pneumonia, intravenous tocilizumab (lot number: unknown, dose and frequency not reported) for COVID-19 and pneumonia, intravenous linezolid (lot number: unknown, dose and frequency not reported) for acute respiratory insufficiency. On 19/Mar/2020, she developed acute pancreatitis, hepatitis, hypocoagulable state and failure kidney acute. Therapy with linezolid, amphotericin B, liposome and hydroxychloroquine sulfate was withdrawn. She died on (b) (6) due to pulmonary tricosporonosis, respiratory insufficiency and septic shock.

At the time of the report, acute pancreatitis, hepatitis, hypocoagulable state and failure kidney acute was persisting. Therapy with tocilizumab was maintained.

The physician did not report a causality between acute pancreatitis, hepatitis, hypocoagulable state and failure kidney acute with amphotericin B, liposome, hydroxychloroquine sulfate, tocilizumab and linezolid.

The physician assessed the acute pancreatitis, hepatitis, hypocoagulable state and failure kidney acute as medically significant.

No further information was provided.

Relevant Medical History:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17829521

Disease/Surgical Procedure

Stem cell transplant

Start Date

(b) (6)

End Date

Continuing?

Medical History Product(s)

Start Date

End Date

Indications

Events

Relevant Laboratory Data:

Test Name

Result

Unit

Normal Low Range

Normal High Range

Info Avail

Concomitant Products:

Product Name

**Dose/
Frequency**

Route

Dosage Text

Indications(s)

Start Date

End Date

**Interval 1st
Dose to Event**

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

**503B Compounding
Outsourcing Facility?:**

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17834089

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ESP **Event Date:** 31-Mar-2020 **Outcomes:** DE, **Application Type:** ANDA

FDA Rcvd Date: 28-May-2020 **Mfr Rcvd Date:** 13-May-2020 **Mfr Control #:** ES-SUN PHARMACEUTICAL INDUSTRIES LTD-2020RR-248216 **Application #:** 090923

Patient Information:

Age: 26 YR **Sex:** Female **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Azithromycin		500 MG/	Oral	500 MG DIA	COVID-19 pneumonia	23-Mar-2020	24-Mar-2020
2	DEXAMETASONA (722A)		20 MG/	Intravenous (not otherwise specified)	20 milligram, Daily	Product used for unknown indication	28-Mar-2020	01-Apr-2020
3	DEXKETOPROFENO (7312A)		25 MG/Q8H	Intravenous (not otherwise specified)	25 milligram, tid	Product used for unknown indication	27-Mar-2020	01-Apr-2020
4	ENOXAPARINA (2482A)		40 MG/	Subcutaneous	40 milligram, Daily	Product used for unknown indication	27-Mar-2020	01-Apr-2020
5	HIDROXICLOROQUINA (2143A)		400 MG/	Oral	400 milligram, Daily	COVID-19 pneumonia	23-Mar-2020	01-Apr-2020
6	TOCILIZUMAB (8289A)		600 MG/	Intravenous (not otherwise specified)	600 MG ; IN TOTAL	Severe acute respiratory syndrome	29-Mar-2020	29-Mar-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Azithromycin	9 Day	NA	NA				SUN	
2	DEXAMETASONA (722A)	4 Day	NA	NA					
3	DEXKETOPROFENO (7312A)	5 Day	NA	NA					
4	ENOXAPARINA (2482A)	5 Day	NA	NA					
5	HIDROXICLOROQUINA (2143A)	9 Day	NA	NA					



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17834089

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC	
6 TOCILIZUMAB (8289A)	3 Day	NA	NA						

Event Information:

Preferred Term (MedDRA Version: 23.1)

ReC

Coagulopathy

NA

Event/Problem Narrative:

This case, manufacturer control number 2020RR-248216 from SPAIN refers to a 26 year-old female patient, who experienced the following event (Preferred Term): coagulopathy. The patient received the following suspect products: azithromycin, dexamethasone, enoxaparin, tocilizumab, dexamethasone and hydrochloroquine.

The case was reported by a physician via AGEMED and EMA.

The case was reported as serious because the patient died.

Sun Pharma medical reviewer's assessment:

The case is rated as serious and related to the use of suspect drug. Temporal association between drug administration and onset of the ADR suggests that coagulopathy is related to administration of azithromycin.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Caesarean section	(b) (6)	(b) (6)	

Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17834089

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: RANBAXY

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17834132

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: PAK Event Date: 18-May-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 28-May-2020 Mfr Rcvd Date: 22-May-2020 Mfr Control #: PK-ROCHE-2608047 Application #: 125276

Patient Information:

Age: 62 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ACTEMRA		200 MG/	Intravenous (not otherwise specified)		COVID-19			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2608047 is a spontaneous case, received on 22/May/2020 from a physician in Pakistan. It concerns a 62 year old male patient who died due unknown cause while being treated with tocilizumab (Actemra) for off label use (Actemra intentional use for unapproved indication).

The patient's concomitant medications included supplementary oxygen therapy. No medical history, past drugs or concurrent conditions were reported. He had no travel history.

On an unknown date, the patient started therapy with intravenous tocilizumab (lot number not reported) 200 mg (frequency not reported) for COVID-19 (for off label use (Actemra intentional use for unapproved indication)). It was reported that only one dose of tocilizumab was administered to him after which he showed slight improvement in his health. However, his condition deteriorated and he could not survive. On (b) (6) he died due to unknown cause. It was not reported if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17834132

The reporter did not assess the causality of death with tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	OXYGEN							

Reporter Source:

Reporter Source:
Sender Report?: No **Sender Organization:** ROCHE **503B Compounding Outsourcing Facility?:**



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17834132

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17835460

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 20-Apr-2020 Outcomes: DE,HO, Application Type: BLA

FDA Rcvd Date: 25-Jun-2020 Mfr Rcvd Date: 12-Jun-2020 Mfr Control #:US-SA-2020SA116327 Application #: 761037

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	SARILUMAB		1X	Intravenous (not otherwise specified)	1X, REGN88 or placebo, 200 mg or 400 mg intravenously (IV) single or multiple doses for 1 hour	COVID-19	15-Apr-2020	15-Apr-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	9 Day	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Coronavirus infection	NA
Pneumonia staphylococcal	NA
Pneumothorax	NA
Pneumothorax	NA
Transaminases increased	NA
Urinary tract infection	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17835460

Event/Problem Narrative:

Initial information received on 30-Apr-2020 regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference RGN MCN: 2020-35112, in the scope of company sponsored study (b) (6)

Initial information from the Company sponsored study (b) (6) was received on 30-Apr-2020.

Center ID: (b) (6) Patient ID (b) (6) Country: United States

Study Title: (b) (6)

(b) (6)

A 56-year-old, Asian male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6) The patient experienced Methacillin susceptible Staphylococcus aureus pneumonia (grade 3) on (b) (6) Elevated AST and ALT (grade 4), Pneumothorax without tension (grade: 3), on (b) (6) Urinary tract infection (grade 3) on (b) (6) Right apical pneumothorax (grade 3) on (b) (6) and Death due to Coronavirus infection (B34.2) (grade 5) on (b) (6) after receiving the study drug.

The patient's medical history included diabetes mellitus and acute respiratory failure with hypoxemia.

Relevant concomitant medications included acetaminophen, hydrocortisone and methylprednisolone.

On (b) (6) the patient had earliest onset of pneumonia symptoms. The patient required treatment in intensive care unit and supplemental oxygen was applied via invasive mechanical ventilation.

On (b) (6) chest X-ray scan showed bilateral patchy groundglass opacities. This pattern could be seen with COVID-19 pneumonia, other atypical/viral pneumonias were not excluded. Bilateral pulmonary infiltrates compatible with covid pneumonitis.

On (b) (6) chest X-ray scan showed slight decreased consolidation at both lung fields.

On (b) (6) chest X-ray scan showed persistent bilateral pulmonary infiltrates.

On (b) (6) chest x-ray scan showed extensive bilateral infiltrates with right effusion, without significant change.

On (b) (6) oxygen saturation (SpO2) was 96 %, blood pressure 141/73 mmHg, pulse 100 bpm, respiratory rate 28 rpm, temperature 99.2 F, alanine aminotransferase (ALT) was 66 U/L (reference ranges 14-63), aspartate aminotransferase (AST) 19 U/L (15-41), total bilirubin 1.3 mg/dl (0.3-1.2). Haematology results showed platelets at 198 K/ul (142-424), white blood cells (WBC) 9.0 K/ul (4.6-10.2), neutrophils (absolute) 90.5 K/ul (2-6.9).



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17835460

On (b) (6) chest x-ray scan showed persistent pulmonary infiltrates.

On (b) (6) (b) (6) days 22 hours 30 minutes after taking study drug, the patient developed Methacillin susceptible Staphylococcus aureus pneumonia (intensity: grade 3). The event was considered as serious AESI (Clinically significant invasive bacterial or fungal infections) and lead to Hospitalization. Body temperature was 102.7 degree Fahrenheit, WBC were 18.8 and neutrophils were 18. No culture test result was reported. Unspecified drug therapy was introduced as corrective treatment. Chest x-ray scan showed bilateral pulmonary parenchymal disease, increased on the left side.

On (b) (6) (b) (6) days after taking study drug, the patient developed Elevated AST and ALT (intensity: grade 4), with ALT level of 360 and AST level of 308. The event was considered as Serious AESI (ALT or AST increase) and lead to Hospitalization. It was reported that vasopressors were given for shock, as corrective treatment. WBC and neutrophils increased to 20.9 and 19.5, respectively. The patient experienced pneumothorax without tension (intensity: grade 3). The event lead to Hospitalization. Chest tube insertion was performed as corrective treatment. On the same day, pneumothorax without tension was considered resolved. Respiratory rate was 32 rpm and SpO2 was 97 %.

On (b) (6) (b) (6) days after taking study drug, the patient developed Urinary tract infection (intensity: grade 3). The event was considered as Serious AESI (Clinically significant invasive bacterial or fungal infections) and lead to Hospitalization. Body temperature increased to 104.3 degree Fahrenheit, WBC were 16.5 and neutrophils were 15.5. No culture test result was reported. Unspecified drug therapy was introduced as corrective treatment. ALT and AST increased to 729 and 592, respectively.

On (b) (6) ALT and AST further increased to 903 and 656, respectively. WBC and neutrophils also increased (WBC-22.2 neutrophils-20.9). Respiratory rate was 30 rpm and Spo2 was 95 %. Chest x-ray scan showed bilateral airspace disease noted, mildly increased. On same day, (b) (6) days after taking study drug, the patient experienced right apical pneumothorax (intensity: grade 3).

On (b) (6) SpO2 decreased to 90%, blood pressure to 92/61, pulse rate 76, respiratory rate was 33 and body temperature decreased to 96.8 degree Fahrenheit. ALT and AST increased to 703 and 424 respectively and total bilirubin increased to 7.8. Platelets decreased to 81, while WBC and neutrophils increased up to 25.3 and 23.5 respectively. Chest tube insertion was performed as corrective treatment for right apical pneumothorax. On the same day, right apical pneumothorax was considered resolved.

On (b) (6) at 00:00, SpO2 was 81%, blood pressure 106/60 mmHg, pulse 89 bpm. Chest x-ray scan showed unchanged diffuse bilateral pleural-parenchymal opacities grossly. At 02:28 (b) (6) days after administration of study drug, the patient was pronounced dead due to Coronavirus infection (B34.2) (intensity: grade 5). No autopsy was performed.

(b) (6) Treatment assignment unblinded for regulatory reporting purpose.

Action taken with study drug in response to the event was not applicable.

At the time reporting, patient had not recovered from methacillin susceptible staphylococcus aureus pneumonia, elevated AST and ALT and



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17835460

urinary tract infection.

For event of Death due to Coronavirus infection (B34.2):

Relationship with IP according to investigator: no reasonable possibility

Investigator causality rationale: No alternative explanation was provided.

Relationship with IP according to company: not reportable.

Company causality rationale: A 56-year-old male patient enrolled in the trial, dead due to corona virus infection (b) (6) days after administration of the blinded study drug. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug is the most plausible cause for the death in this subject. Therefore, event is assessed as unrelated to the study drug or to any clinical trial procedure.

For event of Methacillin susceptible Staphylococcus aureus pneumonia and Urinary tract infection

Relationship with IP according to investigator: no reasonable possibility

Relationship with IP according to company: not reportable

For event of Elevated AST and ALT:

Relationship with IP according to investigator: no reasonable possibility

Relationship with IP according to company: reportable

Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 56-year-old male patient with severe or critical COVID-19 and worsening pneumonia experienced staphylococcal pneumonia, increased transaminases and urinary tract infection, after receiving the study drug. Patient's baseline WBC and neutrophil values were within reference ranges, however, they've further increased following study drug administration. COVID-19 is commonly associated with superinfections. Presence of catheters and use of concomitant medications, such as methylprednisolone and hydrocortisone also confound causality and therefore, the causality for staphylococcal pneumonia and urinary tract infection is assessed as not related to study drug or any clinical trial procedure. Patient's baseline AST and ALT values were within reference ranges, however, they've further increased following study drug administration. Based on a plausible temporal association between study drug administration and the reported event and known potential effect of study drug on functional liver enzymes, causality for the event of increased transaminases is assessed as related to study drug. It was observed that higher rate of patients treated with sarilumab experience transaminase elevation. The event is not related to any clinical trial procedure.

For pneumothorax without tension and right apical pneumothorax:

Relationship with IP according to investigator: no reasonable possibility

Investigator causality rationale: not applicable.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17835460

Relationship with IP according to company: not reportable.

Company causality rationale: A 56-year-old male patient enrolled in the trial, experienced pneumothorax without tension (b) (6) days after administration of the blinded study drug and right apical pneumothorax (b) (6) t days after receipt of study drug. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug is the most plausible cause for the mentioned events. Therefore, the events are assessed as unrelated to the study drug or to any clinical trial procedure.

Relationship to study conduct or study procedure: The Investigator assessed the event as not related to study conduct or study procedure.

Follow up received date: 06-May-2020

The Investigator provided the following updates: previously reported clinical course confirmed with no updates to the case narrative required. Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up: 19-May-2020 and 20-May-2020 (processed together)

The Investigator provided the following updates: new events added, clinical course and concomitant medications updated.

Follow up: 12-Jun-2020:

The Investigator provided the following updates: new events added, medical history, concomitant medications, relevant tests and clinical course updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Thyroid disorder	26-Nov-2016	(b) (6)	NO	
Arthritis	28-Nov-2016	(b) (6)	NO	
Acute respiratory failure	(b) (6)	(b) (6)	NO	
Diabetes mellitus	(b) (6)	(b) (6)	NO	
Catheter placement	(b) (6)	(b) (6)	NO	
Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17835460

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	66	U/L	14	63	N
Systolic blood pressure	141	mmHg			N
Chest X-ray					Y
Neutrophil count	20.9	10 ³ /uL	2	6.9	N
Oxygen saturation	96	%			N
Respiratory rate	32	breaths/min			N
White blood cell count	18.8	10 ³ /uL	4.6	10.2	N
White blood cell count	16.5	10 ³ /uL	4.6	10.2	N
Bilirubin total	1.3	mg	0.3	1.2	N
Diastolic blood pressure	61	mmHg			N
Chest X-ray					Y
Pulse rate	100	beats/min			N
Oxygen saturation	95	%			N
White blood cell count	9	10 ³ /uL	4.6	10.2	N
White blood cell count	22.2	10 ³ /uL	4.6	10.2	N
White blood cell count	25.3	10 ³ /uL	4.6	10.2	N
Alanine aminotransferase	703	U/L	14	63	N
Aspartate aminotransferase	424	U/L	15	41	N
Body temperature	99.2	Cel			N
Chest X-ray					Y
Neutrophil count	19.5	10 ³ /uL	2	6.9	N
Respiratory rate	30	breaths/min			N
Diastolic blood pressure	60	mmHg			N
Body temperature	102.7	degF			Y
Chest X-ray					Y
Neutrophil count	9.05	10 ³ /uL	2	6.9	N
Neutrophil count	18	10 ³ /uL	2	6.9	N
Oxygen saturation	90	%			N
Respiratory rate	28	breaths/min			N
Alanine aminotransferase	729	U/L	14	63	N
Alanine aminotransferase	903	U/L	14	63	N
Aspartate aminotransferase	592	U/L	15	41	N
Bilirubin total	7.8	mg	0.3	1.2	N
Systolic blood pressure	92	mmHg			N
Systolic blood pressure	106	mmHg			N
Platelet count	81	10 ³ /uL	142	424	N
Aspartate aminotransferase	656	U/L	15	41	N



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FOIA Case Report Information

Case ID: 17835460

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Diastolic blood pressure	73	mmHg			N
Chest X-ray					Y
Chest X-ray					Y
Neutrophil count	23.5	10 ³ /uL	2	6.9	N
Oxygen saturation	97	%			N
Alanine aminotransferase	360	U/L	14	63	N
Body temperature	96.8	degF			Y
Chest X-ray					Y
Pulse rate	76	beats/min			N
Platelet count	198	10 ³ /uL	142	424	N
Aspartate aminotransferase	19	U/L	15	41	N
Aspartate aminotransferase	308	U/L	15	41	N
Body temperature	104.3	degF			Y
Body temperature	96.8	Cel			Y
Chest X-ray					Y
Pulse rate	89	beats/min			N
Neutrophil count	15.5	10 ³ /uL	2	6.9	N
Oxygen saturation	81	%			N
Respiratory rate	33	breaths/min			N
White blood cell count	20.9	10 ³ /uL	4.6	10.2	N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/	Other	650 mg, PRN	Fever	15-Apr-2020	25-Apr-2020	14548 MIN
2	AMIKACIN	1 DF/1X	Intravenous (not otherwise specified)	100 mg in 5% dextrose in water infusion 100 ml, once	Product used for unknown indication	22-Apr-2020	22-Apr-2020	4468 MIN
3	CEFAZOLIN	2000 MG/Q8H	Intravenous (not otherwise specified)	2000 mg, tid	Product used for unknown indication	23-Apr-2020	23-Apr-2020	3028 MIN
4	FLUCONAZOLE	200 MG/QD	Intravenous (not otherwise specified)	200 mg in NS 100 ml, qd	Product used for unknown indication	23-Apr-2020	23-Apr-2020	3028 MIN
5	HYDROCORTISONE	300 MG/1X	Intravenous (not otherwise specified)	300 mg, single	Product used for unknown indication	20-Apr-2020	20-Apr-2020	7348 MIN



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Case ID: 17835460

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
6	HYDROCORTISONE	100 MG/Q8H	Intravenous (not otherwise specified)	100 mg, tid		20-Apr-2020	25-Apr-2020	7348 MIN
7	LINEZOLID	Q12H	Intravenous (not otherwise specified)	600 mg in D5W 300 ml, bid	Product used for unknown indication	20-Apr-2020	23-Apr-2020	7348 MIN
8	METHYLPREDNISOLONE	40 MG/Q12H	Intravenous (not otherwise specified)	40 mg, bid	Product used for unknown indication	11-Apr-2020	21-Apr-2020	20308 MIN
9	MICAFUNGIN	1 DF/	Intravenous (not otherwise specified)	100 mg in 0.9% sodium chloride infusion 100 ml	Product used for unknown indication	23-Apr-2020	25-Apr-2020	3028 MIN
10	MIDAZOLAM		Intravenous (not otherwise specified)	100 mg in NS 100 ml		14-Apr-2020	19-Apr-2020	15988 MIN
11	MIDAZOLAM		Intravenous (not otherwise specified)	100 mg in NS 100 ml		21-Apr-2020	23-Apr-2020	15988 MIN
12	MIDAZOLAM	10 MG/1X	Intravenous (not otherwise specified)	10 mg, single	Product used for unknown indication	17-Apr-2020	17-Apr-2020	15988 MIN
13	NYSTATIN	Q8H	Topical	1 application, tid	Product used for unknown indication	23-Apr-2020	25-Apr-2020	3028 MIN
14	REMDESIVIR	1 DF/1X	Intravenous (not otherwise specified)	2000 mg in 0.9% sodium chloride infusion 210 ml, single	Product used for unknown indication	17-Apr-2020	17-Apr-2020	11668 MIN
15	REMDESIVIR	1 DF/1X	Intravenous (not otherwise specified)	100 mg in 0.9% sodium chloride infusion 230 ml, single		18-Apr-2020	21-Apr-2020	11668 MIN
16	RIFAXIMIN	550 MG/Q12H	Intravenous (not otherwise specified)	550 mg, bid	Product used for unknown indication	24-Apr-2020	25-Apr-2020	1588 MIN
17	ZOSYN	Q6H	Intravenous (not otherwise specified)	4500 mg in D5W 100 ml, qid	Product used for unknown indication	20-Apr-2020	23-Apr-2020	7348 MIN
18	ZOSYN	Q6H	Intravenous (not otherwise specified)	3375 mg in D5W 50 ml, qid		23-Apr-2020	23-Apr-2020	7348 MIN



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17835460

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17835846

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 15-May-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 30-Jun-2020 Mfr Rcvd Date: 26-Jun-2020 Mfr Control #: US-ROCHE-2610679 Application #: 125276

Patient Information:

Age: 56 YR Sex: Female Weight: 113.4 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		200 MG/1X	Intravenous (not otherwise specified)	The date of last dose of tocilizumab prior to adverse event: 14/May/2020.	COVID-19 pneumonia	14-May-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	1 Day	NA	NA	MJM34755,MJM43481,MJM51470,MJM93388				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC

Septic shock NA

Event/Problem Narrative:

AER 2610679 is a clinical study case, received on 22/May/2020 from a physician (pulmonary and critical care medicine) in the USA. It concerns a 56 year old female patient (patient number: (b) (6)) who died due to septic shock whilst enrolled in (b) (6)

(b) (6)

(b) (6)

Medical history included spina bifida, congenital hydrocephalus. Concurrent conditions included asthma, obstructive sleep apnea, hypertension, chronic skin ulcer, obesity, gastroesophageal reflux disease, restrictive lung disease, disorder of diaphragm, neurogenic bladder and anxiety. Concomitant medications included cefepime as broad coverage antibiotic, vancomycin as broad coverage antibiotic, salbutamol (Albuterol), pantoprazole, fluticasone, ertapenem as broad coverage antibiotic, enoxaparin for venous thromboembolism prophylaxis. No past drugs were reported.

(b) (6)



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(b) (6) On 15/May/2020, she developed septic shock (initial severity: grade 3) of unknown pathogen type. Unspecified medication was given for the septic shock. She was transitioned to comfort care by family choice. On an unreported date, her arterial blood gas, blood counts, coagulation and general chemistry were tested (results: not reported). On (b) (6) she died due to septic shock. It was unknown if an autopsy was performed or not.

The physician assessed the causality of fatal septic shock as possibly related to blinded tocilizumab and other suspected causes included disease under study, medical history or concurrent illness (unspecified).

The company assessed events fatal septic shock as possibly related to blinded tocilizumab as the role of tocilizumab cannot be ruled out at this moment. Tocilizumab is a recombinant humanized monoclonal antibody of the immunoglobulin IgG1 subclass which acts on interleukin 6 receptors. Infections are commonly observed. Contributory factors include the underlying condition of severe COVID-19 pneumonia.

The physician assessed the septic shock as a serious adverse event of special interest under serious and or medically significant infections.

No further information was reported.

This case is cross reference with AER 2611864 (same patient).

AER 2611864 was identified as a duplicate of AER 2610679. All information from AER 2611864 was added to AER 2610679, which remains the active case. The following data was added to the case: patient's date of birth updated, medical history, concurrent condition, concomitant medications, lot numbers of tocilizumab, and new event suspected secondary infection worsening septic shock with event description.

Additional information was received on 02/Jun/2020 and following information was added to the case: The event term suspected secondary infection worsening septic shock was amended to septic shock. Lab details were (arterial blood gas, blood counts, coagulation, general chemistry) added. Reporter details were updated. Batch/lot number added for blinded tocilizumab MJM43481.

Additional information was received on 23/Jun/2020, following information was added to the case: concurrent conditions (asthma, obstructive sleep apnea, hypertension, chronic skin ulcer, obesity, gastroesophageal reflux disease, restrictive lung disease, disorder of diaphragm, neurogenic bladder and anxiety); medical history (spina bifida, congenital hydrocephalus).

Additional information was received on 26/Jun/2020, following information was added to the case: Query reply was received and it was reported that septic shock was the only adverse event recorded in the rave form for this patient. Hence the event infection superimposed was deleted.

Analysis of similar events (PT- Septic shock)

On 3/Jun/2020 the Roche safety database was searched with MedDRA preferred term of Septic shock for Tocilizumab for the treatment of



FDA - Adverse Event Reporting System (FAERS)

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COVID-19 pneumonia. The search was based on both open label and blinded data.

The following 10 previously submitted IND Safety report was found (AER 1051710, AER 1052000, AER 1073639, AER 1353826, AER 422599, AER 430729, AER 475887, AER 492910, AER 575719, AER 2591648)

In addition, 151 non IND reports of serious case with similar events were identified.

In the index case AER 2610679, event fatal septic shock occurred (b) (6) after initiating tocilizumab therapy, for the indication of COVID-19 pneumonia. Other contributing/risk and etiological factors include age of the patient and the underlying condition COVID-19. Based on review of available data, there is some evidence suggesting that administration of Tocilizumab can be associated with life-threatening septic shock.

After review of the clinical details of the index case and similar previous cases, the sponsor does not believe that changes to the conduct of the clinical trial are warranted in response to this case report at this time.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Anxiety			
Asthma			
Congenital hydrocephalus			
Gastroesophageal reflux disease			
Hypertension			
Neurogenic bladder			
Obesity			
Restrictive pulmonary disease			
Skin ulcer			
Sleep apnoea syndrome			
Spina bifida			



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17835846

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ALBUTEROL [SALBUTAMOL]	90 UG/	Unknown		Asthma	14-May-2020	18-May-2020	1 DAY
2	CEFEPIME	2 G/	Unknown	BROAD COVERAGE		14-May-2020	14-May-2020	1 DAY
3	ENOXAPARIN	40 MG/BID	Unknown	ANTICOAGULATION	Thrombosis prophylaxis	14-May-2020	20-May-2020	1 DAY
4	ERTAPENEM	1 G/QD	Unknown	BROAD COVERAGE		14-May-2020	14-May-2020	1 DAY
5	PANTOPRAZOLE	40 MG/QD	Unknown		Gastroesophageal reflux disease	14-May-2020	18-May-2020	1 DAY
6	VANCOMYCIN	2 G/	Unknown	BROAD COVERAGE		14-May-2020	14-May-2020	1 DAY

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17840537

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 26-Mar-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 29-May-2020 Mfr Rcvd Date: 26-May-2020 Mfr Control #: IT-ROCHE-2609951 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB			Intravenous (not otherwise specified)		COVID-19 pneumonia	14-Mar-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	12 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC

Multiple organ dysfunction syndrome NA

Event/Problem Narrative:

AER 2609951 is a clinical study case, received on 26/May/2020 from a physician in Italy. It concerns a patient of unknown demographics (patient number: (b) (6)) who died due to multi-organ failure whilst enrolled in (b) (6)

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

(b) (6) The patient was with acute kidney injury and acute respiratory distress. On (b) (6) the patient died due to multi-organ failure (severity: grade 5). It was not reported if an autopsy was performed or not.

The physician did not report a causality between multi-organ failure with tocilizumab.

The company assessed a causality of multi-organ failure as unrelated with tocilizumab but to the disease under study i.e. COVID-19



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17840537

pneumonia as multi organ failure is one of the complications.

No further information was reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17840537

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17840870

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: BRA
Event Date:
Outcomes: DE,OT,
Application Type: BLA
FDA Rcvd Date: 29-May-2020
Mfr Rcvd Date: 26-May-2020
Mfr Control #: BR-ROCHE-2611296
Application #: 125276

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
COVID-19	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2611296 is a spontaneous case, received on 26/May/2020 from a consumer in Brazil. It concerns a patient of unknown demographics who was died due to worsening of covid-19 and used tocilizumab (Actemra) for unlabeled indication (off-label use).

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On an unknown date, the patient started therapy with tocilizumab (lot number and dosing regimen not reported) for covid-19 unlabeled indication (off-label use). On an unknown date, the patient experienced worsening of covid-19 and due to which was died. It was unknown if an autopsy was performed or not.

At the time of death, it was unknown if therapy with tocilizumab was altered or not in response to the worsening of covid-19.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17840870

The consumer did not report a causality of worsening of covid-19 with tocilizumab.

Company assessed the off label use as medically significant.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17840870

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17845906

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 25-Apr-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 01-Jun-2020 Mfr Rcvd Date: 28-May-2020 Mfr Control #: IT-ROCHE-2612458 Application #: 125276

Patient Information:

Age: 90 YR Sex: Female Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB			Intravenous (not otherwise specified)		COVID-19 pneumonia	13-Apr-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	12 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC

Pulmonary oedema NA

Event/Problem Narrative:

AER 2612458 is a clinical study case, received on 28/May/2020 from a physician in Italy. It concerns a 90 year old female patient (patient number: (b) (6)) who died due to pulmonary edema whilst enrolled in (b) (6)

The patient's concurrent conditions included arterial hypertension, diabetes. Concomitant medications included enoxaparin, furosemide and insulin. No medical history and past drugs were reported.

On (b) (6) the patient was admitted for severe COVID-19 pneumonia (40% bilateral involvement of lungs at the chest CT (computerized tomography)). During the first week of hospital stay, she progressively developed severe respiratory failure despite treatment with antivirals and broad spectrum antibiotics (piperacillin/tazobactam). High-flow oxygen therapy was administered. (b) (6)

(b) (6) . On (b) (6) non-invasive mechanical ventilation (C-pap) was initiated (PEEP 8 and FIO2 100 %) and respiratory conditions remained stable during the following week. The clinical course was characterized by episodes of hyperactive delirium, severe hyperglycemia required continuous infusion of insulin and



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peripheral thrombosis required enoxaparin (decoagulation dose). On ^{(b) (6)} the clinical conditions were rapidly worsened with sudden onset of severe dyspnea, tachypnea and chest pain. Blood examinations showed the presence of severe anemia of new onset and troponin elevation. Lung ultrasound showed signs of severe pulmonary edema. Due to extremely critical conditions, she was not examined with chest or abdominal CT. She was administered with furosemide. On ^{(b) (6)} she died due to pulmonary edema (severity: grade 5). It was unknown if an autopsy was performed or not.

The physician assessed the pulmonary edema as unlikely related to tocilizumab.

The company assessed the causality of pulmonary edema as unrelated to tocilizumab considering that the event is more related with underlying disease of COVID-19 pneumonia and its complications rather than tocilizumab therapy. Other significant confounding factors for causing the event include advanced age (90 years) of the patient, concurrent conditions of arterial hypertension and diabetes and prolonged hospitalization with immobility. Therefore, the causal relationship with tocilizumab cannot be established.

No further information was reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Diabetes mellitus			
Hypertension			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Computerised tomogram					N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17845906

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ENOXAPARIN							
2	FUROSEMIDE							
3	INSULIN							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17848643

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 03-Apr-2020 Outcomes: DE,LT,OT, Application Type: BLA

FDA Rcvd Date: 07-Aug-2020 Mfr Rcvd Date: 03-Aug-2020 Mfr Control #:US-SA-2020SA102906 Application #: 761037

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	SARILUMAB		1X	Intravenous (not otherwise specified)	REGN88 or placebo 200 mg or 400 mg, single	COVID-19	26-Mar-2020	26-Mar-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	79137 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Lower respiratory tract infection	NA
Pneumonia	NA
Respiratory failure	NA
Respiratory failure	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17848643

Event/Problem Narrative:

Based on information received on 23-Jul-2020, the case was downgraded to Non-SUSAR, with causality for the event of secondary bacterial infection updated to not reportable.

Based on information received on 28-May-2020, the case has been upgraded to SUSAR (seriousness criteria for the event of secondary bacterial infection was updated) and the overall company causality has been upgraded to reportable.

Initial information received on 05-Apr-2020 regarding a solicited valid serious case received from (Ip) REGENERON-USA GSA-PCP under reference 2020-28441 on 05-Apr-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6)
Patient ID (b) (6) Site: (b) (6) Country: United States.

Protocol: (b) (6)

A 69-year-old, Hispanic, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)
(b) (6)
The patient experienced Respiratory failure ([Respiratory failure]: Medically Significant; Onset date: (b) (6) Severity: Grade 4; Outcome: Recovered/Resolved; Event resolved on: 20-May-2020), Secondary Bacterial Infection of the trachea [Lower respiratory tract infection] (Initially reported as Secondary Bacterial Infection [Bacterial infection]): Medically Significant; Onset date: (b) (6) Severity: Grade 3; Outcome: Recovered/Resolved; Event resolved on: 17-May-2020), Lung infection ([Pneumonia]: Life-threatening; Onset date: 15-May-2020; Severity: Grade 2; Outcome: Not recovered/Not resolved; Event resolved on: Ongoing) and Hypoxemic respiratory failure ([Respiratory failure]: Death; Onset date (b) (6) Severity: Grade 5; Outcome: Fatal; Event resolved on (b) (6) after receiving study drug.

No relevant medical history was reported.

No relevant concomitant medications were reported.

On 17-Mar-2020, the patient started experiencing earliest symptoms of pneumonia.

On 24-Mar-2020, chest X-ray was performed and showed interval development of multiple new moderate bilateral hazy and patchy pulmonary opacities, with a lower lung distribution. Differential included multi-focal pneumonia.

On (b) (6) the patient was admitted to hospital, with one week of progressive coughs, fevers, headache, and dyspnoea. The patient presented with a temperature of 38.8 degrees C, peripheral capillary oxygen saturation (SpO2) of 95% on room air, positive SARS COV-2 testing, and bilateral infiltrates on chest radiograph, along with thrombocytopenia (platelets 55 10E9/L (150-450)), mild transaminitis (alanine aminotransferase (ALT) 46 U/L (1-45), aspartate aminotransferase (AST) 55 U/L (1-35)). The patient was treated with hydroxychloroquine. Electrocardiogram (ECG) was performed and showed normal sinus rhythm, left axis deviation and pulmonary disease.

On (b) (6) baseline lung auscultation, rales/crackles were present. The patient was noted to have an oxygen saturation in the low 90%



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range on 100% non-rebreather (NRB). He had fever, with the highest temperature recorded within 24 hours prior to dosing of 39.8 degrees Celsius (C), measured orally. His SpO₂ was 96-99%, with the oxygen flow rate of 12 liters/min. Patients blood pressure was between 121/75 mmHg and 128/76 mmHg, pulse 75-76 beats per minute (bpm), respiratory rate 32-39 respirations per minute (rpm), highest temperature measured during the day 37.8 degrees C, measured at evening and bedtime, axillary, and the patient was alert. Patients pre-dose temperature was 36.7 degrees C. Patients blood chemistry results were: ALT 34 U/L, AST 55 U/L, carbon dioxide (bicarbonate) 22.1 mEq/L (reference range: 22-30), lactate dehydrogenase (LDG) 682 U/L and increasing (reference range: 100-220), total bilirubin 0.5 mg/dl (reference range: 0.1-1.2). Patients haematology results were: platelets 69x10⁹/L (reference range: 150-450), white blood cells (WBC) 3.8x10⁹/L (reference range: 4.5-11), neutrophils (absolute) 2.7x10⁹/L (reference range: 1.9-8), lymphocytes (absolute) 1.0x10⁹/L (reference range: 1-4.5). Arterial blood gas (ABG) test results were: pH 7.38, partial pressure of carbon dioxide (PaCO₂) 39 mmHg and arterial partial pressure of oxygen (PaO₂) 39 mmHg. The patient had persistent high fevers, developed a rapid escalation of oxygen requirements, and was transferred to the intensive care unit (ICU), requiring 100% NRB.

On (b) (6) the patient became confused. His SpO₂ was 93-97%. On (b) (6) the patient became alert again, with SpO₂ of 88-97%.

Between (b) (6) and (b) (6) patients vital parameters did not change significantly.

On (b) (6) the patient again became confused. His SpO₂ was 91%, and blood pressure decreased to 116/50 mmHg.

On (b) (6) the patient started using a nasal cannula with non-rebreather and his SpO₂ increased to 97%.

On (b) (6) the patient became unresponsive and was put on invasive mechanical ventilation.

On (b) (6) at 06:30 (b) (6) days 14 hrs. 35 min after the first IP administration, the patient experienced respiratory failure and was intubated. The patients hospital course was complicated by septic shock, secondary bacterial infections including Citrobacter koseri and dependence on pressor support. The patient was transitioned to a tracheostomy, however, failed to be weaned from mechanical ventilation. Chest imaging revealed extensive diffuse fibrosis throughout lungs, bilateral consolidations and bilateral pleural effusions.

On (b) (6) chest X-ray revealed improving now moderate diffuse hazy densities throughout the lungs with more confluent opacities in the lower lobes.

On (b) (6) the patient developed new recurrent fevers, with body temperature 38.7 C. The patient was started on new pressor support, as well as new antibiotics, including cefepime and vancomycin. Blood cultures showed no growth.

On (b) (6) absolute neutrophil count was 7.2 and the patient was given cefepime, at an unknown dose and frequency for secondary bacterial infection, until (b) (6). He was also given vancomycin at a dose of 1 g, once daily, intravenously, until (b) (6) for the same indication.



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On (b) (6) days 8 hrs. 5 min after the first IP administration, the patient developed secondary bacterial infection of the trachea, with body temperature 39.6 C, and new tracheal secretions. Respiratory cultures demonstrated new developing infection, including gram negative bacilli. Gram stain revealed rare polymorphonuclear gram positive cocci in pairs, and rare gram-negative bacilli. Vancomycin was discontinued on the same day, however, patient continued treatment with cefepime 1g twice daily.

On (b) (6) WBC and absolute neutrophils were 9.6 and 9.5, respectively.

On (b) (6) respiratory cultures demonstrated moderate growth of *Citrobacter koseri*. Patients temperature peaked and was 38.3 C. WBC was measuring 8.1 and absolute neutrophils 7.13. Cefepime was discontinued, and ceftriaxone treatment 2g once daily, intravenously, was started. Blood culture results pending.

On (b) (6) WBC increased to 8.6, and absolute neutrophil count was 7.3. The patient received ceftriaxone at a dose of 2 g, daily until (b) (6) intravenously, for secondary bacterial infection.

On (b) (6) patient received 1 g of vancomycin, once, intravenously, for secondary bacterial infection. From (b) (6) to (b) (6) (b) (6) the patient was receiving unspecified dose of meropenem.

On (b) (6) patient received 750 mg of vancomycin, intravenously, for secondary bacterial infection.

On (b) (6) the patient developed body temperature of 100.9 F and tachycardia (pulse-107 bpm); SpO2 decreased to 84%, escalating oxygen requirements with FiO2 up to 100% and increasing pressor requirements. WBC and neutrophils increased to 16.0 and 14.72, respectively. Chest X-ray showed persistent diffuse opacities. Cefepime was introduced again for concern about septic shock at a dose of 2 g, once daily until (b) (6) intravenously for secondary bacterial infection.

On (b) (6) (b) (6) days 8 hrs. 5 min after the first IP administration, the patient developed life-threatening lung infection. Sputum culture grew *Citrobacter koseri* again. SpO2 was 94%, body temperature was 38 C, WBC were 10.4 and neutrophils were 8.63. On the same day, he was given vancomycin at a dose of 1 g, intravenously, for secondary bacterial infection.

On (b) (6) WBC and neutrophils increased to 16.4 and 14.5, respectively. On the same day, the patient recovered from secondary bacterial infection of the trachea.

On (b) (6) the patients SpO2 was dropped on 62 %, blood pressure 105/58, pulse was 103. WBC 17.0 and neutrophils (absolute) 15.30.

On (b) (6) WBC was 20.5, neutrophils (absolute) 19.6, ALT 19 and AST 25. SpO2 was 75%, blood pressure 130/59, pulse 104.



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On (b) (6) the patient recovered from respiratory failure. On the same day, (b) (6) days 22 hrs. 57 min after the first Ip administration, the patient had rapidly increasing pressor requirements and developed hypoxemic respiratory failure with SpO2 decreasing into 50s and 60s. Blood pressure was 74/44, with pulse of 115. The patient experienced pulseless electrical activity (arrest) at 14:26 with return of spontaneous circulation after 1 round of chest compression and epinephrine. Patient developed ventricular fibrillation afterwards and received 2 shocks with defibrillator. Sodium bicarbonate, calcium, insulin, dextrose 50 at an unknown dose and amiodarone at a dose of 300 mg, once, intravenously, was administered. The patient developed pulseless electrical activity for the second time and despite subsequent chest compression and shocks, he died at 14:52. Cause of death was reported as hypoxemic respiratory failure. No autopsy was performed.

Action taken with study drug in response to the events was not applicable.

Causality assessment is as follows:

(b) (6)

Respiratory failure: Severity = Grade 5; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Other suspected cause included Covid-19 pneumonia.

Company causality rationale: A 69-year-old, male patient with severe or critical COVID-19 infection experienced respiratory failure and subsequent death, approximately (b) (6) months after receiving the study drug. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug are the most plausible causes for the respiratory failure in this subject. Therefore, the event is assessed as not related to the study drug or to any clinical trial procedure.

Pneumonia: Severity = Grade 2; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Other suspected causes included COVID pneumonia with respiratory failure and prolonged mechanical ventilation.

Company causality rationale: A 69-year-old male patient with severe or critical COVID-19 infection and pneumonia experienced lung infection month and a half after receiving the study drug. The event of lung infection is assessed as not related to study drug. The event is secondary to progression of COVID-19 infection and pneumonia and patient's prolonged stay on invasive mechanical ventilation. The event of secondary bacterial infection is not related to any clinical trial procedure.

Respiratory failure: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Underlying COVID-19 infection.

Company causality rationale: A 69-year-old, Hispanic or Latino, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced Respiratory failure (b) (6) days after receiving the study drug. The event of Respiratory failure is assessed as not related to study drug. The event is secondary to progression of COVID-19 infection and pneumonia. The event Respiratory failure is not related to any clinical trial procedure.

Lower respiratory tract infection: Severity = Grade 3; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: No alternative explanation was provided. Other suspect causes were reported as underlying Covid 19



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infection, secondary bacterial infection.

Company causality rationale: A 69-year-old, Hispanic or Latino, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced Secondary Bacterial Infection of the trachea (b) (6) days after receiving the study drug. The event of Secondary Bacterial Infection of the trachea is assessed as not related to study drug. The event is secondary to progression of COVID-19 infection and pneumonia and patient's prolonged stay on invasive mechanical ventilation. Respiratory cultures demonstrated moderate growth of Citrobacter Koseri. The event is not related to any clinical trial procedure.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up received date: 15-Apr-2020:

The Investigator provided the following updates: outcome updated, units and referent ranges for some labs added

Follow up received date: 24-Apr-2020:

The Investigator provided the following updates: medical history and concomitant medications added, new event with relevant laboratory tests added, and clinical course updated.

Follow up received date: 18-May-2020:

The Investigator provided the following updates: new event Lung infection added, clinical course updated.

Follow up received date: 22-May-2020:

The Investigator provided the following updates: new event (Hypoxemic respiratory failure) added. Clinical course and lab test information updated.

Follow up received date: 28-May-2020:

The Investigator provided the following updates: event course, outcome and resolution date for the event Respiratory failure updated.

Follow up received date: 23-Jul-2020:

The Investigator provided the following updates: outcome of the events Secondary bacterial infection and Lung infection, corrective treatment and clinical course updated. Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up received date: 03-Aug-2020:

The Investigator provided the following updates: event term for the event Secondary Bacterial Infection of the trachea updated.



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Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Shingles	30-Jan-2016	05-Feb-2016	NO
Diabetes			YES
Hyperlipidemia			YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood culture					Y
Systolic blood pressure	59	mmHg			N
Carbon dioxide	22.1	meq/L	22	30	N
Culture					Y
Neutrophil count	14.5	10 ⁹ /L	1.9	8	N
Neutrophil count	15.30	10 ⁹ /L	1.9	8	N
Oxygen saturation	96	%			N
Oxygen saturation	96	%			N
Respiratory rate	39	breaths/min			N
Alanine aminotransferase	46	U/L	1	45	N
Alanine aminotransferase	19	U/L	1	45	N
Aspartate aminotransferase	55	U/L	1	35	N
Body temperature	100.9	degF			Y
Body temperature	39.8	Cel			N
Chest X-ray					Y
Culture					Y
Neutrophil count	14.72	10 ⁹ /L	1.9	8	N
White blood cell count	17.0	10 ⁹ /L	4.5	11	N
Aspartate aminotransferase	55	U/L	1	35	N
Auscultation					Y
Bilirubin	0.5	mg/dL	0.1	1.2	N
Diastolic blood pressure	105	mmHg			N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Systolic blood pressure	121	mmHg			N
Body temperature	36.7	Cel			N
Chest X-ray					Y
Lymphocyte count	1.0	10 ⁹ /L	1	4.5	N
Neutrophil count	7.2	10 ⁹ /L	1.9	8	N
Neutrophil count	9.5	10 ⁹ /L	1.9	8	N
Oxygen saturation	95	%			N
Oxygen saturation					Y
Oxygen saturation	94	%			N
PaO2					Y
White blood cell count	8.1	10 ⁹ /L	4.5	11	N
Aspartate aminotransferase	25	U/L	1	35	N
Lactate dehydrogenase	682	U/L	100	220	N
Body temperature	39.6	Cel			N
Neutrophil count	2.7	10 ⁹ /L	1.9	8	N
Neutrophil count	7.13	10 ⁹ /L	1.9	8	N
Oxygen saturation	96	%			N
Oxygen saturation	97	%			N
PaO2	39	mmHg			N
White blood cell count	20.5	10 ⁹ /L	4.5	11	N
Diastolic blood pressure	50	mmHg			N
Diastolic blood pressure	130	mmHg			N
Systolic blood pressure	58	mmHg			N
Electrocardiogram					Y
Neutrophil count	8.63	10 ⁹ /L	1.9	8	N
Oxygen saturation	84	%			N
Oxygen saturation	94	%			N
PCO2	39	mmHg			N
White blood cell count	9.6	10 ⁹ /L	4.5	11	N
White blood cell count	16.4	10 ⁹ /L	4.5	11	N
Diastolic blood pressure	75	mmHg			N
Chest X-ray					Y
Chest X-ray					Y
Pulse rate	107	beats/min			N
Oxygen saturation	91	%			N
Oxygen saturation	62	%			N
Platelet count	55	10 ⁹ /L	150	450	N
Sputum culture					Y
Alanine aminotransferase	34	U/L	1	45	N
Blood culture					Y



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Case ID: 17848643

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Systolic blood pressure	116	mmHg			N
Body temperature	38.3	Cel			N
Pulse rate	76	beats/min			N
pH	7.38	UNK			Y
SARS-CoV-2 PCR test					N
White blood cell count	16.0	10 ⁹ /L	4.5	11	N
Body temperature	37.8	Cel			N
Chest X-ray					Y
Pulse rate	103	beats/min			N
Pulse rate	104	beats/min			N
Neutrophil count	7.3	10 ⁹ /L	1.9	8	N
Neutrophil count	19.6	10 ⁹ /L	1.9	8	N
Oxygen saturation	88	%			N
Platelet count	69	10 ⁹ /L	150	450	N
White blood cell count	3.8	10 ⁹ /L	4.5	11	N
White blood cell count	8.6	10 ⁹ /L	4.5	11	N
White blood cell count	10.4	10 ⁹ /L	4.5	11	N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN				Fever			
2	AZITHROMYCIN				COVID-19			
3	HYDROXYCHLOROQUIN E			UNK	COVID-19	25-Mar-2020		13350 MIN
4	NOREPINEPHRINE				COVID-19			
5	VANCOMYCIN			UNK	COVID-19			2 DAY

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17849592

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 2020 Outcomes: DE, Application Type: NDA

FDA Rcvd Date: 26-Oct-2020 Mfr Rcvd Date: 21-Oct-2020 Mfr Control #:US-PFIZER INC-2020211375 Application #: 050679

Patient Information:

Age: 59 YR Sex: Female Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	CEFEPIME HCL				UNK	SARS-CoV-2 acute respiratory disease	2020	
2	CEFEPIME HCL					Empiric treatment		
3	DOXYCYCLINE HYCLATE				UNK	Antibiotic therapy	2020	
4	DOXYCYCLINE HYCLATE					SARS-CoV-2 acute respiratory disease		
5	HYDROXYCHLOROQUIN E		200 MG/		200 mg, daily(for days 1-4)		2020	
6	HYDROXYCHLOROQUIN E		400 MG/BID		400 mg, 2x/day(on day 0)	SARS-CoV-2 acute respiratory disease	2020	
7	LINEZOLID				UNK	Leukocytosis	2020	
8	LINEZOLID					SARS-CoV-2 acute respiratory disease		
9	LOPINAVIR + RITONAVIR		400 MG/BID		400 mg, 2x/day	SARS-CoV-2 acute respiratory disease	2020	
10	LOPINAVIR + RITONAVIR					Antiviral treatment		
11	OSELTAMIVIR				UNK	Empiric treatment	2020	
12	OSELTAMIVIR					SARS-CoV-2 acute respiratory disease		
13	SULFAMETHOXAZOLE/T RIMETHOPRIM				UNK (DS)	Pneumocystis jirovecii pneumonia	2020	
14	SULFAMETHOXAZOLE/T RIMETHOPRIM					SARS-CoV-2 acute respiratory disease		
15	TOBRAMYCIN				UNK	Leukocytosis	2020	



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17849592

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
16 TOBRAMYCIN					SARS-CoV-2 acute respiratory disease		
17 TOCILIZUMAB		400 MG/	Intravenous (not otherwise specified)	400 mg, single (1 dose)	SARS-CoV-2 acute respiratory disease	2020	
18 VANCOMYCIN HCL				UNK	SARS-CoV-2 acute respiratory disease	2020	
19 VANCOMYCIN HCL					Empiric treatment		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	CEFEPIME HCL		Unk	NA				PFIZER	
2	CEFEPIME HCL		Unk	NA				PFIZER	
3	DOXYCYCLINE HYCLATE		Unk	NA				PFIZER	
4	DOXYCYCLINE HYCLATE		Unk	NA				PFIZER	
5	HYDROXYCHLOROQUIN E		Unk	NA					
6	HYDROXYCHLOROQUIN E		Unk	NA					
7	LINEZOLID		Unk	NA				PFIZER	
8	LINEZOLID		Unk	NA				PFIZER	
9	LOPINAVIR + RITONAVIR		Unk	NA					
10	LOPINAVIR + RITONAVIR		Unk	NA					
11	OSELTAMIVIR		Unk	NA					
12	OSELTAMIVIR		Unk	NA					
13	SULFAMETHOXAZOLE/T RIMETHOPRIM		Unk	NA				PFIZER	
14	SULFAMETHOXAZOLE/T RIMETHOPRIM		Unk	NA				PFIZER	



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Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
15 TOBRAMYCIN		Unk	NA				PFIZER	
16 TOBRAMYCIN		Unk	NA				PFIZER	
17 TOCILIZUMAB		Unk	NA					
18 VANCOMYCIN HCL		Unk	NA				PFIZER	
19 VANCOMYCIN HCL		Unk	NA				PFIZER	

Event Information:

Preferred Term (MedDRA ® Version: 23.1)

ReC

Drug ineffective for unapproved indication

NA

Multiple organ dysfunction syndrome

NA

Off label use

NA

Event/Problem Narrative:

This is a literature report from the American Journal of Transplantation, 2020, pp 1-7, (doi: 10.1111/ajt.15982) entitled Early experience of COVID-19 in 2 heart transplant recipients: Case reports and review of treatment options.

The coronavirus disease 2019 (COVID-19) pandemic poses special challenges to immunocompromised transplant patients. Given the paucity of proven data in treating COVID-19, management of these patients is difficult, rapidly evolving, and mainly based on anecdotal experience. The authors reported 2 cases of heart transplant (HT) recipients with COVID-19. The first is a 59-year-old female with HT in 2012 who presented on March 20, 2020 with fever, hypoxia, and ground-glass opacities on chest X-ray. She quickly progressed to acute hypoxic respiratory failure and vasoplegic shock. Despite reduction in immunosuppression and treatment with tocilizumab, intravenous immunoglobulin, hydroxychloroquine, lopinavir/ritonavir, and broad-spectrum antibiotics, she ultimately died from multiorgan failure. The second case is a 75-year-old man with HT in 2000 who presented on April 2, 2020 after curbside testing revealed positive COVID-19. Given a milder presentation compared to the first patient, antimetabolite was discontinued and only hydroxychloroquine was started. Because of a lack of clinical improvement several days later, tocilizumab, methylprednisolone, and therapeutic anticoagulation were initiated. The patient clinically improved with decreasing oxygen requirements and was discharged home. These 2 cases highlight the wide range of different presentations of COVID-19 in HT recipients and the rapidity with which the management of these patients is evolving. The authors reported 2 cases of COVID-19 in HT patients. CASE 1 The patient is a 59-year-old race female with history of nonischemic cardiomyopathy and left



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ventricular assist device prior to HT in 2012. Her posttransplant course was complicated by cardiac allograft vasculopathy (CAV, Stanford class II, International Society for Heart and Lung Transplantation 0), diabetes mellitus (DM), hypertension (HTN), and chronic kidney disease (CKD) G3b-4/A3, with no graft dysfunction. Immunosuppression regimen consisted of tacrolimus 6 mg twice daily with goal trough level of 4-6 ng/mL and mycophenolic acid (MPA) 360 mg twice daily. She had no recent hospitalizations, travel history, or sick contacts. She presented on March 20, 2020 with fever, myalgia, fatigue, diarrhea, productive cough, and shortness of breath for 3 days. Temperature was 38.8C, heart rate 108 bpm, blood pressure 120/90mm Hg, respiratory rate 25, and oxygen saturation 92% on 3L nasal cannula (NC). Notable laboratory values include interleukin (IL)-6 62.7 pg/mL, immunoglobulin G (IgG) 1426 mg/dL, tacrolimus trough 8.5 ng/mL, and creatinine (Cr) 2.6 mg/dL (baseline 1.8- 2.0 mg/dL). Additional laboratory values indicating severe disease in COVID-19 are shown in Table 1.4-6. Chest X-ray showed consolidative opacity in the left upper lobe perihilar region and diffuse bronchial wall thickening with patchy peribronchial ground-glass opacities bilaterally (Figure 1: left: Chest X-ray of case 1. Left (admission): bilateral diffuse bronchial wall thickening and patchy peribronchial ground-glass opacities as well as consolidative opacity in the left upper lobe perihilar region. Right). While awaiting testing for respiratory viruses and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the patient was started on empiric cefepime, vancomycin, and oseltamivir. Given high suspicion for SARS-CoV-2, MPA was stopped and tacrolimus was held to achieve a goal of 4-6 ng/mL. Within hours of presentation on day 0, worsening respiratory failure developed, requiring high flow NC (HFNC). Arterial blood gas (ABG) at time of decompensation was pH 7.3, pCO₂ 32 mm Hg, and pO₂ 64 mm Hg on 0.8 FiO₂. SARS-CoV-2 resulted positive. Hydroxychloroquine (400 mg twice daily on day 0, followed by 200 mg twice daily for days 1-4) and tocilizumab 400 mg intravenous (1 dose) were initiated. Antibiotic coverage was broadened to include doxycycline. A single dose of intravenous immunoglobulin (IVIG) 10g was given but not continued after a normal IgG level returned. Underlying CKD precluded enrollment into a remdesivir trial (excluded if CrCl < 50 mL/min). As a second option, antiviral therapy with lopinavir/ritonavir 400 mg twice daily for 5 days was added. Consideration was given to drug-drug interactions with tacrolimus. She initially improved on day 1 and was transitioned to NC. However, she subsequently developed worsening renal failure and acute respiratory distress syndrome (ARDS, Figure 1, right (day 4): endotracheal tube and worsening of pulmonary opacities). She was intubated on day 2 and started on continuous veno-venous hemodialysis (CVVHD). ABG at this time showed pH 7.25, pCO₂ 30mm Hg, pO₂ 59 mm hg on Fio₂ 0.8 and tacrolimus trough was 7.0 ng/mL. She required norepinephrine for vasoplegic shock and antifungal coverage with micafungin 100mg daily was added. Despite decreasing C-reactive protein, other inflammatory markers including ferritin, d-dimer, and creatinine kinase continued to uptrend (Table 1). High sensitivity troponin (Hs-Tn) remained stable and bedside echocardiogram showed preserved graft function. On days 3 and 4, low tidal volume ventilation was continued with FiO₂ 0.6 and PEEP 18mmH₂O, and on day 5, the patient was prone positioned. Given tacrolimus trough of 6.7 ng/mL, 1 dose of tacrolimus with 60% dose reduction was given, however because of rapidly rising levels, it was held thereafter. On day 7, given rising white blood count and markedly elevated fungitell assay (259 pg/mL, <60 pg/ mL), sulfamethoxazole-trimethoprim-DS was started for presumed pneumocystis jirovecii pneumonia. At this point, veno-venous extracorporeal membrane oxygenation (VV-ECMO) was considered for progressive ARDS; however, the difficult decision was made not to offer VV-ECMO due to age, comorbidities, and poor prognosis. Heparin drip was started as the CVVHD line was clotting with rising d-dimer levels. Tobramycin and linezolid were given for worsening leukocytosis. On day 10, the patient's family was notified of her grave prognosis and care was withdrawn.

Discussion: In patients not eligible for remdesivir, such as in these patients, hydroxychloroquine with addition of lopinavir/ritonavir (LPV/r) could be considered, acknowledging the limited evidence for these treatments. Chloroquine has been successfully used as a treatment adjunct in China demonstrating clinical and virologic benefit versus a comparison group. Hydroxychloroquine has relatively higher in vitro



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activity against SARS-CoV-2 than chloroquine and is better tolerated. Gautret et al demonstrated that use of hydroxychloroquine in COVID-19 patients alone or in combination with azithromycin reduces detection of SARS-CoV-2 RNA in upper respiratory tract secretions. Notably, comparison was done with a nonrandomized control group with no analysis of clinical outcomes, underlining need for further investigation. Hydroxychloroquine has a significant side effect profile, and in particular with concurrent use of azithromycin, close monitoring of QTc intervals is warranted. For this reason, doxycycline was used in the patient. In addition to hydroxychloroquine, the group used lopinavir, a human immunodeficiency virus 1 protease inhibitor administered in combination with ritonavir, a potent CYP3A4 inhibitor that boosts lopinavir, inhibiting viral replication. The combination of LPV/r with steroids has been shown to reduce the incidence of ARDS, intubation, and mortality in patients with newly diagnosed SARS-CoV-1. The compelling mortality difference in SARS-CoV-1 and continued investigation in MERS-CoV led to inclusion of LPV/r in the Chinese SARS-CoV-2 guidelines at a dose of 400mg/100mg twice daily for no more than 10 days. Notably, in a recent randomized controlled trial in COVID-19 pneumonia, there was no benefit seen with LPV/r; however, the median time from symptom onset to initiation of therapy was 13 days, and in the SARS-CoV-1 experience, therapy appeared effective if started early. It is important to note that protease inhibitors such as ritonavir are potent inhibitors of the metabolism of immunosuppressive drugs including calcineurin inhibitors (CNI) and must be used with caution in transplant patients. As CNI are known to affect kidney function, close monitoring is imperative when given with LPV/r, especially in light of observed acute kidney injury in COVID-19 patients and adverse effects on mortality. In the first case, during the course of treatment with LPV/r, daily tacrolimus troughs ranged from 6-8 ng/mL and was 7 ng/mL at the time of initiation of CVVHD on day 2. Following completion of LPV/r, 1 dose of tacrolimus was given at 60% dose reduction. Tacrolimus levels then increased, ranging from 11-13 ng/mL with a peak of 19 ng/mL. Notably, tacrolimus levels peaked after clinical decompensation and development of refractory ARDS, thus it is unclear if supra-therapeutic levels contributed to further deterioration. Although it is a common practice to withhold or reduce immunosuppression in transplant patients during an acute infection, it must be noted that doing so is not benign and warrants close monitoring of graft function. In the first patient, bedside echocardiography showed normal graft function and stable Hs-Tn levels (Table 1) despite worsening vasoplegic shock. Furthermore, daily tacrolimus troughs never decreased below 6ng/mL. Interestingly there is now a hypothesis that immunosuppression could potentially be protective. The authors, Antonio and Silvia recently suggested that CNI T cell inhibition could be protective against the partially. T cell-mediated detrimental immune system overactivation and could diminish acute lung injury observed in COVID-19. It is interesting to note that in the 2 cases reported in China and these patients, all were on relatively low doses of baseline immunosuppression, potentially supporting this hypothesis. Much more data are needed to confirm or dismiss this hypothesis. Aside from the potential benefit of immunosuppression in the well-described cytokine storm of COVID-19, anti-inflammatory treatment options are also available. The authors used tocilizumab in both of the cases to counteract the hyperinflammatory state and cytokine storm associated with increased mortality in COVID-19 patients in China. Tocilizumab is a humanized monoclonal antibody that inhibits IL-6 receptors. IL-6 is one of the main drivers of the immunologic response in patients with cytokine-release syndrome. Immunotherapy with tocilizumab is part of the Chinese COVID-19 Diagnosis and Treatment Guide (400 mg IV once, option to repeat at 12 hours for max of 800 mg). A Chinese case series of 21 patients treated with tocilizumab reported rapid resolution of fever and C-reactive protein, decreased oxygen requirements, and resolution of lung opacities without adverse events. Optimal timing of tocilizumab administration is not yet defined. Similar to other severe respiratory tract infections, there is significant controversy surrounding the role of corticosteroids for management of severe pneumonia due to coronaviruses. The potential benefit of steroids, which is to blunt the inflammatory cascade seen in severe disease, needs to be carefully weighed against the concerns for secondary infections and adverse events of corticosteroid therapy. In MERS-CoV, corticosteroids was associated with delayed time to viral clearance. However, recent evidence in SARS-CoV-2 suggested a decrease in



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mortality in patients with ARDS with use of corticosteroids. Thus, steroids must be considered carefully but could be helpful in the postviremic hyperinflammatory phase. A consensus statement from the Chinese Thoracic Society recommends ≤ 0.5 -1 mg/kg/day methylprednisolone for ≤ 7 days in select patients, after careful consideration of risks. In contrast to a reported COVID-19 HT case from China with a milder course, the authors opted to not use steroids in the first patient case given long-standing immunosuppression and fear of delayed viral clearance. The authors revised this strategy in the management of their second patient by initiating methylprednisolone 0.5 mg/kg/day as recommended by the Chinese Thoracic Society. Following treatment with tocilizumab and steroids, oxygen requirements decreased. A phenomenon observed in COVID-19 patients is high incidence of thrombotic events suggesting a disease-specific coagulopathic state. In severe cases, use of anticoagulation with heparin has been shown to decrease mortality. The evidence for anticoagulation has accumulated following the death of the first patient, who received prophylactic dosing of heparin. For the second patient, the authors opted for empiric therapeutic anticoagulation following worsening hypoxia and rising d-dimer levels. The authors cannot rule out the possibility of pulmonary embolism (PE) as a contributor to the first patient's decompensation; however, Hs-Tn levels remained stable at a low level, decreasing suspicion for a hemodynamically significant PE. The second patient improved significantly following treatment with steroids, tocilizumab, and therapeutic anticoagulation and was discharged home. The first patient had a severe presentation ultimately leading to death, and the second patient had a milder presentation and was discharged home. It is interesting to compare the authors experience with the first reported cases of COVID-19 in HT patients in China in which both patients had good outcomes. The first Chinese patient described was similarly far from transplant like the patient, and immunosuppression level was comparable. His course was similar to the second case, with mild symptoms for several days at home, followed by more severe disease with hypoxia, requiring hospitalization. The second HT patient from China had a milder course and was managed as an outpatient. Interestingly, he was transplanted in 2017, but with a similar level of immunosuppression to the first Chinese patient and these patients. Though more data are needed, the Chinese experience with 87 HT recipients indicates that this special population does not have a higher risk of infection compared to the general population, as long as appropriate prevention measures are taken. However, aside from susceptibility, in the presence of comorbidities such as DM, HTN, and CKD as commonly seen in HT recipients and our cases, the risk for adverse COVID-19 outcomes might be substantially increased. In light of HTN as a risk factor, it is notable that renin-angiotensin-aldosterone system (RAAS) inhibitors have the potential to upregulate angiotensin-converting enzyme 2, the entry receptor for SARS-CoV-2. Despite theoretical concerns regarding the effect of RAAS inhibitors on angiotensin-converting enzyme 2, continuation of therapy is recommended in stable patients and there is now evidence for a potentially beneficial effect of RAAS inhibitors in hospitalized patients with COVID-19. In our first patient, losartan was stopped at time of admission given acute kidney injury. The second patient was treated with an alternate class of antihypertensives. CONCLUSION The appropriate management of SARS-CoV-2 is a rapidly evolving therapeutic challenge and optimal strategy remains unknown, particularly for the critically ill and special populations. It is prudent to quickly initiate supportive therapy with consideration of additional measures for high-risk populations. Importantly, this strategy is not without risk and needs to be weighed against potential adverse events, which remain poorly defined. Another pressing issue is impending drug shortages with increases in use of these agents and disruptions in supply chain. Caution should be applied, as available clinical data are largely uncontrolled, not peer reviewed, or still unpublished. It is of utmost interest to focus on improving our understanding of the pathophysiology and treatment of COVID-19. Thus, we believe it is essential for clinicians to report their experiences treating COVID-19 in transplant recipients so we may further optimize treatment options.

Table 1: Case 1. Parameter and cutoff for adverse outcome: Laboratory values: D-Dimer (> 1000 ug/mL): 1.29 (d0), 1.19 (d1), 1.22 (d2), 3.88 (d3), 1.06 (d4), 2.1 (d5), 1.68 (d6), 4.78 (d7), 12.65 (d8), 8.27 (d9); creatine phosphokinase (CPK, normal: 9-185 U/L) [$> 2x$ upper limit of



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normal (ULN) U/L]: none (d0), none (d1), 86 (d2), 1941 (d3), 1505 (d4), 2714 (d5), 2396 (d6) 1975 (d7), 2038 (d8), 1273 (d9); C-reactive protein (CRP; normal <5 mg/L) (> 100 mg/L): 82 (d0), 110 (d1), 86 (d2) , 44 (d3), 42 (d4), 56 (d5), 46 (d6), 46 (d7), 50 (d8), 63 (d9); lactate dehydrogenase (LDH; normal: 116-245 U/L) (> 245 U/L): 252 (d0), none (d1), 301 (d2), none (d3), none (d4), 778 (d5), 806 (d6), none (d7), 827 (d8), 761 (d9); high sensitivity troponin (normal: <22 ng/mL) (Hs-Tn), ng/L: 55 (d0), 52 (d1), 52 (d2), 51 (d3), 51 (d4), none (d5), none (d6), 37, (d7), 33 (d8), 34 (d9); Abs Lymphocyte count (< 0.810*3/uL): 1.49 (d0), none (d1), none (d2), 1.36 (d3), 1.52 (d4), none (d5), none (d6), 1.85 (d7), 2.18 (d8); 4.05 (d9); Ferritin (> 300 ng/mL): 281 (d0), 889 (d1), 927 (d2), 1417 (d3), none (d4), 3991 (d5), 4342 (d6), 3593 (d7), 3299 (d8), 2732 (d9); aspartate aminotransferase (AST; normal: 8-37 U/L): 39 (d0), none (d1), 34 (d2), none (d3), none (d4), none (d5), 322 (d6), 265 (d7), 197 (d8), 160 (d9); alanine aminotransferase (ALT; normal: 8-35 U/L): 25 (d0); none (d1), 22 (d2), none (d3), none (d4), none (d5), 143 (d6), 129 (d7), 129 (d8), 125 (d9).

Follow-up (21Oct2020): This is a literature report from the American Journal of Transplantation, 2020, vol 20 (10); pp 2916-2922 (DOI: 10.1111/ajt.15982). This is a follow-up report based on the receipt of the publication; the case has been updated to include additional information identified in the publication.

Pfizer is a marketing authorization holder of vancomycin hydrochloride, doxycycline hyclate, trimethoprim, sulfamethoxazole, tobramycin, linezolid, cefepime hydrochloride in the country of incidence. This may be a duplicate report if another marketing authorization holder of vancomycin hydrochloride, doxycycline hyclate, trimethoprim, sulfamethoxazole, tobramycin, linezolid, cefepime hydrochloride has submitted the same report to the regulatory authorities.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Heart transplant	2012		UNKNOWN
Left ventricular assist device insertion	2012		UNKNOWN
Hospitalisation	(b) (6)		UNKNOWN
Cardiac valvulopathy			
Cardiomyopathy			
Chronic kidney disease			YES
Diabetes mellitus			YES
Hypertension			YES



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Immunosuppression

Medical History Product(s)	Start Date	End Date	Indications	Events
LOSARTAN			Hypertension	Acute kidney injury

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
CPK	2714	IU/l	9	185	Y
Blood creatine phosphokinase	continued to uptrend				N
LDH	827	IU/l	116	245	Y
C-reactive protein	44	mg/l		5	Y
Creatinine clearance	less than 50	ml/min			N
Echocardiogram	showed preserved graft function				N
Fibrin D dimer	1.68	ug/ml	1000		Y
Absolute lymphocyte count	1.36	x10 ³ /mm ³		0.8	Y
pH	7.25				N
Ferritin	927	ng/ml	300		Y
Ferritin	1417	ng/ml	300		Y
Ferritin	4342	ng/ml	300		Y
Ferritin	3299	ng/ml	300		Y
Troponin	51	ng/L		22	Y
Troponin	34	ng/L		22	Y
Aspartate aminotransferase	39	IU/l	8	37	Y
CPK	86	IU/l	9	185	Y
Arterial blood gases	was pH 7.3, pCO ₂ 32 mm Hg, and pO ₂ 64 mm Hg on 0				Y
C-reactive protein	50	mg/l		5	Y
Drug level	rapidly rising				Y
Drug trough level	7.0	ng/ml			N
Fibrin D dimer	1.29	ug/ml	1000		Y
FIO ₂	0.8				N
Absolute lymphocyte count	1.52	x10 ³ /mm ³		0.8	Y
PCO ₂	32	mmHg			N
pH	7.3				N
Ferritin	3991	ng/ml	300		Y



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Troponin	55	ng/L		22	Y
Troponin	33	ng/L		22	Y
Alanine aminotransferase	22	IU/l	8	35	Y
Alanine aminotransferase	125	IU/l	8	35	Y
Aspartate aminotransferase	160	IU/l	8	37	Y
CPK	2038	IU/l	9	185	Y
IgG	normal IgG level returned.				N
LDH	778	IU/l	116	245	Y
LDH	806	IU/l	116	245	Y
C-reactive protein	82	mg/l		5	Y
C-reactive protein	63	mg/l		5	Y
Drug trough level	6.7	ng/ml			N
Fibrin D dimer	1.06	ug/ml	1000		Y
Fibrin D dimer	2.1	ug/ml	1000		Y
Fibrin D dimer	8.27	ug/ml	1000		Y
Oxygen saturation	92	%			Y
Troponin	52	ng/L		22	Y
Aspartate aminotransferase	34	IU/l	8	37	Y
Aspartate aminotransferase	322	IU/l	8	37	Y
CPK	2396	IU/l	9	185	Y
C-reactive protein	46	mg/l		5	Y
Fibrin D dimer	12.65	ug/ml	1000		Y
Interleukin-6	62.7	pg/mL			N
Absolute lymphocyte count	4.05	x10 3/mm3		0.8	Y
PO2	59	mmHg			N
Alanine aminotransferase	143	IU/l	8	35	Y
Alanine aminotransferase	129	IU/l	8	35	Y
CPK	1941	IU/l	9	185	Y
LDH	301	IU/l	116	245	Y
Chest X-ray	consolidative opacity in the left upper lobe perih				Y
C-reactive protein	42	mg/l		5	Y
FIO2	0.6				N
Absolute lymphocyte count	1.85	x10 3/mm3		0.8	Y
Absolute lymphocyte count	2.18	x10 3/mm3		0.8	Y



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
SARS-CoV-2 test	positive				N
Ferritin	continued to uptrend				N
Ferritin	889	ng/ml	300		Y
WBC count	rising				N
CPK	1975	IU/l	9	185	Y
LDH	761	IU/l	116	245	Y
Blood pressure	120/90	mmHg			N
C-reactive protein	56	mg/l		5	Y
Drug trough level	8.5	ng/ml			N
Investigation NOS	18				Y
PCO2	30	mmHg			N
PO2	64	mmHg			N
Ferritin	3593	ng/ml	300		Y
Troponin	37	ng/L		22	Y
Alanine aminotransferase	25	IU/l	8	35	Y
Aspartate aminotransferase	265	IU/l	8	37	Y
Aspartate aminotransferase	197	IU/l	8	37	Y
CPK	1273	IU/l	9	185	Y
LDH	252	IU/l	116	245	Y
Body temperature	38.8	Centigrade			N
C-reactive protein	86	mg/l		5	Y
Fibrin D dimer	1.19	ug/ml	1000		Y
Fibrin D dimer	1.22	ug/ml	1000		Y
Fibrin D dimer	3.88	ug/ml	1000		Y
Fibrin D dimer	4.78	ug/ml	1000		Y
Fungal test	259	pg/mL		60	Y
Troponin	remained stable				N
Viral test	Unknown result				N
CPK	1505	IU/l	9	185	Y
Creatinine	2.6	mg/dl	1.8	2.0	N
Arterial blood gases	pH 7.25, pCO2 30mm Hg, pO2 59 mm Hg on FiO2 0.8, a				Y
Immunoglobulin G	1426	mg/dl			N
C-reactive protein	continued to uptrend				N
C-reactive protein	110	mg/l		5	Y



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Fibrin D dimer	rising				N
Heart rate	108				Y
Absolute lymphocyte count	1.49	x10 3/mm3		0.8	Y
Respiratory rate	25				N
Ferritin	281	ng/ml	300		Y
Ferritin	2732	ng/ml	300		Y

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	HEPARIN		Intravenous drip	UNK	Anticoagulant therapy	2020		
2	IMMUNOGLOBULIN [IMMUNOGLOBULIN HUMAN NORMAL]	10 G/	Intravenous (not otherwise specified)	10 g, single	Immunosuppressio n	2020		
3	MICAFUNGIN	100 MG/		100 mg, daily	Antifungal treatment	2020		
4	MYCOPHENOLIC ACID	360 MG/BID		360 mg, 2x/day	Immunosuppressio n		2020	
5	NOREPINEPHRINE			UNK	Shock vascular	2020		
6	TACROLIMUS			UNK(60% dose reduction)		2020		
7	TACROLIMUS	6 MG/BID		6 mg, 2x/day(with goal trough level of 4-6 ng/ml)	Immunosuppressio n			

Reporter Source:

Study Report?: No

Sender Organization: PFIZER

503B Compounding
Outsourcing Facility?:

Literature Text: Holzhauser, L.. Early experience of COVID-19 in 2 heart transplant recipients: Case reports and review of treatment options. American Journal of Transplantation. 2020;20 (10):2916-2922



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FOIA Case Report Information

Case ID: 17851578

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 05-May-2020 Outcomes: DE,HO, Application Type: BLA
 FDA Rcvd Date: 25-Jun-2020 Mfr Rcvd Date: 12-Jun-2020 Mfr Control #:US-SA-2020SA131841 Application #: 761037

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	1X, REGN88 or placebo 200 mg or 400 mg, single or multiple doses	COVID-19	22-Apr-2020	22-Apr-2020
2	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	1X, REGN88 or placebo 200 mg or 400 mg, single or multiple doses		23-Apr-2020	23-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	24451 MINUTES	NA	NA				SANOFI	
2	SARILUMAB	24451 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Acute kidney injury	NA
Pulmonary embolism	NA
Shock	NA
Transaminases increased	NA
Urinary tract infection bacterial	NA



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FOIA Case Report Information

Case ID: 17851578

Event/Problem Narrative:

Based on additional information received on 12-Jun-2020 and 15-Jun-2020 (processed together), company causality for the event Increased ALT and AST >3 times was updated from reportable to not reportable. Consequently, the case was downgraded from SUSAR to non-SUSAR.

Based on follow up: 19-May-2020: this case has been upgraded to SUSAR (suspected unexpected serious adverse reaction) from NON-SUSAR as the related serious event Increased ALT and AST >3 times has been added.

Initial information received on 15-May-2020 regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference (2020-38148) on 15-May-2020 and transmitted to Sanofi on 20-May-2020, in the scope of company sponsored study (b) (6)

Center ID (b) (6) Patient ID: (b) (6) Country: United States.

Study title: (b) (6)

(b) (6)

A 64-year-old, Hispanic, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6) The patient experienced Urinary tract infection *Morganella morganii* on (b) (6)

(b) (6) and increased ALI and AST >3 times, acute kidney injury and shock on (b) (6) and Death due to pulmonary embolism with acute cor pulmonale (I26.09) on (b) (6) after receiving study drug.

The patient's medical history included diabetes mellitus, high blood pressure, hyperglycemia and acute respiratory failure with hypoxemia.

No relevant concomitant medications were reported.

On 15-Apr-2020, the patient experienced earliest symptoms of pneumonia with evidence of pneumonia present based on historical X-ray chest and fever documented in medical record.

The highest temperature recorded within 24 hours prior to dosing was 101 degrees Fahrenheit (degree F).

On 17-Apr-2020, chest X-ray scan showed diffuse bilateral mostly peripheral groundglass opacities suggestive of COVID-19 pneumonitis vs. other atypical/viral pneumonias in the appropriate clinical context.

On 22-Apr-2020, oxygen saturation (SpO2) was 88% and the patient was receiving supplemental oxygen via non-rebreather mask, blood pressure was 139/67 mmHg, pulse 90 beats per minute (bpm), respiratory rate 95 respirations per minute (rpm) and body temperature



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101degree F. Laboratory tests were performed, and results reported alanine aminotransferase (ALT) 50 U/L (14-63), aspartate aminotransferase 74 U/L (15-41), bilirubin total 0.2 mg/dL (0.3-1.2) and creatinine 1.3 mg/dl (0.44-1.24). Performed haematology test results reported white blood cells (WBC) 12.7 K/uL (4.6 -10.2), neutrophils (absolute) 10.8 K/uL (2 - 6.9) and platelets 233 K/uL (142 - 424). Rales/crackles on lung auscultation were not present. Chest X-ray scan showed significant increase in extensive bilateral pulmonary parenchymal disease.

On 23-Apr-2020, respiratory rate decreased to 21 rpm.

On 24-Apr-2020, chest x-ray scan showed stable appearance of extensive bilateral pulmonary disease.

On (b) (6) at 17:33, the patient developed *Morganella morganii* urinary tract infection (intensity: grade 3) and was hospitalized. The event was assessed as serious adverse event of special interest (AESI). WBC and neutrophils were 20.7 and 17.5, respectively. Results of urinary culture tests were not reported. Piperacillin and tazobactam were introduced, at a dose of 3375 mg in dextrose 5% in Water (D5W) 50 ml, per six hours, intravenously, as corrective treatment for *Morganella morganii* urinary tract infection. Chest x-ray scan showed persistent bilateral airspace disease.

On (b) (6) (b) (6) days 8 hrs 20 min after the first administration of study drug, blood pressure was 155/81 mmHg, with pulse of 81 bpm and respiratory rate of 36 rpm. SpO2 dropped to 58%. WBC were 54.5. The patient was unresponsive. On the same day, the patient started experiencing increased ALT and AST >3 times (intensity: grade 4), with ALT level of 731 and AST level of 1590, acute kidney injury (AKI) (intensity: grade 3) with creatinine 2.7, and shock (intensity: grade 4). The event Increased ALT and AST >3 times was assessed as serious AESI. Vasopressin at a dose of 50 units in normal saline (NS) 50 ml, via continuous infusion, intravenously and epinephrine at a dose of 16 mg, intravenously, were introduced for shock and shock liver, as corrective treatment. Chest x-ray scan showed increased bilateral airspace disease. Echocardiogram showed that subject had pulmonary embolism with right ventricular pressure overload, moderately to severely enlarged right ventricle, right ventricle (RV) apex appears hypermobile. Findings consistent with acute cor pulmonale considered pulmonary embolism and compared to the study performed on 13-Jul-2012, right ventricular pathology was new. Piperacillin and tazobactam were discontinued.

On (b) (6) blood pressure decreased to 135/57 mmHg and pulse increased to 128 bpm. SpO2 was 97%, body temperature 101.1 degree F, WBC 39.5 and neutrophils 35.7. ALT and AST were 776 and 874, respectively. Creatinine increased to 3.8. Line placement, bedside procedure was performed as corrective treatment for AKI, due to need for hemodialysis/continuous veno-venous hemofiltration. The patient started with heparin drip at a dose of 25 000 units in D5W 250 ml, intravenously, as corrective treatment for shock.

On (b) (6) at 10:00 SpO2 was 93 %, blood pressure 125/52 mmHg, pulse 118 bpm and respiratory rate was 32 rpm. ALT and AST were 829 and 847, respectively. Haematology tests were as follows: platelets - 152, WBC - 40.3, neutrophils - 37.4. Chest x-ray scan showed no significant change in bilateral pulmonary parenchymal disease. Vasopressors and epinephrine were discontinued. On the same day at 15:11, (b) (6) days 23 hrs 31 min after the first administration of study drug, the patient developed pulmonary embolism with acute cor pulmonale



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and passed away. No corrective treatment was applied. Autopsy was not performed.

The patient had not recovered from Increased ALT and AST >3, acute kidney injury, shock and urinary tract infection morganella morganii times at the time of death.

For death due to pulmonary embolism with acute cor pulmonale (i26.09):
Relationship with IP according to investigator: no reasonable possibility
Relationship with IP according to company: not reportable.

Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 64-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced fatal pulmonary embolism with acute cor pulmonale (b) (6) days after receiving the study drug. The event is assessed as not related to study drug or any clinical trial procedure. The event is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age. It's been recently observed that patients with underlying COVID-19 disease are at a higher risk for thrombotic and thromboembolic events.

For Increased ALT and AST >3 and urinary tract infection morganella morganii:
Relationship with IP according to investigator: no reasonable possibility
Relationship with IP according to company: not reportable.

Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 64-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced bacterial urinary tract infection and increased transaminases, (b) (6) and (b) (6) days after receiving the study drug. Patient's baseline ALT values were within reference ranges and baseline AST values were increased. The patient experienced shock and acute kidney injury on the same day which provide likely aetiology for transaminase increase. Therefore, causality for the event of increased transaminases is assessed as not related to study drug or any clinical trial procedure. Patient's baseline WBC and neutrophil values were increased, however, they've further increased following study drug administration. COVID-19 is commonly associated with bacterial infections and therefore, the causality for the event of bacterial urinary tract infection is assessed as not related to the study drug or to any clinical trial procedure. Presence of catheters and patient's medical history of diabetes mellitus also confound causality for the event of bacterial urinary tract infection.

For acute kidney injury and shock:
Relationship with IP according to investigator: no reasonable possibility
Relationship with IP according to company: not reportable.

Investigator causality rationale: Not related. Likely developed secondary to pulmonary embolism.

Company causality rationale: A 64-year-old, male patient with severe or critical COVID-19 infection and worsening pneumonia experienced



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shock and acute kidney injury (b) (6) days after receiving the study drug. Echocardiogram showed that subject had pulmonary embolism with right ventricular pressure overload consistent with acute cor pulmonale. It's been recently observed that patients with underlying COVID-19 disease are at a higher risk for thrombotic and thromboembolic events. The events are assessed as not related to study drug or any clinical trial procedure. The events are secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and comorbidities like diabetes mellitus and high blood pressure. Shock is likely cause of acute kidney injury.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure. Follow up: 19-May-2020: The Investigator provided the following updates: new events Urinary tract infection *Morganella morganii* and Increased ALT and AST >3 times added, clinical course updated.

Follow-up: 27-May-2020

The Investigator provided the following updates: clinical course updated. Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow-up: 12-Jun-2020 and 15-Jun-2020 (processed together).

The Investigator provided the following updates: new events added, medical history, relevant tests and clinical course updated, outcome and seriousness criterion updated for urinary tract infection and increased ALT and AST.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Blood pressure high	29-Sep-2013		YES
Diabetes mellitus	24-Apr-2017		YES
Hyperglycemia	21-Sep-2019		YES
Osteomyelitis	21-Sep-2019		YES
Acute respiratory failure	15-Apr-2020		YES
Catheter placement	(b) (6)	(b) (6)	NO
Endotracheal intubation	(b) (6)	(b) (6)	NO
Endotracheal intubation	(b) (6)	(b) (6)	NO



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Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Chest X-ray					Y
Oxygen saturation	58	%			N
WBC	20.7	10 ³ /uL	4.6	10.2	N
Bilirubin total	0.2	mg/dL	0.3	1.2	N
Creatinine	3.8	mg/dL	0.44	1.24	N
Chest X-ray					Y
Neutrophils	10.8	10 ³ /uL	2	6.9	N
Neutrophils	37.4	10 ³ /uL	2	6.9	N
Platelet count	233	10 ³ /uL	142	424	N
Respiratory rate	95	breaths/min			N
Alanine aminotransferase	731	U/L	14	63	N
Body temperature	101.1	degF			Y
Body temperature	96.8	degF			Y
Chest X-ray					Y
Pulse rate	81	beats/min			N
Pulse rate	118	beats/min			N
Oxygen saturation	97	%			N
Platelet count	152	10 ³ /uL	142	424	N
Alanine aminotransferase	776	U/L	14	63	N
Chest X-ray					Y
Chest X-ray					Y
Echocardiogram					Y
Neutrophils	17.5	10 ³ /uL	2	6.9	N
Oxygen saturation	88	%			N
WBC	12.7	10 ³ /uL	4.6	10.2	N
Blood pressure	139/67	mmHg			N
Blood pressure	135/57	mmHg			N
Blood pressure	125/52	mmHg			N
Neutrophils	35.7	10 ³ /uL	2	6.9	N
Respiratory rate	36	breaths/min			N
WBC	28.1	10 ³ /uL	4.6	10.2	N
Body temperature	101	degF			Y
Pulse rate	90	beats/min			N



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FOIA Case Report Information

Case ID: 17851578

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Respiratory rate	32	breaths/min			N
WBC	40.3	10 ³ /uL	4.6	10.2	N
Alanine aminotransferase	50	U/L	14	63	N
Aspartate aminotransferase	874	U/L	14	41	N
Chest X-ray					Y
Platelet count	285	10 ³ /uL	142	424	N
WBC	54.5	10 ³ /uL	4.6	10.2	N
WBC	39.5	10 ³ /uL	4.6	10.2	N
Alanine aminotransferase	829	U/L	14	63	N
Aspartate aminotransferase	74	U/L	14	41	N
Aspartate aminotransferase	1590	U/L	14	41	N
Aspartate aminotransferase	847	U/L	14	41	N
Creatinine	1.3	mg/dL	0.44	1.24	N
Creatinine	2.7	mg/dL	0.44	1.24	N
Blood pressure	155/81	mmHg			N
Pulse rate	128	beats/min			N
Neutrophils	26.4	10 ³ /uL	2	6.9	N
Oxygen saturation	93	%			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17852173

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 08-May-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 05-Jun-2020 Mfr Rcvd Date: 02-Jun-2020 Mfr Control #: US-ROCHE-2611175 Application #: 125276

Patient Information:

Age: 67 YR Sex: Male Weight: 95.7 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		200 MG/	Intravenous (not otherwise specified)	Most recent dose on 22/Apr/2020 at 13:00: 200mg	COVID-19 pneumonia	22-Apr-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	16 Day	Unk	NA	MJM12069,MJM14493,MJM24734, MJM66180				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC

Respiratory failure NA

Event/Problem Narrative:

AER 2611175 is a clinical study case, received on 27/May/2020 from a physician in the USA and concerns a 67 year old male patient (patient number: (b) (6)) who died due to respiratory failure whilst enrolled in (b) (6) (b) (6)

The patient's concurrent conditions included coronary artery disease, chronic obstructive pulmonary disease, hypertension, hyperlipidemia, type 2 diabetes, chronic kidney disease stage 3, congestive heart failure, benign prostatic hyperplasia, diabetic peripheral neuropathy, chronic hypercapnic respiratory failure, pleural effusion, hypoxemia, fever, shortness of breath, glaucoma, anxiety disorder, vomiting, vitamin D deficiency, cataract, neuropathic pain and gastrointestinal bleed. Concomitant medications included paracetamol (Acetaminophen), salbutamol (Albuterol), acetylsalicylic acid (Aspirin), brimonidine tartrate, alprazolam, colecalciferol, citalopram, dorzolamide, digoxin, dulaglutide, heparin, insulin, latanoprost, macrogol (Polyethylene Glycol), ipratropium, melatonin, pregabalin, ondansetron, cefepime, linezolid and famotidine. Medical history and past drugs were not reported.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

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(b) (6)
(b) (6) prior to serious adverse event (SAE). On (b) (6), he developed respiratory failure (initial severity: grade 4). Relevant diagnostic test were none. No medication was give for respiratory failure. No procedure/surgery performed. On (b) (6) he died due to respiratory failure (severity: grade 5). He was discontinued from study due to respiratory failure. It was unknown if an autopsy was performed or not.

At the time of death, it was not reported if therapy with blinded tocilizumab was ongoing or not.

The physician assessed the causality of respiratory failure as not related with blinded tocilizumab, while assessed it as related to disease under study.

The sponsor assessed the causality of event respiratory failure as not related to blinded tocilizumab considering the event is more related with underlying disease of COVID-19 pneumonia, its complications and concurrent conditions like chronic hypercapnic respiratory failure, pleural effusion, chronic obstructive pulmonary disease and hypoxemia rather than tocilizumab therapy.

No further information was provided.

Additional information was received on 02/Jun/2020. Following information was added to the case: New secondary reporter, causality of suspect drug updated to not related, new concurrent conditions (fever, shortness of breath, glaucoma, anxiety disorder, vomiting, vitamin d deficiency and gastrointestinal bleed), concomitant medications and event description updated accordingly.

This case no longer meets expedited reporting requirements because causality of event respiratory failure updated to not related (previous: not reported).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Anxiety disorder			YES
Benign prostatic hyperplasia			YES
Cardiac failure congestive			YES
Cataract			
Chronic kidney disease			YES



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Chronic obstructive pulmonary disease	YES
Chronic respiratory failure	YES
Coronary artery disease	YES
Diabetic neuropathy	YES
Dyspnoea	YES
Gastrointestinal haemorrhage	YES
Glaucoma	YES
Hyperlipidaemia	YES
Hypertension	YES
Hypoxia	YES
Neuralgia	
Pleural effusion	YES
Pyrexia	YES
Type 2 diabetes mellitus	YES
Vitamin D deficiency	YES
Vomiting	YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

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Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/	Unknown		Pyrexia	17-Apr-2020	08-May-2020	21 DAY
2	ALBUTEROL [SALBUTAMOL]		Unknown	2 Puff	Dyspnoea	14-Jan-2020	08-May-2020	115 DAY
3	ALPRAZOLAM	.25 MG/	Unknown		Anxiety	07-Feb-2020	08-May-2020	91 DAY
4	ASPIRIN [ACETYLSALICYLIC ACID]	81 MG/QD	Unknown		Coronary artery disease	14-Jan-2020	08-May-2020	115 DAY
5	BRIMONIDINE TARTRATE	.2 PCT/BID	Unknown		Glaucoma	14-Jan-2020	08-May-2020	115 DAY
6	CEFEPIME	2 G/BID	Unknown		Pneumonia	30-Apr-2020	06-May-2020	8 DAY
7	CHOLECALCIFEROL	QD	Unknown	Dose- 50 other	Vitamin D deficiency	05-Feb-2020	08-May-2020	93 DAY
8	CITALOPRAM	20 MG/QD	Unknown		Anxiety	07-Feb-2020	08-May-2020	91 DAY
9	DIGOXIN	.125 MG/	Unknown		Cardiac failure congestive	25-Jul-2018	08-May-2020	653 DAY
10	DORZOLAMIDE	QID	Unknown	Dose- 1 other	Glaucoma	07-Sep-2018	08-May-2020	609 DAY
11	DULAGLUTIDE	1.5 MG//wk	Unknown		Type 2 diabetes mellitus	06-Jan-2020	27-Apr-2020	123 DAY
12	FAMOTIDINE	40 MG/QD	Unknown		Gastrointestinal haemorrhage	28-Apr-2020	08-May-2020	10 DAY
13	HEPARIN	BID	Unknown	500 U (Unit)	Thrombosis prophylaxis	22-Apr-2020	08-May-2020	16 DAY
14	INSULIN	QID	Unknown	50 U (unit)	Type 2 diabetes mellitus	03-Jul-2013	08-May-2020	7 YR
15	IPRATROPIUM	QID	Unknown	Dose- 1 Ampule	Dyspnoea	04-May-2018	08-May-2020	735 DAY
16	LATANOPROST	QD	Unknown	1 other	Cataract	28-Apr-2020	08-May-2020	10 DAY
17	LINEZOLID	600 MG/BID	Unknown		Pneumonia	30-Apr-2020	06-May-2020	8 DAY
18	MELATONIN	3 MG/	Unknown		Anxiety	05-May-2018	08-May-2020	734 DAY
19	ONDASETRON [ONDANSETRON]		Unknown	Dose- Unknown	Vomiting	01-May-2020	08-May-2020	7 DAY



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FOIA Case Report Information

Case ID: 17852173

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
20	POLYETHYLENE GLYCOL [MACROGOL]	17 G/	Unknown		Constipation prophylaxis	15-May-2018	08-May-2020	724 DAY
21	PREGABALIN	300 MG/BID	Unknown		Neuralgia	30-Jan-2015	08-May-2020	5 YR

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17852176

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 01-Apr-2020 Outcomes: DE,HO, Application Type: BLA

FDA Rcvd Date: 02-Jun-2020 Mfr Rcvd Date: 01-Jun-2020 Mfr Control #: ES-ROCHE-2612707 Application #: 125276

Patient Information:

Age: 70 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		600 MG/1X	Intravenous (not otherwise specified)	600 MG	Coronavirus infection	27-Mar-2020	27-Mar-2020
2	AZITROMICINA		500 MG/QD	Intravenous (not otherwise specified)	500 MG DIA	COVID-19 pneumonia	26-Mar-2020	30-Mar-2020
3	AZITROMICINA					Pneumonia		
4	HYDROXYCHLOROQUIN E					Pneumonia		
5	HYDROXYCHLOROQUIN E		400 MG/QD	Oral	400 MG DIA	COVID-19 pneumonia	26-Mar-2020	30-Mar-2020
6	TOCILIZUMAB					Severe acute respiratory syndrome		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	11 Day	NA	NA	UNKNOWN				
2	AZITROMICINA	12 Day	NA	NA	UNKNOWN				
3	AZITROMICINA	12 Day	NA	NA	UNKNOWN				
4	HYDROXYCHLOROQUIN E	12 Day	NA	NA	UNKNOWN				
5	HYDROXYCHLOROQUIN E	12 Day	NA	NA	UNKNOWN				
6	TOCILIZUMAB	11 Day	NA	NA	UNKNOWN				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17852176

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
Atrial flutter	NA
Bundle branch block right	NA
Hypertension	NA
Hypofibrinogenaemia	NA
Pneumonia escherichia	NA
Ventricular tachycardia	NA

Event/Problem Narrative:

AER 2612707 is a spontaneous case, received on 01/Jun/2020 from a physician in Spain via health authority spain (AEMPS (Spanish Agency of Medicines and Medical Devices, reference number: ESAEMPS624232) via European Medicines Agency (EMA). It concerns a 70 year old male patient who died due to atrial flutter, complete right bundle branch block, arterial hypertension, pneumonia due to escherichia coli (e. coli), hypofibrinogenemia and recurrent ventricular tachycardia whilst being treated with hydroxychloroquine, tocilizumab and azithromycin (Azitromicina).

No medical history, past drug, concurrent condition and concomitant medication were reported.

On 26/Mar/2020, the patient started therapy with oral hydroxychloroquine (lot number: unknown) at 400 mg once a day and intravenous azithromycin (lot number: unknown) at 500 mg once a day for neumonia covid19 and pneumonia. On 27/Mar/2020, the patient started therapy with intravenous tocilizumab (lot number: unknown) at 600 mg 1 total for coronavirus infection and SRAS COVID19 (severe acute respiratory syndrome). On 30/Mar/2020, he received most recent dose of hydroxychloroquine and azithromycin prior to event. On ^{(b) (6)} he developed hypofibrinogenemia which led to hospitaliation. On ^{(b) (6)} he developed pneumonia due to escherichia coli (e. coli). On ^{(b) (6)} he developed arterial hypertension. On ^{(b) (6)} he developed atrial flutter. On ^{(b) (6)} he developed complete right bundle branch block. On ^{(b) (6)} he developed recurrent ventricular tachycardia. On an unspecified date, he died due to atrial flutter, complete right bundle branch block, arterial hypertension, pneumonia due to escherichia coli (e. coli), hypofibrinogenemia and recurrent ventricular tachycardia. It was not reported if an autopsy was performed or not.

The physician did not report a causality between fatal events atrial flutter, complete right bundle branch block, arterial hypertension, pneumonia due to escherichia coli (e. coli), hypofibrinogenemia and recurrent ventricular tachycardia and hydroxychloroquine, tocilizumab, azithromycin.

No further information was available.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17852176

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17865779

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 25-Apr-2020
Outcomes: DE,LT,
Application Type: BLA
FDA Rcvd Date: 26-Jun-2020
Mfr Rcvd Date: 18-Jun-2020
Mfr Control #: US-SA-2020SA115324
Application #: 761037

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB		1X	Intravenous (not otherwise specified)	1X, 200 mg IV or 400 mg IV at single or multiple doses	COVID-19	23-Apr-2020	23-Apr-2020
2	SARILUMAB		1X	Intravenous (not otherwise specified)	1X, 200 mg IV or 400 mg IV at single or multiple doses		24-Apr-2020	24-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	6012 MINUTES	NA	NA				SANOFI	
2	SARILUMAB	6012 MINUTES	NA	NA				SANOFI	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Cardiac arrest	NA
Pulseless electrical activity	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17865779

Event/Problem Narrative:

Based on additional information received on 18-Jun-2020, the case was downgraded from SUSAR to Non-SUSAR as the event elevated AST/ALT was deleted

Initial information received on 29-Apr-2020 regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference RGN MCN: 2020-32031 on 29-Apr-2020 and transmitted to Sanofi on 01-May-2020, in the scope of company sponsored study (b) (6)

Patient ID: (b) (6) Center ID: (b) (6) Country: United States

Study title: (b) (6)
(b) (6)

A 50-year-old, Hispanic, male patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6)

The patient's relevant medical history included diabetes.

Relevant concomitant medications included acetaminophen, azithromycin, cefepime, ceftriaxone, hydroxychloroquine, piperacillin, tazobactam, vancomycin.

On 18-Apr-2020, the patient experienced earliest symptoms of pneumonia. Chest X-ray showed ill-defined extensive bilateral lung infiltrates.

On 21-Apr-2020, Chest X-ray showed worsening bilateral lung infiltrates.

On 22-Apr-2020, Chest X-ray showed moderately extensive bilateral infiltrates but improved aeration in both lungs relative to previous study.

On (b) (6) Chest X-ray showed extensive bilateral lung infiltrates with minimal improvement in left midlung field component. CT scan showed multiple bilateral pulmonary filling defects, bilateral pneumonia, patchy ground glass density throughout lungs that might have been related to oedema. It also showed trace ascites in the upper abdomen. Rales/crackles were not present on lung auscultation at baseline. There was fever documented in medical record; the highest temperature recorded within 24 hours prior to study drug dosing was 39.4 C (degree Celsius) measured axillary. Chest X-ray showed ill-defined extensive bilateral lung infiltrates. The patient required treatment in the intensive care unit. The patient started using vasopressors and was receiving supplemental oxygen by nasal cannula, face mask, non-rebreather mask, high-flow nasal cannula, and invasive ventilation (mechanical ventilation).

On the same day, baseline vital signs reported for peripheral oxygen saturation (SpO2) was 98%, temperature was 39.4 C, blood pressure



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was 106/79 mmHg, pulse 109 beats per minute (bpm) and respiratory rate was 15 respirations per minute (rpm). Biochemistry values reported for alanine aminotransferase (ALT) was 40 U/L (reference range: 15-41), aspartate aminotransferase (AST) was 81 U/L (3-34), total bilirubin was 1.0 mg/dL (0.2-1.3), potassium was 4.4 mmol/L (3.5-5.1), sodium was 136 mmol/L (137-145), carbon dioxide (bicarbonate) was 21 mmol/L (21-32), and creatinine was 1.08 mg/dL (0.66-1.5). Haematology results were as follows: platelets 128 K/uL (145-400), white blood cells (WBC) 10.6 K/uL (4-10.8), neutrophils (absolute) 8.7 K/uL (1.7-8.1), and lymphocytes (absolute) were 1.4 K/uL (0.6-4.9).

On (b) (6) C-reactive protein (CRP) was above 190, pulse rate increased to 127 bpm, AST value was 63U/L, and increased total bilirubin was 2.0 mg/dL. Platelet count decreased to 74 K/uL.

On (b) (6) at 12:35, (b) (6) 23 hrs 15 min after the first administration of investigational product (IP), the patient experienced pulseless electrical activity (PEA) arrest (intensity: Grade 4). The event was assessed as life threatening. Unspecified medications were given as corrective treatment for the event. The event resolved on the same day at 12:45. Respiratory rate increased to 30 rpm, blood pressure was 120/70 mmHg, pulse rate was 125 bpm, total bilirubin to 3.0 mg/dL, creatinine to 3.99 mg/dL, and platelets decreased to 83 K/uL. CRP was above 190. AST decreased to 25 U/L and ALT increased to 97 U/L.

On (b) (6) the patient's temperature decreased to 33.3 C, blood pressure increased to 142/71 mmHg, pulse rate was 100 bpm, total bilirubin was 2.2 mg/dL and creatinine to 4.23 mg/dL. CRP was above 190.

On (b) (6) temperature increased to 37.3 C, blood pressure decreased to 92/48 mmHg, pulse rate decreased to 104, respiratory rate decreased to 17 rpm, creatinine decreased to 2.65 mg/dL, total bilirubin 3.0 mg/dL, AST decreased to 105 U/L, ALT was 23 U/L and platelets increased to 150 K/uL. On the same day, (b) (6) days 4 hrs 12 min after the first administration of IP, the patient experienced cardiac arrest secondary to heparin-induced thrombocytopenic thrombosis (intensity: grade 5). Unspecified medications were given as a corrective treatment for the event. Patient died at 17:32. The cause of death was reported as cardiac arrest. Autopsy was not performed.

Action taken with study drug in response to PEA arrest was dose not changed, and in response to Cardiac arrest secondary to heparin-induced thrombocytopenic thrombosis was not applicable.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

For Cardiac arrest and Pulseless electrical activity:

Relationship to IP according to investigator: Not Related

Relationship to IP according to company: not reportable

Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 50-year-old male patient enrolled in the trial, experienced PEA arrest, fatal cardiac arrest, (b) (6) days after second dose of the study drug, respectively. The patient's medical history included diabetes. Based on the information provided, severe or critical COVID-19 with pneumonia before initiation of the study drug is the most plausible cause for PEA arrest, while fatal cardiac arrest is



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considered to be secondary to heparin-induced thrombocytopenic thrombosis. Therefore, both these events are assessed as unrelated to the study drug or to any clinical trial procedure.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up received date: 07-May-2020 and 08-May-2020 (processed together)

The Investigator provided the following updates: action taken with study drug, relevant tests, concomitant medications and clinical course updated.

Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up received date: 18-May-2020

The Investigator provided the following updates: seriousness criterion for event Acute kidney injury updated from Death to Life-threatening, action taken and outcome for same event updated.

Follow-up: 27-May-2020, 28-May-2020 and 29-May-2020 (processed together)

The Investigator provided the following updates: event term updated from Acute kidney injury to Elevated AST/ALT; AESI criteria clarified (ALT or AST increase) and event Elevated AST/ALT updated to serious AESI, concomitant medication details added; relevant concomitant medication, cause of death and clinical course updated.

Follow up: 15-Jun-2020

The Investigator provided the following updates: event term Cardiac arrest updated.

Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow up: 18-Jun-2020 and 22-Jun-2020 (processed together):

The Investigator provided following updates: event elevated AST/ALT downgraded to non-serious non-AESI and deleted, cause of death updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Diabetes			YES



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Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Aspartate aminotransferase	63	U/L	3	34	N
Aspartate aminotransferase	25	U/L	3	34	N
Body temperature	33.3	Cel			N
Chest X-ray					Y
Platelet count	83	10 ³ /uL	145	400	Y
White blood cell count	10.6	10 ³ /uL	4	10.8	N
Alanine aminotransferase	97	U/L	15	41	N
Blood bilirubin	2	mg/dL	0.2	1.3	N
Blood bilirubin	2.2	mg/dL	0.2	1.3	N
Blood creatinine	4.23	mg/dL	0.66	1.5	N
Blood potassium	4.4	mmol/L	3.5	5.1	N
Blood pressure measurement	142/71	mmHg			N
Chest X-ray					Y
C-reactive protein					Y
Heart rate	100	beats/min			N
Chest X-ray					Y
C-reactive protein					Y
Neutrophil count	8.7	10 ³ /uL	1.7	8.1	Y
Platelet count	71	10 ³ /uL	145	400	Y
Respiratory rate	30	breaths/min			N
Blood bilirubin	1.0	mg/dL	0.2	1.3	N
Blood creatinine	2.65	mg/dL	0.66	1.5	N
Blood pressure measurement	106/79	mmHg			N
Heart rate	104	beats/min			N
Respiratory rate	17	breaths/min			N
Alanine aminotransferase	23	U/L	15	41	N
Blood creatinine	1.08	mg/dL	0.66	1.5	N
Blood sodium	136	mmol/L	137	145	N
CT scan					Y
Aspartate aminotransferase	81	U/L	3	34	N
Aspartate aminotransferase	106	U/L	3	34	N
Blood bilirubin	3.0	mg/dL	0.2	1.3	N
Body temperature	37.3	Cel			N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Carbon dioxide	21	mmol/L	21	32	N
Chest X-ray					Y
Lymphocyte count	1.4	10 ³ /uL	0.6	4.9	N
Platelet count	85	10 ³ /uL	145	400	Y
Platelet count	150	10 ³ /uL	145	400	Y
Alanine aminotransferase	40	U/L	15	41	N
Alanine aminotransferase	23	U/L	15	41	N
Aspartate aminotransferase	105	U/L	3	34	N
Blood bilirubin	3.0	mg/dL	0.2	1.3	N
Blood pressure measurement	120/70	mmHg			N
Blood pressure measurement	92/48	mmHg			N
Body temperature	39.4	Cel			N
C-reactive protein					Y
Heart rate	109	beats/min			N
Heart rate	127	beats/min			N
Heart rate	125	beats/min			N
Oxygen saturation	98	%			N
Platelet count	128	10 ³ /uL	145	400	Y
Blood creatinine	3.99	mg/dL	0.66	1.5	N
Respiratory rate	15	breaths/min			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	975 MG/1X	Oral	975 mg, 1x (OTO)	Headache	18-Apr-2020	18-Apr-2020	14012 MIN
2	ACETAMINOPHEN	1000 MG/1X	Intravenous (not otherwise specified)	1000 mg, 1X (OTO)		23-Apr-2020	23-Apr-2020	14012 MIN
3	ACETAMINOPHEN	650 MG/	Oral	650 mg, PRN	Fever	19-Apr-2020	21-Apr-2020	14012 MIN
4	ACETAMINOPHEN	650 MG/Q6H		650 mg, q6h	Fever	21-Apr-2020	25-Apr-2020	14012 MIN
5	AZITHROMYCIN	500 MG/QD	Intravenous (not otherwise specified)	500 mg, qd		21-Apr-2020	22-Apr-2020	14012 MIN
6	AZITHROMYCIN	500 MG/1X	Intravenous (not otherwise)	500 mg, 1X (OTO)		19-Apr-2020	19-Apr-2020	14012 MIN



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Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
7 AZITHROMYCIN	500 MG/1X	specified) Intravenous (not otherwise specified)	500 mg, 1X (OTO)	Community acquired pneumonia	18-Apr-2020	18-Apr-2020	14012 MIN
8 CEFEPIME	1 G/Q12H	Intravenous (not otherwise specified)	1 g, q12h	Sepsis	23-Apr-2020	26-Apr-2020	6812 MIN
9 CEFTRIAZONE	1 G/QD	Intravenous (not otherwise specified)	1 g, qd		19-Apr-2020	19-Apr-2020	14012 MIN
10 CEFTRIAZONE	1 G/1X	Intravenous (not otherwise specified)	1 g, 1X (OTO)	Sepsis	18-Apr-2020	18-Apr-2020	14012 MIN
11 CONVALESCENT PLASMA	1 IU/1X		1 iU, 1X (OTO)	COVID-19 pneumonia	23-Apr-2020	23-Apr-2020	6812 MIN
12 HYDROXYCHLOROQUIN E	200 MG/Q12H	Oral	200 mg, bid		20-Apr-2020	22-Apr-2020	12572 MIN
13 HYDROXYCHLOROQUIN E	400 MG/Q12H	Oral	400 mg, bid	COVID-19	19-Apr-2020	19-Apr-2020	12572 MIN
14 PIPERACILLIN TAZOBACTAM	4.5 G/Q6H	Intravenous (not otherwise specified)	4.5 g, q6h	Sepsis	21-Apr-2020	21-Apr-2020	9692 MIN
15 VANCOMYCIN	1 G/1X	Intravenous (not otherwise specified)	1g, 1x (OTO)		24-Apr-2020	24-Apr-2020	6812 MIN
16 VANCOMYCIN	1 G/1X	Intravenous (not otherwise specified)	1 g, 1X (OTO)	Sepsis	23-Apr-2020	23-Apr-2020	6812 MIN

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



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FOIA Case Report Information

Case ID: 17867692

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** NIC **Event Date:** **Outcomes:** DE,OT, **Application Type:** BLA

FDA Rcvd Date: 05-Jun-2020 **Mfr Rcvd Date:** 25-May-2020 **Mfr Control #:** NI-ROCHE-2609401 **Application #:** 125276

Patient Information:

Age: **Sex:** Male **Weight:** 90 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		400 MG/	Intravenous (not otherwise specified)		COVID-19 pneumonia		
2	TOCILIZUMAB					Cytokine storm		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		Unk	NA	UNKNOWN				
2	TOCILIZUMAB		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Acute kidney injury	NA
Death	NA
Intentional product use issue	NA
Off label use	NA



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FOIA Case Report Information

Case ID: 17867692

Event/Problem Narrative:

AER 2609401 is a spontaneous case, received on 25/May/2020 from a physician in Nicaragua. It concerns a 49 year old male patient who had acute kidney failure and died due to unknown cause whilst being treated with tocilizumab (Tocilizumab) intentional use for unapproved indication (off label use).

Patient's concurrent conditions included stage 2 hypertension, obesity. Concomitant medications, medical history and past drugs were not reported.

The patient was in serious condition and treated in ICU, with an indeterminate test for COVID-19, with a cytokine storm. He had Ct scan and X-ray which were not well understood. He was undergoing supplementary oxygen therapy. Control volume ventilation support was provided and administration of vasopressors was required. On an unknown date, he started therapy with intravenous (IV) tocilizumab (lot number: unknown) 400 mg for covid-19 pneumonia (intentional use for unapproved indication, off label use). After one dose of tocilizumab he developed acute kidney failure. On ^{(b) (6)} he was died due to unknown cause. It was unknown if an autopsy was performed or not.

At the time of death, the outcome of acute kidney failure was not reported. Therapy ongoing status with tocilizumab was not reported.

The physician did not reported causality of acute kidney failure and unknown cause of death with tocilizumab.

The company assessed seriousness of event acute kidney failure as medically significant.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension			
Obesity			

Medical History Product(s)	Start Date	End Date	Indications	Events



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Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
X-ray					N
Coronavirus test					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No Sender Organization: ROCHE 503B Compounding Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868071

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 25-May-2020 Outcomes: DE,OT, Application Type: BLA
 FDA Rcvd Date: 11-Jun-2020 Mfr Rcvd Date: 04-Jun-2020 Mfr Control #:US-ROCHE-2613670 Application #: 125276

Patient Information:

Age: 34 YR Sex: Male Weight: 130 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB			Intravenous (not otherwise specified)	On 19/May/2020, at 14:41 hours; recent dose of tocilizumab prior to (adverse event) AE/SAE (serious	COVID-19 pneumonia	18-May-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	9 Day	NA	NA	MJM11641,MJM24418,MJM78445, MJM81031				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC
 COVID-19 pneumonia NA
 Platelet count decreased NA

Event/Problem Narrative:

AER 2613670 is a clinical study case, received on 01/Jun/2020 from a physician in the USA. It concerns a 34 year old male patient (patient number: (b) (6)) who developed platelet count decreased and died due to the COVID-19 pneumonia progression whilst enrolled in (b) (6) (b) (6)

Medical history included hypoalbuminemia, bronchospasm, constipation, metabolic acidosis and hypophosphatemia. Past drugs included albumin human (Human Albumin), salbutamol (Albuterol), salbutamol sulfate (Albuterol Sulfate), azithromycin, cefepime, ceftriaxone, ciprofloxacin, enoxaparin, etomidate, famotidine, glycopyrronium, hydrocortisone sodium succinate, lidocaine, lorazepam, methyl naltrexone, metronidazole, morphine, remdesivir, rocuronium, sodium bicarbonate and sodium phosphate. Concurrent conditions included COVID-19, hypocalcemia, paralytic, sedation, itching, diuresis, hyperglycemia, hypokalemia and agitation. Concomitant medications included paracetamol



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(Acetaminophen), aztreonam, calcium gluconate, cisatracurium, dexmedetomidine, diphenhydramine, epinephrine, fentanyl, fluconazole, fludrocortisone, furosemide, heparin, insulin (Insulin Regular), ketamine, magnesium sulfate, midazolam, nitric oxide, norepinephrine, pantoprazole, potassium chloride, propofol, quetiapine, vancomycin, insulin aspart for hyperglycemia and vasopressin.

(b) (6)

(b) (6)

(b) (6). On 25/May/2020, he developed platelet count decrease (severity: grade 4) and no cause had been identified. On 27/May/2020, he developed COVID-19 pneumonia progression (initial severity: grade 4). On 28/May/2020, he had undergone lab test and platelet count was found as 24K/UL. Later, his family made the decision to withdraw his care. He was already noted to have a DNR (do-not-resuscitate) status. On (b) (6) he died due to the COVID-19 pneumonia progression. An autopsy was not performed.

At the time of the death, the platelet count decrease was persisting.

The physician the causality of COVID-19 pneumonia progression and platelet count decreased as unrelated to blinded tocilizumab and related to disease under study.

The company assessed the causality of fatal COVID-19 pneumonia progression and platelet count decreased as unrelated to blinded tocilizumab. As COVID-19 damages the walls and linings of the air sacs in lungs, which causes the inflammatory response of cytokines, overwhelming the immune system response to the infection, which lead to damage of organs, including lungs, heart, and kidneys. Contributory factor includes the underlying condition COVID-19, bronchospasm, metabolic acidosis and hyperglycemia.

The physician assessed the event platelet count decreased as medically significant.

No further information was provided.

This case is cross reference with AER 2611338.

AER 2611338 was identified as a duplicate of AER 2613670. All information from AER 2611338 was added to AER 2613670, which remains the active case.

Additional information was received on 04/Jun/2020, following information was added to the case: secondary reporter, event term "COVID-19 pneumonia" was amended to "COVID-19 pneumonia progression", onset date of the event (COVID-19 pneumonia progression) was updated to 27/May/2020 (previously reported as 13/May/2020), causality updated from not reported to not related and new event platelet count decreased with event description.

This case no longer meets expedited reporting requirements because the reporter causality of "COVID-19 pneumonia progression" updated



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from not reported to not related.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Agitation			
Bronchospasm			
COVID-19			
Constipation			
Hyperglycaemia			
Hypoa buminaemia			
Hypocalcaemia			
Hypokalaemia			
Hypophosphataemia			
Metabolic acidosis			
Paralysis			
Polyuria			
Pruritus			



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Sedation

Medical History Product(s)	Start Date	End Date	Indications	Events
HUMAN ALBUMIN	21-May-2020	23-May-2020	Hypoalbuminaemia	
ENOXAPARIN	16-May-2020	16-May-2020		
SODIUM BICARBONATE	21-May-2020	24-May-2020	Metabolic acidosis	
SODIUM BICARBONATE	21-May-2020	21-May-2020		
SODIUM BICARBONATE	21-May-2020	21-May-2020		
GLYCOPYRROLATE	18-May-2020	18-May-2020		
AZITHROMYCIN	13-May-2020	13-May-2020	COVID-19	
CEFEPIME	21-May-2020	22-May-2020		
HYDROCORTISONE SODIUM SUCCINATE	19-May-2020	19-May-2020	COVID-19	
ROCURONIUM	24-May-2020	24-May-2020		
CEFTRIAZONE	16-May-2020	19-May-2020		
ALBUTEROL SULFATE	16-May-2020	21-May-2020	Bronchospasm	
CEFEPIME	21-May-2020	21-May-2020		
SODIUM BICARBONATE	21-May-2020	21-May-2020		
CIPROFLOXACIN	21-May-2020	21-May-2020		
HYDROCORTISONE SODIUM SUCCINATE	21-May-2020			
METRONIDAZOLE	21-May-2020	21-May-2020		
ENOXAPARIN	17-May-2020	21-May-2020		
REMEDSIVIR	17-May-2020	20-May-2020	COVID-19	
REMEDSIVIR	16-May-2020	16-May-2020		
SODIUM PHOSPHATE	22-May-2020	22-May-2020	Hypophosphataemia	



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SODIUM PHOSPHATE	21-May-2020	22-May-2020	
LORAZEPAM	18-May-2020	18-May-2020	Sedation
ALBUTEROL	16-May-2020	16-May-2020	Bronchospasm
MORPHINE	17-May-2020	17-May-2020	
FAMOTIDINE	17-May-2020	22-May-2020	
ENOXAPARIN	16-May-2020	17-May-2020	
LIDOCAINE	17-May-2020	17-May-2020	
METHYLNALTREXONE	18-May-2020	18-May-2020	Constipation
ETOMIDATE	17-May-2020	17-May-2020	Sedation
ROCURONIUM	17-May-2020	17-May-2020	Paralysis
ROCURONIUM	18-May-2020	18-May-2020	

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Platelet count	24	k/ul			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/	Unknown			18-May-2020	21-May-2020	11 DAY
2	ACETAMINOPHEN	650 MG/	Unknown			21-May-2020	25-May-2020	11 DAY
3	ACETAMINOPHEN	1000 MG/QD	Unknown	ANALGESIA		17-May-2020	17-May-2020	11 DAY
4	ACETAMINOPHEN	650 MG/	Unknown			16-May-2020	18-May-2020	11 DAY
5	AZTREONAM	2000 MG/TID	Unknown	PSEUDOMONAS PROPHYLAXIS		22-May-2020		5 DAY



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	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
6	CALCIUM GLUCONATE	3 G/	Unknown			25-May-2020	25-May-2020	5 DAY
7	CALCIUM GLUCONATE	2 G/	Unknown			22-May-2020		5 DAY
8	CALCIUM GLUCONATE	1 G/	Unknown		Hypocalcaemia	22-May-2020		5 DAY
9	CISATRACURIUM		Unknown	dose: 5 other	Paralysis	18-May-2020		9 DAY
10	DEXMEDETOMIDINE		Unknown	dose: 1.4 other	Sedation	16-May-2020		11 DAY
11	DIPHENHYDRAMINE	50 MG/	Unknown		Pruritus	19-May-2020		8 DAY
12	EPINEPHRINE		Unknown	HEMODYNAMIC SUPPORT, dose: 1.4 other		21-May-2020		6 DAY
13	FENTANYL		Unknown	ANALGESIA, dose: 30 other		17-May-2020		10 DAY
14	FENTANYL	100 UG/QD	Unknown	ANALGESIA		24-May-2020	24-May-2020	10 DAY
15	FLUCONAZOLE	200 MG/QD	Unknown	FUNGAL INFECTION PROPHYLAXIS		21-May-2020		6 DAY
16	FLUDROCORTISONE	100 UG/QD	Unknown	MINERALOCORTICOID REPLACEMENT		21-May-2020		6 DAY
17	FUROSEMIDE	100 MG/QD	Unknown			21-May-2020	21-May-2020	11 DAY
18	FUROSEMIDE		Unknown	dose: 7.5 other	Polyuria	21-May-2020	28-May-2020	11 DAY
19	FUROSEMIDE	40 MG/BID	Unknown			20-May-2020	20-May-2020	11 DAY
20	FUROSEMIDE	20 MG/QD	Unknown			21-May-2020	23-May-2020	11 DAY
21	FUROSEMIDE	10 MG/QD	Unknown			22-May-2020	22-May-2020	11 DAY
22	FUROSEMIDE	40 MG/QD	Unknown			16-May-2020	16-May-2020	11 DAY
23	HEPARIN	QD	Unknown	ANTI-COAGULATION, dose: 20000 unit		21-May-2020	21-May-2020	6 DAY
24	HEPARIN		Unknown	dose: 12 other, ANTI- COAGULATION		21-May-2020		6 DAY
25	INSULIN ASPART		Unknown	dose: 1 unit	Hyperglycaemia	27-May-2020	27-May-2020	



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Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
26 INSULIN, REGULAR		Unknown	dose: 6 other	Hyperglycaemia	21-May-2020	26-May-2020	6 DAY
27 KETAMINE		Unknown	dose: 20 Other	Sedation	18-May-2020		9 DAY
28 MAGNESIUM SULFATE	2 G/	Unknown	RENAL REPLACEMENT THERAPY		21-May-2020		6 DAY
29 MIDAZOLAM		Unknown	dose: 4 other		24-May-2020		5 DAY
30 MIDAZOLAM	5 MG/QD	Unknown			24-May-2020	24-May-2020	5 DAY
31 MIDAZOLAM	4 MG/	Unknown			22-May-2020	23-May-2020	5 DAY
32 MIDAZOLAM	2 MG/	Unknown		Sedation	22-May-2020		5 DAY
33 NITRIC OXIDE		Unknown	dose: 30 Inhalation, CARDIOPULMONARY SUPPORT		21-May-2020		6 DAY
34 NOREPINEPHRINE		Unknown	CARDIOPULMONARY SUPPORT, dose: 1 other		17-May-2020	25-May-2020	10 DAY
35 PANTOPRAZOLE	40 MG/QD	Unknown	STRESS ULCER PROPHYLAXIS		22-May-2020		5 DAY
36 POTASSIUM CHLORIDE		Unknown	dose: 80 other	Hypokalaemia	18-May-2020		9 DAY
37 PROPOFOL		Unknown	dose: 50 Other	Sedation	17-May-2020		10 DAY
38 QUETIAPINE	200 MG/BID	Unknown		Agitation	22-May-2020		5 DAY
39 VANCOMYCIN	1000 MG/BID	Unknown	BACTERIAL INFECTION PROPHYLAXIS		21-May-2020		10 DAY
40 VANCOMYCIN	2500 MG/QD	Unknown	BACTERIAL INFECTION PROPHYLAXIS		17-May-2020	17-May-2020	10 DAY
41 VANCOMYCIN	2000 MG/M**2/BID	Unknown	BACTERIAL INFECTION PROPHYLAXIS		17-May-2020	20-May-2020	10 DAY
42 VASOPRESSIN		Unknown	HEMODYNAMIC SUPPORT, dose: 0.08 Other		21-May-2020		6 DAY

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868071

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868106

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 05-Jun-2020 Mfr Rcvd Date: 29-Mar-2020 Mfr Control #:US-ROCHE-2577176 Application #: 125276

Patient Information:

Age: Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2577176 is a spontaneous case, received on 29/Mar/2020 from a consumer in the USA and concerns a male patient of unspecified age who intentionally used tocilizumab (Actemra) for unapproved indication (off label use) and passed away due to unknown reason.

No medical history, past drugs, concurrent conditions or concomitant medications were reported.

On an unknown date, the patient started therapy with tocilizumab (dosing regimen and lot number: not reported) for COVID-19, off label use. On an unknown date, he passed away due to unknown reason. It was unknown if the autopsy was performed or not. The consent for follow up was denied. Hence, the case was lost to follow up.

At the time of patients death, it was not reported if the therapy with tocilizumab was ongoing or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868106

The reporter did not assess the causality of event patient passed away with tocilizumab.

No further information was provided.

Additional information was received on 29/May/2020 and the following information was added to the case as: Patient's gender was updated and narrative updated accordingly.

Additional information was received on 02/Jun/2020 and the following information was added to the case as: New event (Patient passed away) added and event description updated accordingly.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868106

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868158

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: GBR Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 06-Jun-2020 Mfr Rcvd Date: 30-May-2020 Mfr Control #: GB-ROCHE-2613235 Application #: 125472

Patient Information:

Age: Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		162 MG/wk	Subcutaneous		COVID-19	04-Apr-2019	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1) ReC

Death NA

Event/Problem Narrative:

AER 2613235 is a non-interventional study case, received on 30/May/2020 from a consumer in the United Kingdom. It concerns a male patient (age not reported) (patient number: (b) (6)) who passed away due to unknown cause whilst participating in (b) (6) (b) (6)

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

(b) (6)

(b) (6) On an unknown date, his wife reported that, he passed away due to Covid-19. It was not reported if an autopsy was performed or not.

At the time of death, It was not reported if therapy with tocilizumab was altered or not.

The consumer assessed the patient passed away as related to tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868158

The company assessed the causality of the event patient passed away as not related to tocilizumab and rather related with underlying disease COVID-19 pneumonia.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868158

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868210

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: PAK
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 05-Jun-2020
Mfr Rcvd Date: 01-Jun-2020
Mfr Control #: PK-ROCHE-2613859
Application #: 125276

Patient Information:

Age: 52 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		400 MG/Q12H	Intravenous (not otherwise specified)	Q12H, every 12 hours. Received 2 doses of Actemra	COVID-19		
2	ACTEMRA					Cough		
3	ACTEMRA					Pyrexia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	B2092B01				
2	ACTEMRA		NA	NA	B2092B01				
3	ACTEMRA		NA	NA	B2092B01				

Event Information:

Preferred Term (MedDRA Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868210

Event/Problem Narrative:

AER 2613859 is a spontaneous case, received on 01/Jun/2020 from a consumer (patient's relative) via a company representative in Pakistan. It concerns a 52 year old male patient who received treatment with off label use of tocilizumab for COVID-19 and died while being treated with tocilizumab (Actemra).

The patient had no medical history, past drugs, concurrent conditions and concomitant medications were reported. He did not had a travel history.

On an unknown date, the patient started therapy with intravenous tocilizumab (lot number: B2092B01) 400 mg once in 12 hour for COVID-19 (off label use). It was reported that he was tested COVID-19 positive and was provided with the ventilator support for the treatment. He received two doses of 400 mg for high temperature and cough every 12 hours while on ventilator. It was reported that he did not show any improvement in his health and expired two days after tocilizumab was administered. It was not reported if an autopsy was performed or not.

The reporter assessed the causality of death with tocilizumab as unknown.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868210

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868227

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 02-May-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 01-Jul-2020 Mfr Rcvd Date: 25-Jun-2020 Mfr Control #:US-ROCHE-2594788 Application #: 125276

Patient Information:

Age: 63 YR Sex: Female Weight: 106 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		200 MG/	Intravenous (not otherwise specified)	Date of most recent dose (100 ml) of blinded tocilizumab prior to onset of SAE: 30/Apr/2020 (13:23)	COVID-19 pneumonia	30-Apr-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	2 Day	NA	NA	MJM21375,MJM53750,MJM55579,MJM86723				

Event Information:

Preferred Term (MedDRA Version: 23.1) COVID-19 pneumonia ReC NA

Event/Problem Narrative:

AER 2594788 is a clinical study case, received on 03/May/2020 from a physician in the USA. It concerns 63 year old female patient (patient number: (b) (6)) who had died due to worsening coronavirus disease (COVID-19) pneumonia whilst enrolled in (b) (6) (b) (6) (b) (6)

Concomitant medications included ceftriaxone, chlorhexidine gluconate (Peridex), docusate; senna alexandrina (Docusate; Senna), enoxaparin, heparin, ketamine, levothyroxine, midazolam, other ophthalmologicals (Ocular Lubricant), pantoprazole, piperacillin; tazobactam, potassium chloride, rocuronium, sodium chloride, vancomycin, paracetamol (Acetaminophen), bisacodyl, fentanyl, codeine phosphate; guaifenesin, lorazepam, magnesium hydroxide (Milk Of Magnesia), morphine, ondansetron, epoprostenol, norepinephrine bitartrate (Levophed) and propofol. Concurrent condition included pneumonia, hypersensitivity reaction, constipation, mechanical ventilation, hypothyroidism, GERD (gastroesophageal reflux disease), electrolyte imbalance, fever, pain, cough, anxiety, dyspnea, nausea, hypoxia, progression of COVID-19 pneumonia, obesity, hypertension, vertigo, cholecystitis with cholelithiasis, urine retention, tachypnoea, tachycardia,



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868227

elevated d dimer, acute kidney injury, albuminuria, heart failure and succinylcholine chloride allergy. Past drug included succinylcholine chloride. No medical history was reported.

(b) (6)
(b) (6) Her oxygen saturation (SPO2) was 85-90 % before the event. She developed ARDS (acute respiratory distress syndrome), shock and acute renal failure. There was a difficulty in maintaining her oxygen saturation for 3 days, when she was not given a prone position. On 01/May/2020, the patient was given supine position for dialysis. It was reported that dialysis treatment was three hours long and 2800cc of fluid was removed. On the same day, she had non serious worsening hypoxia (severity: grade 3), at 11:49. The acute decrease in oxygen saturation and blood pressure and increase in heart rate occurred within 24 hours after end of infusion and in less than an hour after dialysis, and while she was on rocuronium drip. The clinical team consulted pharmacy and they stated that although it was unlikely, they could not rule out a hypersensitivity reaction, as the patient had known allergy to succinylcholine chloride. Her chest x-ray was done which showed no significant change and no evidence of lobar collapse. She was treated with diphenhydramine hydrochloride (Benadryl), methylprednisolone, famotidine. Rocuronium drip was stopped. On the same day, the worsening hypoxia was resolved. The investigator could not rule out that this was not related to study drug as it was only (b) (6) after the investigational drug ended. On (b) (6) she was de-saturated, COVID-19 pneumonia worsened (initial NCI CTCAE grade 2), she developed bradycardia and cardiac arrest. She received cardiopulmonary resuscitation (CPR) with no effect. She was pronounced dead due to cardiac arrest and worsening COVID-19 pneumonia (grade 5) after the family (over phone) requested to call the code.

The physician assessed the fatal worsening COVID-19 pneumonia as not related to blinded tocilizumab, but related to disease under study.

The sponsor assessed worsening COVID-19 pneumonia as not related to blinded tocilizumab considering it as related to patients underlying disease of COVID-19 pneumonia, shock and acute renal failure. As COVID-19 pneumonia in an elderly patient and acute renal failure can cause complications like cardiac arrest. Patients with cardiac risk factors and established cardiovascular disease seem to have a heightened vulnerability to develop COVID-19.

No further information was provided.

Additional information was received on 14/May/2020. Following information was added to the case: Event term COVID-19 pneumonia worsening was added. Patient date of birth, age, sex and ethnicity was updated. Event description was updated.

Additional information was received on 30/May/2020. Following information was added to the case: New event acute decrease in oxygen saturation and blood pressure (onset date: 01/May/2020), concurrent condition, concomitant medication, past drug (succinylcholine chloride) added.

Additional information was received on 10/Jun/2020. The following information was added to the case: the onset time of acute decrease in oxygen saturation and acute decrease in blood pressure was updated from 12 to 11:49.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868227

Additional information was received on 25/Jun/2020. Following information was added to the case: Initial NCI CTCAE grade updated to 2 for worsening COVID-19 pneumonia, event worsening hypoxia, event was downgraded to worsening hypoxia, susar status was downgraded and event description was updated.

This case no longer meets expedited reporting requirements because event of acute decrease in oxygen saturation and blood pressure was downgraded to non serious worsening hypoxia.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute kidney injury			YES
Albuminuria			YES
Anxiety			YES
COVID-19 pneumonia			YES
Cardiac failure			YES
Cholecystitis			NO
Constipation			YES
Cough			YES
Dialysis			YES
Drug hypersensitivity			
Dyspnoea			YES
Electrolyte imbalance			YES
Fibrin D dimer increased			YES



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868227

Gastroesophageal reflux disease	YES
Hypersensitivity	YES
Hypertension	YES
Hypothyroidism	YES
Hypoxia	YES
Mechanical ventilation	YES
Nausea	YES
Obesity	YES
Pain	YES
Pneumonia	YES
Pyrexia	YES
Tachycardia	YES
Tachypnoea	YES
Urinary retention	YES
Vertigo	YES

Medical History Product(s)	Start Date	End Date	Indications	Events
SUCCINYLCHOLINE CHLORIDE				

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Chest X-ray					N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868227

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/	Unknown		Pyrexia	26-Apr-2020	26-Apr-2020	6 DAY
2	ACETAMINOPHEN	325 MG/	Unknown			27-Apr-2020	27-Apr-2020	6 DAY
3	BISACODYL	10 MG/	Unknown		Constipation	27-Apr-2020	30-Apr-2020	5 DAY
4	Ceftriaxone	1 G/QD	Unknown		Pneumonia	26-Apr-2020	26-Apr-2020	6 DAY
5	DIPHENHYDRAMINE	50 MG/	Unknown	Dose frequency: Other	Hypersensitivity	01-May-2020	01-May-2020	1 DAY
6	DOCUSATE;SENNA	BID	Unknown	dose 1 tablet	Constipation	27-Apr-2020	01-May-2020	5 DAY
7	ENOXAPARIN	40 MG/QD	Unknown		Thrombosis prophylaxis	23-Apr-2020	27-Apr-2020	9 DAY
8	ENOXAPARIN	40 MG/BID	Unknown			27-Apr-2020	28-Apr-2020	9 DAY
9	EPOPROSTENOL		Unknown	0.5 other	Hypoxia	27-Apr-2020	02-May-2020	5 DAY
10	FAMOTIDINE	20 MG/	Unknown	Dose frequency: Other	Hypersensitivity	01-May-2020	01-May-2020	1 DAY
11	FENTANYL	50 UG/	Unknown		Pain	27-Apr-2020	29-Apr-2020	5 DAY
12	FENTANYL	150 UG/	Unknown			29-Apr-2020	02-May-2020	5 DAY
13	GUAIFENESIN/CODEINE	10 ML/	Unknown		Cough	23-Apr-2020	25-Apr-2020	9 DAY
14	HEPARIN	TID	Unknown	7500 Unit	Thrombosis prophylaxis	28-Apr-2020	01-May-2020	4 DAY
15	KETAMINE	100 MG/	Unknown	dose frequency: other	Mechanical ventilation	27-Apr-2020	27-Apr-2020	5 DAY
16	LEVOPHED	1.4 UG/	Unknown	other	COVID-19 pneumonia	01-May-2020	02-May-2020	1 DAY
17	LEVOTHYROXINE	125 MG/QD	Unknown		Hypothyroidism	23-Apr-2020	01-May-2020	9 DAY
18	LORAZEPAM	.5 MG/	Unknown			26-Apr-2020	01-May-2020	9 DAY
19	LORAZEPAM	.5 MG/	Unknown		Anxiety	23-Apr-2020	24-Apr-2020	9 DAY
20	METHYLPREDNISOLON E	125 MG/QID	Unknown		Hypersensitivity	01-May-2020	01-May-2020	1 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868227

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
21	MIDAZOLAM	2 MG/	Unknown		Mechanical ventilation	27-Apr-2020	27-Apr-2020	5 DAY
22	MIDAZOLAM	4 MG/	Unknown			27-Apr-2020	27-Apr-2020	5 DAY
23	MIDAZOLAM	2 MG/	Unknown	Other		30-Apr-2020	30-Apr-2020	5 DAY
24	MILK OF MAGNESIA	2 MG/	Unknown		Constipation	28-Apr-2020	28-Apr-2020	4 DAY
25	MORPHINE	2 MG/	Unknown		Dyspnoea	23-Apr-2020	23-Apr-2020	9 DAY
26	MORPHINE	2 MG/	Unknown			24-Apr-2020	28-Apr-2020	9 DAY
27	MORPHINE	2 MG/	Unknown			26-Apr-2020	26-Apr-2020	9 DAY
28	ONDANSETRON	4 MG/	Unknown		Nausea	23-Apr-2020	23-Apr-2020	9 DAY
29	PANTOPRAZOLE	40 MG/QD	Unknown		Gastrooesophageal reflux disease	27-Apr-2020	01-May-2020	5 DAY
30	PERIDEX [CHLORHEXIDINE GLUCONATE]	15 ML/BID	Unknown		Prophylaxis	27-Apr-2020	01-May-2020	5 DAY
31	PIPERACILLIN;TAZOBAC TAM	40 MG/BID	Unknown		Pneumonia	27-Apr-2020	01-May-2020	5 DAY
32	POTASSIUM CHLORIDE		Unknown	20 other		28-Apr-2020	28-Apr-2020	4 DAY
33	POTASSIUM CHLORIDE		Unknown	10 other	Electrolyte imbalance	29-Apr-2020	29-Apr-2020	4 DAY
34	PROPOFOL	50 UG/	Unknown		Mechanical ventilation	27-Apr-2020	02-May-2020	5 DAY
35	ROCURONIUM	50 MG/	Unknown	other		01-May-2020	01-May-2020	5 DAY
36	ROCURONIUM	100 MG/	Unknown		Mechanical ventilation	27-Apr-2020	27-Apr-2020	5 DAY
37	ROCURONIUM	8 UG/	Unknown	other		01-May-2020	01-May-2020	5 DAY
38	SODIUM CHLORIDE	3 ML/TID	Unknown			26-Apr-2020	01-May-2020	6 DAY
39	VANCOMYCIN	1500 MG/BID	Unknown		Pneumonia	26-Apr-2020	27-Apr-2020	6 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868227

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868233

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: MEX
Event Date: 01-Jun-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 05-Jun-2020
Mfr Rcvd Date: 02-Jun-2020
Mfr Control #: MX-ROCHE-2614157
Application #: 125276

Patient Information:

Age: 70 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ACTEMRA		400 MG/	Intravenous (not otherwise specified)	one single day dose	COVID-19 pneumonia	01-Jun-2020	01-Jun-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
COVID-19 pneumonia	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2614157 is a spontaneous case, received on 02/Jun/2020 from an other health care professional in Mexico. It concerns a male patient (age not reported) who developed COVID-19 pneumonia and intentionally used tocilizumab (Actemra) for unlabeled indication, off label use.

No medical history, past drugs, concurrent conditions or concomitant medications were reported.

On 01/Jun/2020, the patient started therapy with intravenous tocilizumab 400 mg once in a day (lot number: unknown) for covid-19 pneumonia (drug intentional use for unlabeled indication, off label use). On an unspecified date the test was positive for COVID-19. He had supplementary oxygen therapy and required ventilator support. On (b) (6) he died due to the pneumonia caused by the Covid-19. It was not reported if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868233

It was not reported if therapy with tocilizumab was altered or not in response to the covid-19 pneumonia.

The other health care professional did not assessed the causality between covid-19 pneumonia and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17868233

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17869068

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 04-May-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 08-Jun-2020 Mfr Rcvd Date: 05-May-2020 Mfr Control #:US-ROCHE-2597442 Application #: 125276

Patient Information:

Age: 66 YR Sex: Female Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ACTEMRA		400 MG/	Intravenous (not otherwise specified)	Ongoing: Unknown	COVID-19 pneumonia	04-May-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA	0 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Atrioventricular block	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2597442 is a spontaneous case, received on 05/May/2020 from a pharmacist via consumer in the USA. It concerns a 66 year old female patient who was being treated with tocilizumab for an off label indication and had fatal heart block because of COVID-19 pneumonia (heart block) whilst being treated with tocilizumab (Actemra).

Patient's condition includes hypertension, diabetes and high cholesterol. Past drugs, past conditions and concomitant medications were not reported.

She experienced fever, weakness and short of breath. On (b) (6) she visited to emergency department and was diagnosed with COVID- 19 and went home. She again visited emergency department with worsening of short of breath, cough and weakness. She was diagnosed with COVID-Pneumonia, superimposed bacterial infection and was intubated. On (b) (6) the patient started therapy with



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17869068

tocilizumab (lot number: unknown) (dosage regimen not reported) for COVID-19 pneumonia (off label use). She had elevated d-dimer and was administered hydroxychloroquin. She was still intubated and doing fine. On (b) (6) her respiratory status was declined. She was intubated. Later she was subsequently extubated and transferred to the regular floor. On (b) (6) she became bradycardiac and was called code blue. Later on the same day, she got the rhythm back. After some time on the same day, she was tachycardic and became asystolic. CPR was performed. Unfortunately on the same day, she was passed away due to heart block because of COVID-19 pneumonia. It was unknown that autopsy was performed or not.

At the time of the report, it was unknown whether the therapy with tocilizumab was altered or not.

The reporter did not assessed the causality between the fatal heart block because of COVID-19 pneumonia and tocilizumab.

No further information was provided.

Additional information received on 07/May/2020 and following information was added to the case: Patient's details are added.

Additional information received on 01/Jun/2020. Following information added: indication updated to covid-19 pneumonia from covid-19, new event (heart block because of COVID-19 pneumonia) and accordingly event description updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Blood cholesterol increased			
Diabetes mellitus			
Hypertension			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17869068

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17870754

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: PAK Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 08-Jun-2020 Mfr Rcvd Date: 01-Jun-2020 Mfr Control #: PK-ROCHE-2613852 Application #: 125276

Patient Information:

Age: Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		400 MG/Q12H	Intravenous (not otherwise specified)	Frequency Q12H	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		Unk	NA	B2092B01				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Cardiac failure	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2613852 is a spontaneous case, received on 01/Jun/2020 from a consumer in pakistan. It concerns a 44 year-old-male patient who died due to cardiac failure whilst being treated with tocilizumab (Actemra) for unlabeled indication (off label use in covid 19).

Medical history, past drugs, concurrent conditions and concomitant medications were not reported.

On an unknown date, the patient was on ventilator for one week. He was administered therapy with intravenous (IV) tocilizumab (lot number: B2092B01) at 400 mg tocilizumab once in 12 hr for COVID-19 (drug intentional use for unlabeled indication, off label use). The reporter informed that tocilizumab was administered to his uncle for the treatment of COVID-19 (fever, difficulty in breathing). The ventilator was removed as he showed improvement in his health and spent one day without ventilator. On ^{(b) (6)} his condition then deteriorated and he expired due to cardiac failure. He had no recent travel history. It was unknown if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17870754

At the time of death it was not reported if therapy with tocilizumab was ongoing or not.

The reporter did not reported causality of cardiac failure with tocilizumab,

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Coronavirus test					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17870754

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17871741

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 29-Mar-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 08-Jun-2020 Mfr Rcvd Date: 04-Jun-2020 Mfr Control #: IT-ROCHE-2616313 Application #: 125276

Patient Information:

Age: 67 YR Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		8 MG/KG/Q12H	Intravenous (not otherwise specified)	On 29/Mar/2020, patient received the most recent dose of tocilizumab prior to SAE.	COVID-19 pneumonia			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC

Embolism arterial NA

Event/Problem Narrative:

AER 2616313 is a clinical study case, received on 04/Jun/2020 from a physician in Italy. It concerns a 67 year old patient (unspecified gender) (patient number: (b) (6)) who experienced arterial thromboembolism whilst enrolled in (b) (6)

No medical history, past drug, concurrent conditions and concomitant medications were reported.

(b) (6)

(b) (6) Later the patient experienced arterial thromboembolism (severity: grade 4). On 31/Mar/2020, patient started therapy with eparina sodica, 1400 for the treatment of arterial thromboembolism. On (b) (6) patient died. An autopsy was not performed.

At the time of reporting, it was unknown if therapy with tocilizumab was altered.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17871741

The physician assessed the arterial thromboembolism as related to tocilizumab.

NO further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17871741

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17872273

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 07-Apr-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 08-Jun-2020 Mfr Rcvd Date: 04-Jun-2020 Mfr Control #: IT-ROCHE-2616320 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB			Intravenous (not otherwise specified)	31/Mar/2020, received the most recent dose of tocilizumab prior to fatal Intracranial haemorrhage	COVID-19 pneumonia			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC

Haemorrhage intracranial NA

Event/Problem Narrative:

AER 2616320 is a clinical study case, received on 04/Jun/2020 from a physician in Italy and concerns a patient of unknown demographics (patient number: (b) (6)) who developed fatal intracranial haemorrhage whilst enrolled in (b) (6)

The patient's concomitant medication included low molecular weight heparin. No past medical history, past drugs or concurrent conditions were reported.

(b) (6)

(b) (6) . On (b) (6) the patient developed fatal intracranial haemorrhage (severity: grade 5) and died. It was unknown if an autopsy was performed or not.

At the time of death, therapy ongoing status with tocilizumab was not reported.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17872273

The physician assessed the causality as related between intracranial haemorrhage and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	HEPARIN							

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17872273

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17872325

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** PAK **Event Date:** 24-May-2020 **Outcomes:** DE,

Application Type: BLA

FDA Rcvd Date: 08-Jun-2020 **Mfr Rcvd Date:** 05-Jun-2020 **Mfr Control #:** PK-ROCHE-2616597

Application #: 125276

Patient Information:

Age: 47 YR

Sex: Male

Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		640 MG/	Intravenous (not otherwise specified)	8 injections of 80 mg	COVID-19	24-May-2020	24-May-2020
2	ACTEMRA					Typhoid fever		
3	ACTEMRA					Influenza		
4	ACTEMRA					Pyrexia		
5	ACTEMRA					Haemoptysis		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA	0 Day	NA	NA	B2102B02				
2	ACTEMRA	0 Day	NA	NA	B2102B02				
3	ACTEMRA	0 Day	NA	NA	B2102B02				
4	ACTEMRA	0 Day	NA	NA	B2102B02				
5	ACTEMRA	0 Day	NA	NA	B2102B02				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)

Death

Intentional product use issue

ReC

NA

NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17872325

Off label use

NA

Event/Problem Narrative:

AER 2616597 is a spontaneous case, received on 05/Jun/2020 from a consumer via a company representative of distribution department in Pakistan. It concerns a male patient 47 years who died due to unknown cause while being treated with tocilizumab (Actemra) for off label use (Actemra intentional use for unapproved indication)

No medical history, past drugs, concurrent conditions or concomitant medications were reported. He had no travel history.

It was reported that the patient was tested COVID-19 positive and was provided with the ventilator support in the intensive care unit (ICU) for the treatment of COVID-19. The chest computed tomography (CT) or chest X-ray changes were reported as positive. On 24/May/2020, in the afternoon, he received intravenous tocilizumab (lot number: B2102B02) infusion 640 mg (8 injections of 80 mg) (frequency not reported) for COVID-19 flu, fever and typhoid, blood in sputum (for off label use (Actemra intentional use for unapproved indication)). On (b) (6) he expired due to unknown cause. It was not reported whether the autopsy was performed or not.

The reporter assessed a causality of death with tocilizumab as unknown.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Computerised tomogram thorax					N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17872325

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17872379

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: PAK
Event Date: 29-May-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 08-Jun-2020
Mfr Rcvd Date: 05-Jun-2020
Mfr Control #: PK-ROCHE-2616581
Application #: 125276

Patient Information:

Age: 55 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		560 MG/	Intravenous (not otherwise specified)		COVID-19 pneumonia		
2	ACTEMRA					Dyspnoea		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	B2102B02				
2	ACTEMRA		NA	NA	B2102B02				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17872379

Event/Problem Narrative:

AER 2616581 is a spontaneous case, received on 05/Jun/2020 from a consumer in Pakistan. It concerns a 55 year old male patient who died whilst being treated intentionally with tocilizumab (Actemra) for unapproved indication.

The patient's past history, past drug, concomitant medication and concurrent condition were not reported.

It was reported that that the patient was treated with intravenous tocilizumab ((lot number: B2102B02, frequency not reported) 560 mg for covid 19 pneumonia and shortness of breath which was intentionally treated for unapproved indication (off label use).It was reported that reporter's brother was tested negative for covid 19, but on the basis of his symptoms, he was given tocilizumab. His computed tomography (CT) scan showed changes. He was treated in ICU and given ventilator support. He had no travel history. It was reported that after 8 hours of the second dose of tocilizumab, on ^{(b) (6)} he passed away. It was unknown if an autopsy was performed or not.

The reporter assessed the causality of death as unknown with tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Computerised tomogram					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17872379

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17872487

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Event Date:** **Outcomes:** DE, **Application Type:** BLA

FDA Rcvd Date: 11-Jun-2020 **Mfr Rcvd Date:** 08-Jun-2020 **Mfr Control #:** US-ROCHE-2616409 **Application #:** 125276

Patient Information:

Age: 63 YR **Sex:** Female **Weight:** 94 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		800 MG/1X	Intravenous (not otherwise specified)	once	COVID-19 pneumonia	07-Apr-2020	07-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
COVID-19	NA
Cardio-respiratory arrest	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17872487

Event/Problem Narrative:

AER 2616409 is a spontaneous case, received on 04/Jun/2020 from a physician in the USA. It concerns a 63 year old female patient who died due to cardiopulmonary arrest and COVID-19 whilst being treated with tocilizumab (Actemra) for an unapproved indication (off label use).

The patient's concurrent conditions included hypertension, alveolar hemorrhage and diabetes. Concomitant medications included enoxaparin sodium (Lovenox). No medical history and past drugs were reported.

On 31/Mar/2020, the patient had chest computerized tomogram (CT) or chest X ray which showed diffuse bilateral infiltrates and she was positive for COVID -19 test. On (b) (6) she started therapy with intravenous tocilizumab (lot number: unknown), 800 mg, once, for COVID-19 pneumonia (intentional use for unapproved indication, off label use) and tocilizumab discontinued on the same day. It was reported that she was in intensive care unit (ICU) and intubated as she was not doing well. Diagnosis date was unknown. She had Acute kidney injury (AKI), elevated D-dimer, methicillin-resistant strains of staphylococcus aureus (MRSA) in sputum, acute respiratory distress syndrome (ARDS), she was started on therapeutic anticoagulation, vancomycin, maximum vent support and vasopressors, She also had alveolar hemorrhage, shock liver, ileus, encephalopathy. She received convalescent plasma therapy, supplemental oxygen therapy and was on ventilator from (b) (6). Despite aggressive measures, she died on (b) (6) due to cardiopulmonary arrest and COVID-19. It was unknown whether autopsy was performed or not.

The physician assessed causality of fatal cardiopulmonary arrest and COVID-19 as unknown with tocilizumab.

No further information was provided.

Additional information was received on 08/Jun/2020. The following information was added to the case: cause of death updated as cardiopulmonary arrest and COVID-19 (previously unknown) and event causality updated as unknown (previously not reported).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Diabetes mellitus				
Hypertension				
Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17872487

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Computerised tomogram thorax X-ray					N N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	LOVENOX [ENOXAPARIN SODIUM]							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17875733

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 16-Apr-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 09-Jun-2020 Mfr Rcvd Date: 04-Jun-2020 Mfr Control #: IT-ROCHE-2616328 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		8 MG/KG/	Intravenous (not otherwise specified)	Last tocilizumab administration date was 10/Apr/2020.	COVID-19 pneumonia			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC

Large intestine perforation NA

Event/Problem Narrative:

AER 2616328 is a clinical study case, received on 04/Jun/2020 from a physician in Italy. It concerns a patient of unknown demographics (patient number: (b) (6)) who developed colonic perforation whilst enrolled in (b) (6) (b) (6)

Concomitant medications included furosemide (Lasix), propofol, fentanyl (Fentanest), pantorac and ceftarolina. No medical history, past drugs and concurrent conditions were reported

On an unknown date, (b) (6) (b) (6) . On 16/Apr/2020, the patient developed colonic perforation (severity: grade 5). On an unknown date, patient was died. It was not reported if an autopsy was performed or not. No surgery was performed.

The physician assessed the colonic perforation as possible related to tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17875733

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	FENTANEST [FENTANYL]							
2	LASIX [FUROSEMIDE]							
3	PROPOFOL							



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17875733

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17876548

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ESP **Event Date:** **Outcomes:** DE,OT, **Application Type:** NDA

FDA Rcvd Date: 08-Jul-2020 **Mfr Rcvd Date:** 03-Jun-2020 **Mfr Control #:** ES-ABBVIE-20K-144-3436071-00 **Application #:** 021906

Patient Information:

Age: 72 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LOPINAVIR/RITONAVIR			Oral		COVID-19 pneumonia		
2	AZITHROMYCIN			Unknown		Bilateral pneumonia		
3	CEFTRIAZONE			Unknown		COVID-19 pneumonia		
4	HYDROXYCHLOROQUIN E			Unknown		COVID-19 pneumonia		
5	INTERFERON BETA-1B			Subcutaneous		COVID-19 pneumonia		
6	TOCILIZUMAB			Unknown		COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	LOPINAVIR/RITONAVIR		NA	NA	UNKNOWN				
2	AZITHROMYCIN		NA	NA	UNKNOWN				
3	CEFTRIAZONE		NA	NA	UNKNOWN				
4	HYDROXYCHLOROQUIN E		NA	NA	UNKNOWN				
5	INTERFERON BETA-1B		NA	NA	UNKNOWN				
6	TOCILIZUMAB		NA	NA	UNKNOWN				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17876548

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
Death	NA
Electrocardiogram QT prolonged	NA
Hepatitis toxic	NA
Hyperbilirubinaemia	NA
Hypertransaminaemia	NA
Ischaemia	NA
Obstructive airways disorder	NA
Off label use	NA
Peripheral arterial occlusive disease	NA
Secretion discharge	NA
Thrombosis	NA

Event/Problem Narrative:

Spontaneous report from SPAIN by a physician of a 72 year old male with events of DEATH, PERIPHERIC ARTERIAL DISEASE WORSENING WITH ISCHEMIA, PROLONGED QT, AIRWAY BLOCKING, RECURRENT MUCUS AND BLOOD CLOGGING, HYPERBILIRUBINEMIA WORSENING, HYPERTRANSAMINASEMIA and TOXIC HEPATITIS and non-serious OFF LABEL USE with LOPINAVIR/RITONAVIR. The patient had a relevant medical history of PERIPHERAL ARTERIAL DISEASE INTERMITTENT CLAUDICATION STAGE IIA, PERONEAL MALLEOLUS FRACTURE, APPENDECTOMY, BILATERAL INTERSTITIAL DISEASE, ARTERIAL HYPERTENSION, DYSLIPIDAEMIA, FEVER, DRY COUGH and DYSPNEA WORSENERD.

On unknown dates, the patient experienced DEATH, PERIPHERIC ARTERIAL DISEASE WORSENING WITH ISCHEMIA, PROLONGED QT, AIRWAY BLOCKING, RECURRENT MUCUS AND BLOOD CLOGGING, HYPERBILIRUBINEMIA WORSENING, HYPERTRANSAMINASEMIA, TOXIC HEPATITIS and OFF LABEL USE. On unknown date, the patient died. The cause of death was reported as UNKNOWN CAUSE OF DEATH. It is unknown if an autopsy was performed. HYDROXYCHLOROQUINE, CEFTRIAXONE, AZITHROMYCIN, INTERFERON BETA-1B and TOCILIZUMAB were also considered suspect.

The patient with 7-8 days fever, dry cough and worsening dyspnea. He had slightly prolonged QT transfer to ICU admission. It required amines. On the last day, acute obstruction of the airway by recurrent mucus plugs and blood and Death at 11 days. The corticosteroids were boluses of methyl prednisolone, followed by methyl prednisolone at lower doses (+/- 1 mg / Kg day). He had mild hypertransaminemia and mild hyperbilirubinemia afterwards, which increases with the medication administered and the rest of amine-type support medication and others provided in the ICU.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17876548

Causality for LOPINAVIR/RITONAVIR

The reporter's causality for the event(s) of DEATH, PERIPHERIC ARTERIAL DISEASE WORSENING WITH ISCHEMIA unknown onset, PERIPHERIC ARTERIAL DISEASE WORSENING WITH ISCHEMIA unknown onset, PROLONGED QT, AIRWAY BLOCKING, RECURRENT MUCUS AND BLOOD CLOGGING unknown onset, HYPERBILIRUBINEMIA WORSENING, HYPERTRANSAMINASEMIA, RECURRENT MUCUS AND BLOOD CLOGGING unknown onset, TOXIC HEPATITIS and OFF LABEL USE was not provided.

Relevant Laboratory & Other Diagnostic Tests

Unknown date CREATINE PHOSPHOKINASE: 2095-34592
Unknown date CULTURE: BAS: in strawberry septate hyphae. Culture: Aspergillus fumigatus (8 days)
Unknown date D GLUCAN: 22.35
Unknown date DIMER D: 1522.> 10,000, ... 3350
Unknown date FERRITIN: 4634
Unknown date GALACTOMANNAN: 6.29
Unknown date INTERLEUKIN 6: 11.7
Unknown date LEUCOCYTES: 5360
Unknown date LYMPHOCYTES: 550
Unknown date PCR: 7.24
Unknown date PCR: 14.4
Unknown date PCR: 1.71
Unknown date POLYMERASE CHAIN REACTION TEST: SARS-CoV-2 positive
Unknown date THORAX X-RAY: peripheral alveolar consolidations in both upper lobes
Unknown date TROPONIN: 38
Unknown date TROPONIN: 5200
Unknown date TROPONIN: 986

Change History

Amendment to data received on 03 Jun 2020 with changes to suspect drug information and narrative description.

Amendment to data received on 03 Jun 2020 with changes to narrative description.

Amendment to data received on 03 Jun 2020 with changes to medical history, event information, reporter opinion of causality, suspect drug information and narrative description. The events of "FEVER", "DYSPNEA WORSENER" and "DRY COUGH" were removed.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17876548

Version 3 was created to add the Indication Bilateral SARS-CoV-2 Pneumonia for suspect products interferon beta-1b and tocilizumab. Medical history term was updated from HTA to Arterial Hypertension and DL to Dyslipidaemia.

Version 2 case created to add autonomous community code and city was added for Primary reporter.

Version 1 was created to change the coding for indication BILATERAL SARS-COV-2 PNEUMONIA.

Relevant Medical History:

Patient Medical History

PERIPHERAL ARTERIAL DISEASE INTERMITTENT CLAUDICATION STAGE IIA
PERONEAL MALLEOLUS FRACTURE
APPENDECTOMY
BILATERAL INTERSTITIAL DISEASE
ARTERIAL HYPERTENSION
DYSLIPIDAEMIA
FEVER
DRY COUGH
DYSPNEA WORSENER

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Ankle fracture			
Appendectomy			
Arterial hypertension			
Dry cough			
Dyslipidaemia			
Dyspnea exacerbated			
Fever			
Interstitial lung disease			



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17876548

Peripheral arterial disease

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Leucocyte count					N
Polymerase chain reaction					N
Culture					N
Galactomannan antigen					N
Troponin					N
Creatine phosphokinase					N
Thorax X-ray					N
Interleukin-6					N
Blood beta-D-glucan					N
Lymphocytes					N
Fibrin D dimer					N
PCR					N
Ferritin					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ABBVIE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17876602

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Event Date:** 10-May-2020 **Outcomes:** DE,HO,LT,OT,

Application Type: BLA

FDA Rcvd Date: 24-Sep-2020 **Mfr Rcvd Date:** 17-Sep-2020 **Mfr Control #:** US-SA-2020SA127960

Application #: 761037

Patient Information:

Age: **Sex:** **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	SARILUMAB			Intravenous (not otherwise specified)	REGN88 or placebo 200 mg or 400 mg, single or multiple doses	COVID-19	09-May-2020	09-May-2020
2	SARILUMAB			Intravenous (not otherwise specified)	REGN88 or placebo 200 mg or 400 mg, single or multiple doses		17-May-2020	17-May-2020
3	SARILUMAB			Intravenous (not otherwise specified)	REGN88 or placebo 200 mg or 400 mg, single or multiple doses		24-May-2020	24-May-2020
4	SARILUMAB			Intravenous (not otherwise specified)	REGN88 or placebo 200 mg or 400 mg, single or multiple doses		10-May-2020	10-May-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	3398 MINUTES	Yes	NA				SANOFI	
2	SARILUMAB	3398 MINUTES	Yes	NA				SANOFI	
3	SARILUMAB	3398 MINUTES	Yes	NA				SANOFI	
4	SARILUMAB	3398 MINUTES	Yes	NA				SANOFI	

Event Information:

Preferred Term (MedDRA Version: 23.1)

ReC

Acute respiratory failure

NA

Anaemia

NA



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Atrial fibrillation	NA
Lung infiltration	NA
Thrombocytopenia	NA

Event/Problem Narrative:

Initial information received on 13-May-2020 regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference RGN MCN: 2020-37616 on 13-May-2020 and transmitted to Sanofi, in the scope of company sponsored study (b) (6)

Patient ID: (b) (6) Center ID: (b) (6) Country: United States

Study title: (b) (6)
(b) (6)

Acute respiratory failure with hypoxia [Acute respiratory failure]: Death, Life threatening, Hospitalization; Onset date: (b) (6) Severity: Grade 5; Outcome: Fatal; Event resolved on: (b) (6)

Pulmonary infiltrates on chest X ray [Lung infiltration] (initially reported as Pulmonary infiltrates/pleural effusions [Pleural effusion]): Life threatening, Hospitalization; Onset date: (b) (6) Severity: Grade 4; Outcome: Recovered/resolved; Event resolved on: (b) (6)

Anemia [Anaemia]: Life-threatening; Onset date: (b) (6) Severity: Grade 3; Outcome: Recovered/Resolved; Event resolved on: (b) (6)

Severe thrombocytopenia [Thrombocytopenia]: Life-threatening; Onset date: (b) (6) Severity: Grade 4; Outcome: Recovered/Resolved; Event resolved on: (b) (6)

Atrial fibrillation with RVR [Atrial fibrillation]: Medically significant; Onset date: (b) (6) Severity: Grade 3; Outcome: Recovered/Resolved; Event resolved on: (b) (6)

A 69-year-old, Hispanic, female patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6)

The patient experienced above-referenced SAEs on (b) (6) after receiving study drug. The patient did not complete the study due to death.

Relevant medical history included diabetes mellitus and hypertension.

Relevant concomitant medications included furosemide, acetaminophen, azithromycin, enoxaparin, clonidine and guaifenesin LA.



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On (b) (6) the patient experienced earliest symptoms of pneumonia. Rales/crackles on lung auscultation were not present at baseline. Highest temperature recorded within 24 hours prior to dosing was 38.2 degrees Celsius (C). Patient condition indicated use of supplemental oxygen by high-flow nasal cannula and treatment in the intensive care unit (ICU).

(b) (6) vital signs reported oxygen saturation (SpO2) 97%, blood pressure 107/57 mmHg, pulse 75 beats per minute (bpm), respiratory rate 24 respirations per minute (rpm) and body temperature 99.4 degrees Fahrenheit (F). Laboratory tests were performed, and results reported alanine aminotransferase (ALT) 74 IU/L (13-56), aspartate aminotransferase 95 U/L (15-37), potassium 4.2 mEq/L (3.5-5.1), carbon dioxide (bicarbonate) 26 mEq/L (21- 32) and bilirubin total 1.0 mg/dL (0.2-1). Haematology tests were performed, and results reported red blood cells (RBC) $4.13 \times 10^6/\mu\text{L}$ (4-5.4), haemoglobin 12.3 g/ dl (12-16), haematocrit 38.3% (36-47), white blood cells (WBC) $4.4 \times 10^3/\mu\text{L}$ (4.5-11), neutrophils (absolute) $2.64 \times 10^3/\mu\text{L}$ (2.03-8.25), and platelets $218 \times 10^3/\mu\text{L}$ (140-440).

On (b) (6) i.e. (b) (6) after the first IP administration, the patient experienced fluid in the chest. SpO2 dropped to 96% and respiratory rate was 22. Chest X-ray scan was performed, and results reported pulmonary infiltrates /pleural effusions anticipated due COVID-19 with ARDS (acute respiratory distress syndrome). No corrective treatment was given for the event.

On (b) (6) oxygen saturation further decreased to 95% while respiratory rate was 28 and carbon dioxide 16. Patient was placed on AIRVO device.

On (b) (6) at 02:38 i.e. (b) (6) days 8 hrs 38 min after the first IP administration, the patient experienced acute respiratory failure with hypoxia. Oxygen saturation increased to 98 %, blood pressure decreased to 110/66 mmHg, pulse increased to 90 bpm, respiratory rate decreased to 25 rpm and the patient was unresponsive. Propofol was given at a dose of 1000 mg continuously and another single 100 mg for sedation. As a paralytic, the patient received single dose of 100 mg of intravenous rocuronium and intravenous vecuronium at a dose of 20 mg, given once and 10 mg as needed. On the same day, endotracheal tube was repositioned and event Pulmonary infiltrates on chest X-ray was deemed resolved.

On (b) (6) patient's SpO2 was 96% and blood pressure 100/54. Potassium level was 3.2 and bicarbonate level was 31.

On (b) (6) at 12:05 i.e. (b) (6) days 18 hrs 5 min after the first IP administration, the patient experienced atrial fibrillation with rapid ventricular response (RVR) and was started on an unspecified dose of amiodarone. SpO2 was 99%, blood pressure was 124/66, potassium was 3.3, carbon dioxide was 30, respiratory rate 25 rpm, fraction of inspired oxygen (FI02) 100%, positive end-expiratory pressure (PEEP) was 14, was unresponsive and paralytic was started.

On (b) (6) amiodarone was discontinued. Carbon dioxide was 38. The patient continued to have intermittent episodes of atrial fibrillation with RVR and amiodarone was continued until the patient converted to normal sinus rhythm. Blood pressure was 75/47 and pulse 73.



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On (b) (6) hypoxemia worsened, and the patient was placed on Veletri (epoprostenol).

On (b) (6) the patient had a left sided chest tube placement as a corrective treatment for acute respiratory failure with hypoxia.

On (b) (6) patient's RBC count was 2.43, haemoglobin value was 7.2 and haematocrit was 23.2.

On (b) (6) patient's SpO2 was 90%, with the respiratory rate of 23 and potassium 1.9. Platelet count was 212. On the same day i.e. (b) (6) days 6 hrs after the first IP administration, the patient was diagnosed with anemia. RBC count was 2.12, haemoglobin 6.5 and hematocrit 19.8%. The patient was given one unit of packed red blood cells (PRBCs).

On (b) (6) i.e. (b) (6) days 6 hrs after the first investigational product (IP) administration, platelets were very low, 7 and the patient experienced severe thrombocytopenia and received two transfusions of platelets as a corrective treatment for the event.

On (b) (6) platelet count was 13 and the patient again received one unit of platelets (PLTs). On (b) (6) WBC increased to 33.1 and neutrophils absolute increased to 30.45, platelets were 15.

On (b) (6) chest tube was adjusted as left lateral wall pneumothorax was noted.

On (b) (6) red blood cells were 2.13, hemoglobin was 6.7 and the patient was given one unit of PRBCS. Platelets were 32.

On (b) (6) the patient was again given one unit of PRBCS as platelets were 13. On the same day, anemia was considered resolved.

On (b) (6) platelets were 48 and hemoglobin increased to 10.6.

On (b) (6) SpO2 dropped to 86%, blood pressure to 85/44 and respiratory rate to 18.

On (b) (6) patient continued to desaturate, SpO2 was 68% and respiratory rate 18. At 13:00, the patient passed away due to acute respiratory failure with hypoxia. Autopsy was not performed.

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

Study drug was permanently withdrawn in response to the event Severe thrombocytopenia. Study drug was continued in response to all other events



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Causality assessment is as follows: (b) (6)

Acute respiratory failure: Severity = Grade 5; Investigator Causality = Not Related; Company Causality = Not Related

Lung infiltration: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: No alternative explanation was provided. Company causality rationale: A 69-year-old female patient with severe or critical COVID-19 experienced lung infiltration and acute respiratory failure, (b) (6) days after receiving the first dose of study drug. The events are assessed as not related to study drug or any clinical trial procedure since they are secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and comorbidities like diabetes mellitus and hypertension.

Anaemia: Severity = Grade 3; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 69-year-old, female patient enrolled in the trial experienced anemia (b) (6) days after (b) (6) and (b) (6) dose of study drug was administered. The event of anemia is assessed as not related to study drug or any clinical trial procedure. The event is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and comorbidities like diabetes mellitus. Concomitant drugs like acetaminophen, clonidine and azithromycin also confounds causality.

Thrombocytopenia: Severity = Grade 4; Investigator Causality = Related; Company Causality = Related Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 69-year-old, female patient enrolled in the trial experienced thrombocytopenia after study drug administration. Patient's baseline platelet count was within reference range and decreased severely (b) (6) days after receiving the (b) (6) dose of the study drug. Based on a plausible temporal association between study drug administration and the reported event and known potential effect of study drug on platelet count, causality for the event is assessed as related to study drug and not related to any clinical trial procedure. The concomitant medication of furosemide is also associated with thrombocytopenia and provides a plausible explanation for the event.

Atrial fibrillation:

Severity = Grade 3; Investigator Causality = Not Related; Company Causality = Not Related Investigator causality rationale: No alternative explanation was provided.

Company causality rationale: A 69-year-old, female patient enrolled in the trial experienced atrial fibrillation with RVR on the same day when



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(b) (6) dose of study drug was administered. The event of atrial fibrillation with RVR is assessed as not related to study drug or any clinical trial procedure. The event is secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and comorbidities like diabetes mellitus and hypertension.

Previous causality assessment on 13- May-2020 was as follows:

Pleural effusion: Severity = Grade 4; Investigator Causality = Not Related; Company Causality = Not

Related Investigator causality rationale: No alternative explanation was provided. Company causality rationale: A 69-year-old female patient with severe or critical COVID-19 experienced pleural effusion and acute respiratory failure, (b) (6) days after receiving the study drug. The events are assessed as not related to study drug or any clinical trial procedure since they are secondary to progression of COVID-19 infection and pneumonia further aggravated by patient's advanced age and comorbidities like diabetes mellitus and hypertension.

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow Up: 15-May-2020 and 18-May-2020 (processed together) The investigator provided the following updates: concomitant medications, treatment, medical history, relevant test results and event term updated.

Follow Up: 01-Jun-2020 The investigator provided the following updates: new event added (severe thrombocytopenia), dosing details and clinical course updated

Follow up: 12-Jun-2020, 16-Jun-2020 and 17- Jun-2020 (processed together): The investigator provided the following updates: events anemia and atrial fibrillation with RVR added, seriousness criteria of the event Acute respiratory failure with hypoxia updated, clinical course updated.

Follow-up: 04-Aug- 2020 The Investigator provided the following updates: event outcome, resolution date and clinical course updated, autopsy updated. Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow-up: 17-Sep-2020 The Investigator provided the following updates: outcome and resolution date for events Atrial fibrillation with RVR, Severe thrombocytopenia and Anemia and clinical course updated.

Expectedness Assessment per



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current IB (version 14): Acute respiratory failure with hypoxia: unexpected Pulmonary infiltrates on chest Xray: unexpected Anemia: unexpected Severe thrombocytopenia: unexpected Atrial fibrillation with RVR: unexpected Expectedness Assessment for initially reported event term Pulmonary infiltrates/pleural effusions on chest Xray: Expectedness Assessment per current IB (version 14): Pulmonary infiltrates/pleural effusions on chest Xray: unexpected

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Metabolic encephalopathy	(b) (6)		YES
Dyslipidemia			YES
Hypertension			YES
Type 2 diabetes mellitus			YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Bilirubin total	1.0	mg/dL	0.2	1	N
Potassium	3.2	meq/L	3.5	5.1	N
Carbon dioxide	16	meq/L	21	32	N
Haemoglobin	6.7	g/dL	12	16	N
Haemoglobin	10.6	g/dL	12	16	N
Oxygen saturation	96	%			N
Platelet count	218	10 ³ /uL	140	440	N
Platelet count	32	10 ³ /uL	140	440	N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Platelet count	13	10*3/uL	140	440	N
Blood pressure	124/66	mmHg			N
Blood pressure	75/47	mmHg			N
Body temperature	99.4	degF			Y
Chest X-ray					Y
Haemoglobin	6.5	g/dL	12	16	N
Absolute neutrophil count	2.64	10*3/mm3	2.03	8.25	N
Oxygen saturation	96	%			N
Oxygen saturation	95	%			N
Respiratory rate	28	breaths/min			N
Respiratory rate	18	breaths/min			N
WBC	4.4	10*3/uL	4.5	11	N
Blood pressure	100/54	mmHg			N
Carbon dioxide	31	meq/L	21	32	N
Hematocrit	19.8	%	36	47	N
Pulse rate	73	breaths/min			N
Respiratory rate	23	breaths/min			N
Blood pressure	143/89	mmHg			N
Blood pressure	85/44	mmHg			N
Carbon dioxide	26	meq/L	21	32	N
Carbon dioxide	30	meq/L	21	32	N
Carbon dioxide	38	meq/L	21	32	N
Oxygen saturation	90	%			N
Platelet count	212	10*3/uL	140	440	N
Platelet count	7	10*3/uL	140	440	N
Platelet count	13	10*3/uL	140	440	N
Potassium	4.2	meq/L	3.5	5.1	N
Potassium	1.9	meq/L	3.5	5.1	N
Hematocrit	23.2	%	36	47	N
Haemoglobin	12.3	g/dL	12	16	N
Pulse rate	75	breaths/min			N
Oxygen saturation	98	%			N
Oxygen saturation	99	%			N
Oxygen saturation	68	%			N
Platelet count	13	10*3/uL	140	440	N



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Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Platelet count	15	10 ³ /uL	140	440	N
Red blood cell count	2.12	10 ⁶ /uL	4	5.4	N
Respiratory rate	24	breaths/min			N
Blood pressure	110/66	mmHg			N
Body temperature	38.2	Cel			N
Haemoglobin	7.2	g/dL	12	16	N
Oxygen saturation	86	%			N
Red blood cell count	4.13	10 ⁶ /uL	4	5.4	N
Red blood cell count	2.13	10 ⁶ /uL	4	5.4	N
Alanine aminotransferase	74	iU/L	13	56	N
Aspartate aminotransferase	95	U/L	15	37	N
Potassium	3.3	meq/L	3.5	5.1	N
Chest X-ray					Y
Hematocrit	38.3	%	36	47	N
Absolute neutrophil count	30.45	10 ³ /mm ³	2.03	8.25	N
Platelet count	48	10 ³ /uL	140	440	N
Respiratory rate	25	breaths/min			N
Respiratory rate	25	breaths/min			N
WBC	33.1	10 ³ /uL	4.5	11	N
Blood pressure	107/57	mmHg			N
Chest X-ray					Y
Pulse rate	90	breaths/min			N
Oxygen saturation	97	%			N
Red blood cell count	2.43	10 ⁶ /uL	4	5.4	N
Respiratory rate	22	breaths/min			N
Respiratory rate	18	breaths/min			N

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/	Oral	650 mg, as necessary	Analgesic therapy	08-May-2020	16-May-2020	23 DAY



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	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
2	AZITHROMYCIN	500 MG/QD	Intravenous (not otherwise specified)	500 mg, qd	Ant biotic therapy	08-May-2020	12-May-2020	23 DAY
3	CEFEPIME	2 G/1X	Intravenous (not otherwise specified)	2 g, 1X	COVID-19	09-May-2020	09-May-2020	22 DAY
4	CEFEPIME	1 G/Q12H	Intravenous (not otherwise specified)	1 g, bid		09-May-2020	16-Jun-2020	22 DAY
5	CLONIDINE	.1 MG/	Oral	0.1 mg, as necessary	Hypertension	15-May-2020	16-Jun-2020	16 DAY
6	ENOXAPARIN	40 MG/QD	Subcutaneous	40 mg, qd	Anticoagulant therapy	08-May-2020	16-Jun-2020	23 DAY
7	FENTANYL	1000 UG/	Intravenous (not otherwise specified)	50-100 µg, as necessary	Analgesic therapy	12-May-2020	16-Jun-2020	19 DAY
8	FENTANYL		Intravenous (not otherwise specified)	50-100 µg, as necessary		12-May-2020	16-Jun-2020	19 DAY
9	FUROSEMIDE	20 MG/Q12H	Intravenous (not otherwise specified)	20 mg, bid	Diuretic therapy	13-May-2020	16-May-2020	18 DAY
10	GUAIFENESIN LA	600 MG/1X	Oral	600 mg, 1X	COVID-19	10-May-2020	10-May-2020	21 DAY
11	INSULIN		Subcutaneous	TITRATE PER SLIDING SCALE	Diabetes mellitus	08-May-2020	16-Jun-2020	23 DAY
12	METHYLPREDNISOLON E SODIUM SUCCINATE	40 MG/Q8H	Intravenous (not otherwise specified)	40 mg, TID	COVID-19	10-May-2020	15-May-2020	21 DAY
13	PANTOPRAZOLE	40 MG/QD	Intravenous (not otherwise specified)	40 mg, qd	Gastroesophageal reflux prophylaxis	08-May-2020	16-Jun-2020	23 DAY
14	POTASSIUM CHLORIDE	20 MEQ/	Intravenous (not otherwise specified)	20 mEq, as necessary	Vitamin supplementation	10-May-2020	16-Jun-2020	21 DAY
15	SODIUM PHOSPHATE	15 MMOL/	Intravenous (not otherwise specified)	15 mmol, as necessary	Vitamin supplementation	10-May-2020	13-May-2020	21 DAY



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Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
16 VANCOMYCIN		Intravenous (not otherwise specified)	750 mg, RUN AT 166.67 ML/HR	COVID-19	09-May-2020	13-May-2020	22 DAY
17 VANCOMYCIN	500 MG/1X	Intravenous (not otherwise specified)	500 mg, GIVEN ONCE - RUN AT 100ML/HR,1X		11-May-2020	11-May-2020	22 DAY
18 VANCOMYCIN	1000 MG/1X	Intravenous (not otherwise specified)	1000 mg, GIVEN ONCE - RUN AT 166.67ML/HR, 1X		09-May-2020	15-May-2020	22 DAY

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17877278

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 20-Apr-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 09-Jun-2020 Mfr Rcvd Date: 28-May-2020 Mfr Control #: IT-ROCHE-2612425 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB			Intravenous (not otherwise specified)		COVID-19 pneumonia			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA ® Version: 23.1) ReC

Multiple organ dysfunction syndrome NA

Event/Problem Narrative:

AER 2612425 is a clinical study case, received on 28/May/2020 from a physician in Italy. It concerns a patient of unknown demographics (patient number: 4478) who developed multi organ failure whilst enrolled in (b) (6)

No medical history, past drug, concurrent condition and concomitant medication were reported.

(b) (6)

On (b) (6) the patient developed multi organ failure (severity: grade 5) and the patient died (b) (6) An autopsy was not performed.

At the time of death, it was not reported if therapy with tocilizumab was altered or not in response to the multi organ failure.

The physician assessed the multi organ failure as related to tocilizumab.



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The physician assessed the multi organ failure as not related to tocilizumab as COVID-19 damages the walls and linings of the air sacs in lungs, which causes the inflammatory response of cytokines, overwhelming the immune system response to the infection, which can lead to damage of multiple organs, including lungs, heart, and kidneys and this can explain multi organ failure.

No further information provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



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Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17877952

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** USA **Event Date:** 22-May-2020 **Outcomes:** DE,OT,

Application Type:

FDA Rcvd Date: 08-Jul-2020 **Mfr Rcvd Date:** 01-Jul-2020 **Mfr Control #:** US-GILEAD-2020-0470593

Application #:

Patient Information:

Age: 74 YR **Sex:** Male **Weight:** 95.9 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	BLINDED PLACEBO		100 MG/QD	Intravenous (not otherwise specified)	100 mg, QD	COVID-19	12-May-2020	16-May-2020
2	BLINDED REMDESIVIR		100 MG/QD	Intravenous (not otherwise specified)	100 mg, QD	COVID-19	12-May-2020	16-May-2020
3	BLINDED TOCILIZUMAB		100 MG/QD	Intravenous (not otherwise specified)	100 mg, QD	COVID-19	12-May-2020	16-May-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	BLINDED PLACEBO	13 Day	NA	NA				GILEAD	
2	BLINDED REMDESIVIR	13 Day	NA	NA				GILEAD	
3	BLINDED TOCILIZUMAB	13 Day	NA	NA				GILEAD	

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Pneumothorax	NA
Pseudomonal bacteraemia	NA



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FOIA Case Report Information

Case ID: 17877952

Event/Problem Narrative:

This case, manufacturer control number 2020-0470593 is a spontaneous report "use of Remdesivir was under an EUA", referring to a(n) Elderly (Age: 74 years, Ethnicity: Of African Descent, Gender: Male) patient. The Pharmacist reported the following event(s) for this case: tension pneumothorax, Pseudomonas aeruginosa bacteremia.

Medical history included:

Current condition(s): COVID-19 (COVID-19) Start Date: Date not provided, heart failure with preserved ejection fraction (Cardiac failure) Start Date: Date not provided, presumed coronary artery disease (Coronary artery disease) Start Date: Date not provided, ventricular ectopy (Ventricular extrasystoles) Start Date: Date not provided, insulin-dependent diabetes mellitus type 2 (Type 2 diabetes mellitus) Start Date: Date not provided, hypertension (Hypertension) Start Date: Date not provided, OSA on CPAP (Sleep apnoea syndrome) Start Date: Date not provided, hyperlipidemia (Hyperlipidaemia) Start Date: Date not provided, CKD stage III (Chronic kidney disease) Start Date: Date not provided

Historical condition(s): None Reported

Historical drug(s): None Reported

(b) (6)

(b) (6)

(b) (6)

Concomitant medications included TOCILIZUMAB.

On an unspecified date, the patient experienced continued issues, including Pseudomonas aeruginosa bacteremia from VAP and a tension pneumothorax requiring emergent chest tube placement. Ultimately on (b) (6) family chose to focus on comfort and his vasopressor support was discontinued and he passed away. It was also reported that patient experienced AKI (previously submitted) which required several days of CVVHD.

The patient died on (b) (6) It was unknown if an autopsy was performed.

Cause of Death: Pseudomonas aeruginosa bacteremia, tension pneumothorax,

No laboratory/diagnostic tests were reported.

The action taken with REMDESIVIR was Unknown

The Pharmacist assessed the event of tension pneumothorax as Serious (Death, Medically Significant), causality of Not Reported for



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17877952

REMDESIVIR. The outcome of this event was Fatal

The Pharmacist assessed the event of Pseudomonas aeruginosa bacteremia as Serious (Death, Medically Significant), causality of Not Reported for REMDESIVIR. The outcome of this event was Fatal

The initial report was received on 04-JUN-2020.

Follow-up information was received on 01-JUL-2020. This spontaneous case has been updated to clinical trial "report from study (b) (6)

(b) (6)

(b) (6)

(b) (6)

Additional Current condition(s) included: lethargy (Lethargy) Start Date: Date not provided, bradycardia (Bradycardia) Start Date: Date not provided, worsening hypoxia (Hypoxia) Start Date: Date not provided, Acute hypoxic respiratory failure secondary to COVID-19 pneumonia [Acute respiratory failure] (Acute respiratory failure) Start Date: Date not provided, Acute hypoxic respiratory failure secondary to COVID-19 pneumonia [COVID-19 pneumonia] (COVID-19 pneumonia) Start Date: Date not provided, Edema (Edema) Start Date: Date not provided

(b) (6)

(b) (6)

Additional Concomitant medications included CEFTRIAXONE, DOXYCYCLINE, FUROSEMIDE, HEPARIN, MIDAZOLAM, KETAMINE, ATIVAN, MORPHINE, CONVALESCENT PLASMA (From 15-MAY-2020 to 15-MAY-2020, the patient received Tocilizumab vs placebo (COVACTA) 800 mg Intravenous route of administration for treatment of COVID-19.)

Additional information on event included: The patient was presented to hospital on (b) (6) as a transfer from other hospital in setting of acute hypoxic respiratory failure secondary to COVID-19 pneumonia. The patient's hospital course was complicated by lethargy, bradycardia, worsening hypoxia in setting of Ativan/morphine use, eventually necessitating transfer to the medical ICU, where he was intubated on (b) (6). In terms of treatment for his COVID-19 infection, he received convalescent plasma, remdesivir and tocilizumab vs placebo trial. Nonetheless, his course continued to worsen, and he was prone on (b) (6). During his time in the ICU he received 3 days of CVVHD. This too was complicated and had to be discontinued dialysis as his filter clotted off. On (b) (6) it was noted that he had developed a superimposed bacterial pneumonia likely due to Pseudomonas aeruginosa and blood culture positive for gram negative rods. On (b) (6) he developed a tension pneumothorax requiring an emergent chest tube placement with ongoing atrial fibrillation with RVR (rate in the 120's). Unfortunately, the patient was found to have tension pneumothorax on the left side, the following day after he dropped his oxygen saturation rapidly. This was improved with needle decompression and insertion of a pigtail catheter. Given his inability to tolerate hemodialysis, as well as his worsening and complicated condition, patient was transitioned to DNR/DNI without further escalation of care as per



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conversation with the patient's family. Care was further de-escalated with removal of pressors, ultimately resulting in the patient's death from multiorgan failure here in the setting of COVID- 19 infection. Patient passed away on (b) (6)

Relevant laboratory/diagnostic tests:

Ventricular tachycardia

Test Date: (b) (6) Notes: 120's

Blood culture

Test Date: (b) (6) Notes: Positive for gram negative rods

The action taken with REMDESIVIR was No change.

The Pharmacist assessed the event of tension pneumothorax as Serious (Death, Medically Significant), causality of Not Related for REMDESIVIR + TOCILIZUMAB vs REMDESIVIR + PLACEBO. The outcome of this event was Fatal

The Pharmacist assessed the event of Pseudomonas aeruginosa bacteremia as Serious (Death, Medically Significant), causality of Not Related for REMDESIVIR + TOCILIZUMAB vs REMDESIVIR + PLACEBO. The outcome of this event was Fatal

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute respiratory failure			UNKNOWN
Bradycardia			UNKNOWN
COVID-19			YES
COVID-19 pneumonia			UNKNOWN
Cardiac failure			UNKNOWN
Chronic kidney disease			UNKNOWN
Coronary artery disease			UNKNOWN



FDA - Adverse Event Reporting System (FAERS)

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Hyperlipidaemia	UNKNOWN
Hypertension	UNKNOWN
Hypoxia	UNKNOWN
Lethargy	UNKNOWN
Oedema	UNKNOWN
Sleep apnoea syndrome	UNKNOWN
Type 2 diabetes mellitus	UNKNOWN
Ventricular extrasystoles	UNKNOWN

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood culture					N
Ventricular tachycardia					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ATIVAN							
2	CEFTRIAZONE			UNK		12-May-2020	13-May-2020	13 DAY
3	CONVALESCENT PLASMA							
4	DOXYCYCLINE			UNK		12-May-2020	14-May-2020	
5	FUROSEMIDE			UNK	Oedema	15-May-2020	16-May-2020	10 DAY
6	HEPARIN			UNK		11-May-2020	17-May-2020	
7	KETAMINE			UNK		15-May-2020	15-May-2020	



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17877952

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
8 MIDAZOLAM			UNK		15-May-2020	15-May-2020	
9 MORPHINE							

Reporter Source:

Study Report?: No

Sender Organization: GILEAD

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17878542

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 08-Apr-2020 Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 10-Jun-2020 Mfr Rcvd Date: 19-May-2020 Mfr Control #:US-ROCHE-2605870 Application #: 125276

Patient Information:

Age: 38 YR Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown	Ongoing: No	COVID-19	08-Apr-2020	26-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA	18 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2605870 is a patient support program case, received on 19/May/2020 from a physician in the USA. It concerns a 38 year old patient (gender unspecified) who was being treated with tocilizumab (Actemra) intentionally used for unlabeled indication (off label use) and was deceased whilst participating in (b) (6)

No medical history, past drugs, concurrent condition and concomitant medications were added.

On (b) (6) the patient was hospitalized due to covid 19. On (b) (6) the patient started therapy with tocilizumab (dosage regimen (b) (6) for covid-19 (off label use: intentional use for unlabeled indication). On (b) (6) the patient was died due to COVID-19. It was unknown if an autopsy was performed or not.

The physician assessed the causality of event deceased as unknown with tocilizumab.



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The company assessed the causality of deceased as not related with tocilizumab. There is no information regarding temporal association between occurrence of event and suspect drug, clinical course of event and circumstances surrounding them supporting plausibility. Patient was also suffering from COVID-19 which is likely to be the cause. Considering the etiological nature of event, rules out reasonable possible causal association with tocilizumab.

No further information were provided.

Additional information was received on 02/Jun/2020 and following information was added: reporter causality updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No **Sender Organization:** ROCHE **503B Compounding
Outsourcing Facility?:**



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17878542

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883177

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** PAK **Event Date:** **Outcomes:** DE, **Application Type:** BLA

FDA Rcvd Date: 11-Jun-2020 **Mfr Rcvd Date:** 09-Jun-2020 **Mfr Control #:** PK-ROCHE-2619064 **Application #:** 125276

Patient Information:

Age: **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		640 MG/	Intravenous (not otherwise specified)	eight injections of 80 mg	COVID-19 pneumonia		
2	ACTEMRA					Oropharyngeal pain		
3	ACTEMRA					Dyspnoea		
4	ACTEMRA					Pyrexia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		Unk	NA	B2090B20				
2	ACTEMRA		Unk	NA	B2090B20				
3	ACTEMRA		Unk	NA	B2090B20				
4	ACTEMRA		Unk	NA	B2090B20				

Event Information:

Preferred Term (MedDRA Ⓐ Version: 23.1)	ReC
Intentional product use issue	NA
Off label use	NA
Oxygen saturation decreased	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883177

Event/Problem Narrative:

AER 2619064 is a spontaneous case, received on 09/Jun/2020 from a consumer in Pakistan. It concerns a 62 years old male patient who died due to drop in oxygen saturation and used tocilizumab (Actemra) for unlabelled indication which is covid- 19 (off label use).

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On an unspecified date, the patient started therapy with intravenous (not otherwise specified) tocilizumab (lot number: B2090B20), 640 mg (frequency not reported) (eight injections of 80 mg) for covid-19 pneumonia unlabelled indication (off label use). He was covid positive and had no travel history. On an unspecified date, his oxygen saturation level dropped and was shifted on ventilator. He was died on ^{(b) (6)} It was unknown if an autopsy was performed or not.

At the time of death, it was not unknown if therapy with tocilizumab was altered or not in response to the drop in oxygen saturation.

The consumer assessed the causality of drop in oxygen saturation as unknown with tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883177

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883279

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ROM Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 11-Jun-2020 Mfr Rcvd Date: 05-Jun-2020 Mfr Control #:RO-ROCHE-2617119 Application #: 125276

Patient Information:

Age: 62 YR Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		400 MG/QD	Unknown	for 2 days, total dose: 800 mg	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2617119 is a spontaneous case, received on 05/Jun/2020 from a physician in Romania. It concerns a 62 year old patient (gender unspecified) who developed off label use, death nos and intentional drug use for unapproved indication whilst being treated with tocilizumab (Roactemra).

The patient's concurrent conditions included intracranial expansive process of corpus callosum, tetraparesis, bilateral pneumonia, essential hypertension, diabetes mellitus type 2 and clostridium difficile colitis. No concomitant medications, past medical history and past drugs were reported.

On an unspecified date, the patient started therapy with tocilizumab (lot number, route not reported) 400 mg daily for 2 days, total dose received was 800 mg for covid-19 infection (off label use) with intentional drug use for unapproved indication. After tocilizumab administration, on an unspecified date, the patient was considered healed (negative for SARS COV-2 infection). On an unreported date, patient died due to



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FOIA Case Report Information

Case ID: 17883279

unknown cause. It was not stated if autopsy was performed or not.

At the time of the death, it was not reported if the therapy with tocilizumab was ongoing or not.

The physician did not report the causality between death nos and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Clostridium difficile colitis			
Essential hypertension			
Pneumonia			
Quadriplegia			
Type 2 diabetes mellitus			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883279

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883333

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: BGD
Event Date: 03-Jun-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 11-Jun-2020
Mfr Rcvd Date: 03-Jun-2020
Mfr Control #: BD-ROCHE-2615550
Application #: 125276

Patient Information:

Age: 67 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		400 MG/	Intravenous (not otherwise specified)		COVID-19	03-Jun-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA	0 Day	Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Intentional product use issue	NA
Off label use	NA
Oxygen saturation decreased	NA

Event/Problem Narrative:

AER 2615550 is a spontaneous case, received on 03/Jun/2020 from a physician in Bangladesh. It concerns a 67 year old male patient who died due to oxygen saturation fall and used tocilizumab (Actemra) for unlabelled indication for covid- 19 (off label use).

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On 03/Jun/2020, the patient started therapy with intravenous (not otherwise specified) tocilizumab (lot number: UNKNOWN), 400 mg (frequency not reported) for covid-19 for unlabelled indication (off label use). On (b) (6) he experienced sudden fall of oxygen saturation. He was tested COVID-19 positive and was provided with the supplemental oxygen and treated in the ICU. IL-6 test was not performed and there was no need for ventilation support. After (b) (6) of administration he died. It was unknown if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883333

At the time of death, it was not unknown if therapy with tocilizumab was altered or not in response to the oxygen saturation fall.

The physician did not report a causality of oxygen saturation fall with tocilizumab.

No further information was provided.

Relevant Medical History:

Unknown

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883333

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883540

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: JPN
Event Date: 17-Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 17-Jun-2020
Mfr Rcvd Date: 10-Jun-2020
Mfr Control #: JP-ROCHE-2617843
Application #: 125276

Patient Information:

Age: 74 YR
Sex: Male
Weight: 70 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		560 MG/QD	Intravenous drip		COVID-19 pneumonia	17-Apr-2020	17-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA	0 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Off label use	NA
Product use in unapproved indication	NA
Pyrexia	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883540

Event/Problem Narrative:

AER 2617843 is a spontaneous case, received from a pharmacist at Chugai on 04/Jun/2020 and at Roche on 09/Jun/2020 in Japan. It concerns a 74 year old male patient who used tocilizumab (Actemra) for unapproved indication and developed pyrexia later he died due to unknown cause.

Concurrent conditions included hypertension and hyperlipidaemia. Concomitant medications included favipiravir. No medical history and past drugs were reported.

On 10/Apr/2020, the patient diagnosed with pneumonia associated with coronavirus disease (COVID-19). On (b) (6) he was admitted to the reporting hospital. An endotracheal intubation was performed and his respiration was controlled by a ventilator. On (b) (6) respiratory status was aggravated. He started therapy with intravenous drip tocilizumab 560 mg, daily (lot number: UNKNOWN) for pneumonia associated with coronavirus disease (COVID-19) (off label use). On (b) (6) the status remained unchanged. On (b) (6) respiratory status was aggravated. On (b) (6) he developed pyrexia. On (u) (6) he died due to viral COVID-19 pneumonia. It was unknown if an autopsy was performed or not.

At the time of death, the outcome of the pyrexia was reported as unknown. It was unknown if therapy with tocilizumab was ongoing.

The pharmacist assessed death and pyrexia as not related to tocilizumab.

Further information has been requested.

Additional information received at Chugai on 10/Jun/2020 and at Roche on 16/Jun/2020. The following information was added to this case: added concomitant medication (favipiravir), updated cause of death (viral COVID-19 pneumonia) and event description accordingly.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Hyperlipidaemia			YES	
Hypertension			YES	
Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883540

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	FAVIPIRAVIR		Unknown	Dosage is uncertain.	COVID-19	13-Apr-2020	27-Apr-2020	4 DAY

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883989

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ROM
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 11-Jun-2020
Mfr Rcvd Date: 05-Jun-2020
Mfr Control #: RO-ROCHE-2617366
Application #: 125276

Patient Information:

Age: 78 YR
Sex:
Weight: 110 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		800 MG/	Unknown	400 mg/daily for 2 days	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2617366 is a spontaneous case, received on 05/Jun/2020 from a physician in Romania and concerns a 78 year old patient of an unspecified gender who intentional use drug for unapproved indication (off label use) and died whilst being treated with tocilizumab (Roactemra).

The Patient's concurrent conditions included acute respiratory failure, broncho pneumonia, hypertension, grade 3, diabetes type 2, obesity grade 2, acute renal dysfunction, cholestasis syndrome and acute enterocolitis. No past medical history, past drugs and concomitant medications were reported.

On an unknown date, the patient started therapy with tocilizumab (lot number: UNKNOWN), 400 mg/daily for 2 days, total dose received was 800 mg (route and frequency not reported) for sars cov 2 infection. On an unknown date, the patient intentionally use drug for unapproved indication (off label use). Also reported that, on unspecified date, the patient died due to unknown cause. It was not reported if an autopsy was



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883989

performed or not.

The physician did not report a causality between death and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute respiratory failure			
Cholestasis			
Enterocolitis			
Hypertension			
Obesity			
Pneumonia			
Renal impairment			
Type 2 diabetes mellitus			

Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17883989

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17884171

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ROM Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 11-Jun-2020 Mfr Rcvd Date: 05-Jun-2020 Mfr Control #:RO-ROCHE-2617248 Application #: 125276

Patient Information:

Age: 69 YR Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		800 MG/QD	Unknown	400mg daily dose for two days	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2617248 is a spontaneous case, received on 05/Jun/2020 from a physician in Romania. It concerns a 69 year old patient (gender unspecified) who died and had tocilizumab (Roactemra) intentional use for unapproved indication (off label use).

The patients concurrent conditions included acute respiratory distress syndrome, viral pneumonia, left multiple rib fractures, left drained post-hemothorax status, paroxysmal atrial fibrillation, insulin-treated type II diabetes, grade i obesity, left humerus fracture and odontoid fracture without displacement. No concomitant medication, medical history or past drugs were reported.

On an unspecified date, the patient started therapy with tocilizumab (lot number: unknown) (route not reported), form strength of 400 mg daily dose for two days, 800 mg for sars-cov-2 infection (intentional use for unapproved indication- off label use). On an unspecified date, the patient died. It was not reported if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17884171

The reporter did not report a causality between death nos and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Acute respiratory distress syndrome			YES	
Atrial fibrillation			YES	
Cervical vertebral fracture			YES	
Humerus fracture			YES	
Obesity			YES	
Pneumonia viral			YES	
Rib fracture			YES	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17884171

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17884243

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ROM
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 11-Jun-2020
Mfr Rcvd Date: 05-Jun-2020
Mfr Control #: RO-ROCHE-2617369
Application #: 125276

Patient Information:

Age: 61 YR
Sex:
Weight: 120 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		400 MG/BID	Unknown	400 mg twice daily	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Off label use	NA
Product use in unapproved indication	NA

Event/Problem Narrative:

AER 2617369 is a spontaneous case, received on 05/Jun/2020 from a physician in Romania. It concerns a 61 year old patient of unspecified gender who died (nos), whilst being treated with tocilizumab (Roactemra) (off label use).

Patient's concurrent conditions included sars cov-2 infection, ards (acute respiratory distress syndrome), obesity, type ii diabetes, bronchopneumonia, cardiovascular failure, myocardial infarction, chronic heart failure.No medical history, past drugs or concomitant medications were reported.

On unknown date, hospital admission, patient had the following diagnostics: SARS CoV 2 infection, ARDS (Acute respiratory distress syndrome), grade II Obesity, type II Diabetes, Bronchopneumonia, Cardiovascular failure, Old anterior-external Myocardial infarction and NYHA class II chronic heart failure. On an unknown date, the patient started therapy with tocilizumab (route and lot number: not reported) at 400 mg twice daily (total dose received was 800 mg) for 2 days for sars cov-2 infection as for unlabeled indication (off label use). On an



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17884243

unknown date, the patient died (nos). The exact cause of death was not mentioned. It was not stated if autopsy was performed or not.

At the time of death, It was not reported if therapy with tocilizumab was maintained or not.

The physician did not assessed the causality between death (nos) with tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute respiratory distress syndrome			
COVID-19			
Cardiac failure			
Cardiac failure chronic			
Myocardial infarction			
Obesity			
Pneumonia			
Type 2 diabetes mellitus			

Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17884243

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17884300

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: MEX
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 11-Jun-2020
Mfr Rcvd Date: 04-Jun-2020
Mfr Control #: MX-ROCHE-2617547
Application #: 125276

Patient Information:

Age:
Sex: Female
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Cardiac failure	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2617547 is a spontaneous case, received on 04/Jun/2020 from a consumer in Mexico. It concerns a female patient of an unspecified age who had a heart failure and tocilizumab (Roactemra) intentional use for unapproved indication (off label use).

No medical history, past drugs, concurrent conditions or concomitant medications were reported.

On an unknown date, the patient received therapy with tocilizumab (lot number, frequency, dose, route: not reported) for covid-19. On an unknown date, she had a heart failure (roactemra intentional use for unapproved indication, off label use). She died on (b) (6). It was not reported if an autopsy was performed or not. It was reported that there was no product and that day. However, this disease required administration of the drug as soon as possible since it was vital to administer it as soon as possible. And the bottle was obtained for the time being and reported that as she indicated that he had part of the treatment and was not contacted. On (b) (6) the primary reporter indicated that the relative (patient) died. She was administered two doses of the drug and in principle everything was fine but her heart did not



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17884300

hold. She had heart failure (cause of death) even with the administration of the medication. It was considered as the latest received date on (b) (6) because until that moment it was reported that she used the medication.

At the time of death, the therapy with tocilizumab was maintained.

The consumer did not report a causality between heart failure and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17884300

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17885880

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: PAK
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 11-Jun-2020
Mfr Rcvd Date: 09-Jun-2020
Mfr Control #: PK-ROCHE-2618987
Application #: 125276

Patient Information:

Age:
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		600 MG/	Intravenous (not otherwise specified)	three injections of 200 mg Actemra	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2618987 is a spontaneous case, received on 09/Jun/2020 from a consumer in Pakistan. It concerns a 47 years male patient who intentionally used tocilizumab for unlabeled indication (off label use) and died whilst being treated with tocilizumab (Actemra).

No medical history, past drug, concurrent condition and concomitant medication were reported.

On an unknown date, the patient started therapy with intravenous (IV) tocilizumab (lot number and frequency not provided) 600 mg (three injection of 200 mg tocilizumab) for covid-19 infection [intentional use for unlabeled indication (off label use)]. It was reported that, he tested with covid-19 positive and was provided with the ventilator support prior to administration of tocilizumab. Next day his condition was deteriorated and he died on unknown date. It was unknown autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17885880

The reporter assessed the causality of death as unknown to tocilizumab.

No further information was performed.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17885880

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17886220

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ROM
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 11-Jun-2020
Mfr Rcvd Date: 05-Jun-2020
Mfr Control #: RO-ROCHE-2617078
Application #: 125276

Patient Information:

Age: 26 YR
Sex:
Weight: 120 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Off label use	NA
Product use in unapproved indication	NA

Event/Problem Narrative:

AER 2617078 is a spontaneous case, received on 05/Jun/2020 from a physician in Romania. It concerns a 26 year old patient (unspecified gender) who used actemra for unlabelled indication and died whilst being treated with tocilizumab (Roactemra).

The patient's concurrent conditions included bilateral pneumonia, acute respiratory and cardiocirculatory Insufficiency, high blood pressure, obesity gr III, buttock-operated phlegmon, manifestations of suicidal Intentions and SARS COV -2 infection. No concomitant medications were reported. No medical history, past drugs were reported.

On an unknown date, the patient started therapy with tocilizumab (lot number, route, dose, frequency not reported) for sars cov-2 infection(off label use). Patient received 400 mg daily, for 2 days. The total dose received was 800 mg. On an unknown date, patient died due to unknown reasons. It was unknown if autopsy was performed.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17886220

At the time of death, it was unknown if the therapy with tocilizumab was altered.

The physician did not report a causality between death and tocilizumab.

No further information was provided.

Relevant Medical History:

Buttock-Operated Phlegmon, CARDIOCIRCULATORY INSUFFICIENCY

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute respiratory failure			
COVID-19			
Hypertension			
Obesity			
Pneumonia			
Suicidal ideation			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17886220

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17887554

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 31-Mar-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 12-Jun-2020 Mfr Rcvd Date: 05-Jun-2020 Mfr Control #: ES-ROCHE-2616496 Application #: 125276

Patient Information:

Age: 26 YR Sex: Female Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		600 MG/1X	Intravenous (not otherwise specified)	600 MG	Severe acute respiratory syndrome	29-Mar-2020	29-Mar-2020
2	AZITROMICINA		500 MG/QD	Oral	500 MG DIA	COVID-19 pneumonia	23-Mar-2020	24-Mar-2020
3	DEXAMETASONA [DEXAMETHASONE]		20 MG/QD	Intravenous (not otherwise specified)	20 MG DIA	Product used for unknown indication	28-Mar-2020	01-Apr-2020
4	DEXKETOPROFENO [DEXKETOPROFEN]		25 MG/Q8H	Intravenous (not otherwise specified)	25 MG CADA 8 HORAS	Product used for unknown indication	27-Mar-2020	01-Apr-2020
5	ENOXAPARINA		40 MG/QD	Subcutaneous	40MG DIA	Product used for unknown indication	27-Mar-2020	01-Apr-2020
6	HIDROXICLOROQUINA SULFATO		400 MG/QD	Oral	400 MG DIA	COVID-19 pneumonia	23-Mar-2020	01-Apr-2020
7	TOCILIZUMAB					COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	3 Day	NA	NA	ASKED BUT UNKNOWN				
2	AZITROMICINA	9 Day	NA	NA	UNKNOWN				
3	DEXAMETASONA [DEXAMETHASONE]	4 Day	NA	NA	UNKNOWN				
4	DEXKETOPROFENO [DEXKETOPROFEN]	5 Day	NA	NA	UNKNOWN				
5	ENOXAPARINA	5 Day	NA	NA	UNKNOWN				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17887554

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC	
6 HIDROXICLOROQUINA SULFATO	9 Day	NA	NA	UNKNOWN					
7 TOCILIZUMAB	3 Day	NA	NA	ASKED BUT UNKNOWN					

Event Information:

Preferred Term (MedDRA Version: 23.1)

ReC

Coagulopathy

NA

Event/Problem Narrative:

AER 2616496 is a spontaneous case, received on 05/Jun/2020 from a physician in Spain via Evhuman (reference number: ESAEMPS628824). It concerns a 26 year old female patient who died due to coagulopathy whilst being treated with dexamethasone, enoxaparin sodium (Enoxaparina), tocilizumab, dexketoprofen (Dexketoprofeno), hydroxychloroquine sulfate (Hidroxiclороquina Sulfato), azithromycin (Azitromicina).

Medical history included c-section. No past drugs, concurrent conditions and concomitant medications were reported.

On 23/Mar/2020, the patient started therapy with oral hydroxychloroquine sulfate 400 mg, once a day for covid-19 pneumonia, oral azithromycin 500 mg, once a day for covid-19 pneumonia. On 27/Mar/2020, the patient started therapy with subcutaneous enoxaparin sodium 40 mg, once a day for drug use for unknown indication, intravenous dexketoprofen 25 mg, once in 8 hrs for drug use for unknown indication. On 28/Mar/2020, the patient started therapy with intravenous dexamethasone 20 mg, once a day for drug use for unknown indication. On 29/Mar/2020, the patient started therapy with intravenous tocilizumab (lot number: ASKED BUT UNKNOWN), 600 mg, once a total for severe acute respiratory syndrome. On 31/Mar/2020, the patient developed coagulopathy. Therapy with enoxaparin sodium, tocilizumab, azithromycin, dexamethasone, dexketoprofen, hydroxychloroquine sulfate was withdrawn. She died due to for covid-19 and multiple organ failure on (b) (6). It was unknown if an autopsy was performed or not.

The physician did not report a causality between coagulopathy and dexamethasone, enoxaparin sodium, tocilizumab, dexketoprofen, hydroxychloroquine sulfate, azithromycin.

No further information was provided.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17887554

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Caesarean section	(b) (6)	(b) (6)	

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888179

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 03-Apr-2020 Outcomes: DE,OT, Application Type: BLA

FDA Rcvd Date: 12-Jun-2020 Mfr Rcvd Date: 05-Jun-2020 Mfr Control #: ES-ROCHE-2616531 Application #: 125276

Patient Information:

Age: 62 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		600 MG/1X	Intravenous (not otherwise specified)	600 MG	COVID-19 pneumonia	27-Mar-2020	27-Mar-2020
2	AZITROMICINA			Oral	500 MG DIA	COVID-19 pneumonia	27-Mar-2020	01-Apr-2020
3	CEFTRIAXONA [CEFTRIAZONE]		2 G/	Intravenous (not otherwise specified)	2 GR DIA	Product used for unknown indication	27-Mar-2020	01-Apr-2020
4	DEXAMETASONA [DEXAMETHASONE]		20 MG/	Intravenous (not otherwise specified)	20 MG	COVID-19	29-Mar-2020	01-Apr-2020
5	ENOXAPARINA			Subcutaneous	80 MG	Thrombosis prophylaxis	01-Apr-2020	03-Apr-2020
6	HYDROXYCHLOROQUIN E		400 MG/	Oral	400 MG DIA	COVID-19 pneumonia	27-Mar-2020	02-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	13 Day	Yes	NA	UNKNOWN				
2	AZITROMICINA	13 Day	Yes	NA	UNKNOWN				
3	CEFTRIAXONA [CEFTRIAZONE]	13 Day	Yes	NA	UNKNOWN				
4	DEXAMETASONA [DEXAMETHASONE]	11 Day	Yes	NA	UNKNOWN				
5	ENOXAPARINA	8 Day	Yes	NA	UNKNOWN				
6	HYDROXYCHLOROQUIN E	13 Day	Yes	NA	UNKNOWN				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888179

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
Anaemia	NA
Hypocoagulable state	NA
Hypofibrinogenaemia	NA
Thrombocytopenia	NA

Event/Problem Narrative:

AER 2616531 is a spontaneous case, received on 05/Jun/2020 from a physician in Spain via health authority spain (AEMPS (Spanish Agency of Medicines and Medical Devices) ESAEMPS628603) and the European Medicines Agency (EMA). It concerns a 62 year old male patient who developed thrombocytopenia, hypofibrinogenemia, anaemia and hypocoagulable state whilst being treated with tocilizumab (Roactemra), hydroxychloroquine (Hydroxychloroquine), dexamethasone (Dexametasona), azithromycin (Azitromicina), ceftriaxone (Ceftriaxona) and enoxaparin sodium (Enoxaparina).

No medical history, past drug, concurrent condition and concomitant medication were reported.

On 27/Mar/2020, the patient started therapy with intravenous tocilizumab (lot number: unknown) at 600 mg total, oral hydroxychloroquine (lot number: unknown) at 400 mg every 24 hours, oral azithromycin (lot number: unknown) at 500 mg (frequency not reported) for covid-19 pneumonia and intravenous ceftriaxone (lot number: unknown) at 2 g every 24 hours for an unknown indication. On 29/Mar/2020, he started therapy with intravenous dexamethasone (lot number: unknown) at 20 mg every 24 hours for SARS-COV-2 acute respiratory disease. On 01/Apr/2020, he started therapy with subcutaneous enoxaparin sodium (lot number: unknown, frequency not reported) at 80 mg for thromboembolism prophylaxis. On 03/Apr/2020, he developed hypofibrinogenemia and hypocoagulable state. On 08/Apr/2020, he developed thrombocytopenia. On 14/Apr/2020, he developed anaemia. The dose of dexamethasone and enoxaparin sodium was reduced in response to the thrombocytopenia, hypofibrinogenemia, anaemia, hypocoagulable state. Therapy with ceftriaxone, tocilizumab, azithromycin and hydroxychloroquine was withdrawn in response to the thrombocytopenia, hypofibrinogenemia, anaemia, hypocoagulable state. On 03/Apr/2020, the hypofibrinogenemia resolved. On 10/Apr/2020, the hypocoagulable state resolved. He died on ^{(b) (6)} due to respiratory insufficiency.

At the time of the report, thrombocytopenia and anaemia was persisting.

The physician did not report a causality of events thrombocytopenia, hypofibrinogenemia, anaemia and hypocoagulable state with tocilizumab, hydroxychloroquine, dexamethasone, azithromycin, ceftriaxone, enoxaparin sodium.

The company assessed events thrombocytopenia, hypofibrinogenemia, anaemia and hypocoagulable state as medically significant.

No further information was available.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888179

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No Sender Organization: ROCHE 503B Compounding Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888202

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ROM
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 12-Jun-2020
Mfr Rcvd Date: 05-Jun-2020
Mfr Control #: RO-ROCHE-2617361
Application #: 125276

Patient Information:

Age: 55 YR
Sex:
Weight: 60 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		400 MG/QD	Unknown	400mg daily dose for two days	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2617361 is a spontaneous case, received on 05/Jun/2020 from a physicianvia company representative in Romania. It concerns a 55 year old patient of unspecified gender who died due to unknown reason whilst being treated with tocilizumab (Roactemra) drug intentionally used for unapproved indication (off label use).

Concurrent conditions included acute respiratory failure, pneumonia, dilated heart disease, chronic heart failure, chronic obstructive pulmonary disease, acute heart failure, Acute left subdural hematoma by unspecified mechanism, NYHA class III. No concomitant medications, medical history and past drugs were reported.

On an unknown date, the patient started therapy with tocilizumab 400 mg daily dose for two days (lot number and route not reported) for sars cov 2 infection (drug intentionally used for unapproved indication - off label use). The total dose received was 800 mg. On an unknown date, the patient died due to unknown reason. It was not reported if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888202

At the time of patients death, it was not reported if the therapy with tocilizumab was ongoing or not.

The physician did not report a causality between death nos and tocilizumab.

No further information was provided.

Relevant Medical History:

Acute left subdural hematoma by unspecified mechanism, NYHA class III

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute respiratory failure			YES
Cardiac failure acute			YES
Cardiac failure chronic			YES
Chronic obstructive pulmonary disease			YES
Congestive cardiomyopathy			YES
Pneumonia			YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888202

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888264

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ROM Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 12-Jun-2020 Mfr Rcvd Date: 05-Jun-2020 Mfr Control #:RO-ROCHE-2617189 Application #: 125276

Patient Information:

Age: 26 YR Sex: Weight: 130 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		800 MG/	Unknown	400 mg daily dose for two days	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2617189 is a spontaneous case, received on 05/Jun/2020 from a physician in Romania. It concerns a 26 year old patient (gender unspecified) who experienced drug intentional use for unlabeled indication, off label use and died (death) whilst being treated with tocilizumab (Roactemra).

Concurrent conditions included obesity grade ii, hepatocytolysis syndrome, acute respiratory failure. No medical history, past drugs and concomitant medications were reported.

On an unknown date, the patient started therapy with tocilizumab (lot number: unknown) 800 mg 400 mg daily dose for two days (route and frequency not reported) for sars cov 2 infection. On an unknown date, experienced drug intentional use for unlabeled indication, off label use and died (death). The patient died on an unknown date. The cause of death was unknown. It was not reported if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888264

At the time of death, It was not reported if therapy with tocilizumab was ongoing or not.

The physician did not report the causality of death with tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute respiratory failure			YES
Hepatocellular injury			YES
Obesity			YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888264

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888592

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 02-Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 12-Jun-2020
Mfr Rcvd Date: 04-Jun-2020
Mfr Control #: US-ROCHE-2616462
Application #: 125276

Patient Information:

Age: 69 YR
Sex: Male
Weight: 115 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		800 MG/	Intravenous (not otherwise specified)	once	COVID-19 pneumonia	25-Mar-2020	25-Mar-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA	8 Day	Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Acute kidney injury	NA
Anaemia	NA
Cardiac arrest	NA
Hyperkalaemia	NA
Hypernatraemia	NA
Intentional product use issue	NA
Multiple organ dysfunction syndrome	NA
Off label use	NA
Pneumonia bacterial	NA
Pulmonary mycosis	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888592

Event/Problem Narrative:

AER 2616462 is a spontaneous case, received on 04/Jun/2020 from a pharmacist in USA. It concerns a 69 year old male patient who was treated with tocilizumab (Actemra) intentionally for unapproved indication (off label use) and had cardiac arrest, hyperkalemia, anemia, multiorgan failure, super infected with fungal (super infection lung), super infected with bacterial pneumonia (super infection lung), acute kidney injury and hypernatremia.

The patient's concomitant medication included remdesivir. His medical history, past drugs and concurrent conditions were not reported.

On 25/Mar/2020, the patient started therapy with intravenous tocilizumab (form: not reported) (lot number: not reported) 800 mg, once for COVID-19 pneumonia (off label use). On (b) (6) he experienced cardiac arrest, multiorgan failure, super infected with fungal (super infection lung), super infected with bacterial pneumonia (super infection lung) and acute kidney injury. On an unknown date, he developed hypernatremia, hyperkalemia and anemia. He was tested positive for COVID-19 test and chest CT or X-Ray was also done for him which showed extensive infiltrates bilaterally, he was in ICU on supplementary oxygen therapy. On an unknown date, he died. It was unknown if an autopsy was performed or not.

At the time of death, it was not reported if therapy with tocilizumab ongoing or not.

The reporter assessed the causality related of super infected with fungal (super infection lung) and Super infected with bacterial pneumonia (super infection lung) and tocilizumab. The reporter assessed the causality not related of cardiac arrest, multiorgan failure, acute kidney injury, hypernatremia and hyperkalemia, anemia and tocilizumab.

No further information was provided.

This case is cross-referenced with AER 2616436, same reporter.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888592

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Computerised tomogram thorax					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	REMDESIVIR		Unknown					

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888635

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ROM Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 12-Jun-2020 Mfr Rcvd Date: 05-Jun-2020 Mfr Control #:RO-ROCHE-2617367 Application #: 125472

Patient Information:

Age: 64 YR Sex: Weight: 75 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		800 MG/QD	Subcutaneous	400 mg daily, for 2 days	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Off label use	NA
Product use in unapproved indication	NA

Event/Problem Narrative:

AER 2617367 is a spontaneous case, received on 05/Jun/2020 from a physician in Romania. It concerns a 64 year old patient (gender unspecified) who died and intentionally used drug for unapprove dindication as off label use whilst being treated with tocilizumab (Roactemra).

Patient's concurrent conditions included type II diabetes mellitus, hypertension grade II with high additional risk, left intracranial expansive process, postoperative meningitis, eschar gr II in the sacral area and SARS COV -2 infection. No medical history, past drugs and concomitant medications were reported.

On an unknown date, the patient started therapy with subcutaneous tocilizumab (lot number: unknown) at total doe of 800 mg (400 mg daily), for 2 days for SARS COV-2 infection (intentionally used as off label use (local SmPC does not specify COVID 19 infection as an indication for tocilizumab)). On an unknown date, the patient died. The exact cause of death was not mentioned, not if autopsy was performed or not. The reporting physician did not agree to complete tocilizumab AE form for COVID 19.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888635

The physician did not report a causality between death and tocilizumab.

No further information was provided.

Relevant Medical History:

SARS COV -2 infection
eschar gr II in the sacral area
postoperative meningitis
Left Intracranial Expansive Process

Disease/Surgical Procedure

Hypertension

Type 2 diabetes mellitus

Start Date

End Date

Continuing?

Medical History Product(s)

Start Date

End Date

Indications

Events

Relevant Laboratory Data:

Test Name

Result

Unit

Normal Low Range

Normal High Range

Info Avail

Concomitant Products:

Product Name

Dose/
Frequency

Route

Dosage Text

Indications(s)

Start Date

End Date

Interval 1st
Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17888635

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17889550

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ESP
Event Date: 02-Apr-2020
Outcomes: DE,HO,
Application Type: BLA
FDA Rcvd Date: 12-Jun-2020
Mfr Rcvd Date: 05-Jun-2020
Mfr Control #: ES-ROCHE-2616887
Application #: 125276

Patient Information:

Age: 72 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		600 MG/1X	Unknown		Acute respiratory distress syndrome	27-Mar-2020	27-Mar-2020
2	HIDROXICLOROQUINA SULFATO		400 MG/QD	Oral	400 MG DIA	COVID-19 pneumonia	26-Mar-2020	02-Apr-2020
3	LINEZOLID		600 MG/Q12H	Intravenous (not otherwise specified)	600MG/12H	Product used for unknown indication	28-Mar-2020	16-Apr-2020
4	MEROPENEM		1 G/Q8H	Intravenous (not otherwise specified)	1GR /8H	Product used for unknown indication	04-Apr-2020	19-Apr-2020
5	METAMIZOLE		2 G/Q8H	Intravenous (not otherwise specified)	2 GR C/8H	Product used for unknown indication	13-Apr-2020	16-Apr-2020
6	PIPERACILINA - TAZOBACTAM		1 DF/Q8H	Intravenous (not otherwise specified)	C/8H	Product used for unknown indication	04-Apr-2020	07-Apr-2020
7	ROACTEMRA					COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	21 Day	Yes	NA	UNKNOWN				
2	HIDROXICLOROQUINA SULFATO	22 Day	Yes	NA	UNKNOWN				
3	LINEZOLID	20 Day	Yes	NA	UNKNOWN				
4	MEROPENEM	13 Day	Yes	NA	UNKNOWN				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17889550

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC	
5 METAMIZOLE	4 Day	Yes	NA	UNKNOWN					
6 PIPERACILINA - TAZOBACTAM	13 Day	Yes	NA	UNKNOWN					
7 ROACTEMRA	21 Day	Yes	NA	UNKNOWN					

Event Information:

Preferred Term (MedDRA Version: 23.1)

ReC

Drug reaction with eosinophilia and systemic symptoms

NA

Hypofibrinogenaemia

NA

Upper gastrointestinal haemorrhage

NA

Event/Problem Narrative:

AER 2616887 is a spontaneous case, received on 05/Jun/2020 from a physician in Spain via health authority (Agencia Espanola de Medicamentos y Productos Sanitarios (reference number: ES-AEMPS-627000) and European medical agency (EMA). It concerns a 72 year old male patient who developed dress syndrome, upper gastrointestinal hemorrhage and hypofibrinogenemia whilst being treated with meropenem (Meropenem), tocilizumab (Roactemra), piperacillin sodium;tazobactam sodium (Piperacilina - Tazobactam), metamizole (Metamizole), hydroxychloroquine sulfate (Hidroxyclo-roquina Sulfato) and linezolid.

The patient's medical history, past drug, concurrent condition and concomitant medications were not reported.

On 26/Mar/2020, the patient started therapy with oral hydroxychloroquine sulfate (lot number: unknown) 400 mg, once in a day. On 27/Mar/2020, he started therapy with tocilizumab (lot number: unknown), 600 mg (route not reported) for adult respiratory stress syndrome. On 28/Mar/2020, he started therapy with intravenous linezolid (lot number: unknown) 600 mg,once in 12 hours for drug use for unknown indication. On 02/Apr/2020, he developed hypofibrinogenemia. On 03/Apr/2020, the hypofibrinogenemia resolved. On 04/Apr/2020, he started therapy with intravenous meropenem (lot number: unknown) 1 g once in 8 hours for product used for unknown indication, intravenous piperacillin sodium;tazobactam sodium (lot number: unknown) 1 DF, once per 8 hour for drug use for unknown indication. On 13/Apr/2020, he started therapy with intravenous metamizole (lot number: unknown), 2 g once in 8 hours for drug use for unknown indication. On ^{(b) (6)} the patient developed dress syndrome and upper gastrointestinal hemorrhage and he was hospitalised. On ^{(b) (6)} he was died due to COVID 19 pneumonia and septic shock. It was not reported if autopsy was performed or not.

At the time of death, dress syndrome was persisting, while upper gastrointestinal hemorrhage was improving. Therapy with meropenem,



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17889550

tocilizumab, piperacillin sodium;tazobactam sodium, metamizole, hydroxychloroquine sulfate and linezolid was withdrawn in response to the dress syndrome, upper gastrointestinal hemorrhage and hypofibrinogenemia.

The physician did not report a causality between dress syndrome, upper gastrointestinal hemorrhage and hypofibrinogenemia with meropenem, tocilizumab, piperacillin sodium;tazobactam sodium, metamizole, hydroxychloroquine sulfate and linezolid.

No further information were reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17889550

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17890000

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 15-Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 12-Jun-2020
Mfr Rcvd Date: 19-May-2020
Mfr Control #: US-ROCHE-2605847
Application #: 125276

Patient Information:

Age: 59 YR
Sex: Female
Weight: 86 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		200 MG/1X	Intravenous (not otherwise specified)		Acute respiratory failure	13-Apr-2020	13-Apr-2020
2	ACTEMRA		560 MG/1X	Intravenous (not otherwise specified)			13-Apr-2020	13-Apr-2020
3	ACTEMRA		400 MG/1X	Intravenous (not otherwise specified)		Coronavirus infection	13-Apr-2020	13-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		Unk	NA	UNKNOWN,UNKNOWN,UNKNOWN				
2	ACTEMRA		Unk	NA	UNKNOWN,UNKNOWN,UNKNOWN				
3	ACTEMRA		Unk	NA	UNKNOWN,UNKNOWN,UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Cholecystitis	NA
Intentional product use issue	NA
Liver function test increased	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17890000

Off label use	NA
Pancreatitis	NA
Renal failure	NA
Thrombocytopenia	NA

Event/Problem Narrative:

AER 2605847 is a patient support program case, received on 19/May/2020 from a physician via pharmacist in USA. It concerns a female patient (age not reported) (patient number: (b) (6)) who was intentionally treated with tocilizumab (Actemra) for an unlabeled indication (off label use) and developed thrombocytopenia, renal failure, increased liver function test, cholecystitis, pancreatitis while participating in (b) (6)

The patient's concurrent conditions included hypertension. Concomitant medications included azithromycin, hydroxychloroquine, ceftriaxone, and oxygen. No medical history and past drug were reported.

On 02/Apr/2020, the patient underwent chest x ray which resulted in increased core space spacines and was tested positive for covid-19. (b) (6)

(b) (6)

(b) (6)

(b) (6)

. On 15/Apr/2020, she underwent some laboratory test and it resulted in increased liver function tests. On (b) (6) she developed cholecystitis and pancreatitis. On (b) (6) she developed thrombocytopenia and renal failure. She was treated in an ICU and was on ventilator support for coronavirus infection. On (b) (6) she died due to thrombocytopenia, renal failure, increased liver function test, cholecystitis and pancreatitis. It was unknown if the autopsy was performed or not.

At the time of death, it was unknown if the therapy with tocilizumab was ongoing or not.

The reporter assessed the causality of the event renal failure as unrelated while that of thrombocytopenia, increased liver function test, cholecystitis and pancreatitis as related with tocilizumab.

The company assessed the causality of the events fatal (thrombocytopenia, renal failure, increased liver function test, cholecystitis and pancreatitis) as unrelated with tocilizumab. Hyperinflammatory response to the covid-19 infection can be responsible for causing organ damage. Organ failure is the most common complication of COVID-19 pneumonia which contributed to disease progression and lead to death. As per the safety profile, the events are not expected to occur with tocilizumab. Tocilizumab is a recombinant humanized monoclonal antibody of the immunoglobulin IgG1 subclass which acts on interleukin 6 receptors. Also, only single dose of tocilizumab was administered. Patient's elderly age, underlying condition and her concurrent conditions of hypertension might be the other confounding factors. The causality can be reassessed later as per updated information received.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17890000

Additional information was received on 04/Jun/2020. the following information was added to the case. Primary reporter (pharmacist), patient's weight (86 kg), concurrent condition (hypertension), concomitant medication (azithromycin, hydroxychloroquine, ceftriaxone, and oxygen), events (thrombocytopenia, renal failure, increased liver function test, cholecystitis, pancreatitis), cause of death (thrombocytopenia, renal failure, increased liver function test, cholecystitis, pancreatitis), date of death (b) (6)) and event description updated accordingly.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
SARS-CoV-2 test					N
Chest X-ray					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	AZITHROMYCIN	500 MG/QD	Unknown		COVID-19	02-Apr-2020	07-Apr-2020	13 DAY
2	Ceftriaxone	1 G/QD	Unknown		COVID-19	02-Apr-2020	04-Apr-2020	13 DAY
3	Ceftriaxone	2 G/QD	Unknown			05-Apr-2020	10-Apr-2020	13 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17890000

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
4	HYDROXYCHLOROQUIN E		Unknown	400 mg x 1 then 200 mg BID	COVID-19	05-Apr-2020	09-Apr-2020	10 DAY
5	OXYGEN							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17890402

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: PHL
Event Date: 11-Jun-2020
Outcomes: DE,OT,
Application Type: BLA
FDA Rcvd Date: 12-Jun-2020
Mfr Rcvd Date: 11-Jun-2020
Mfr Control #: PH-ROCHE-2620741
Application #: 125276

Patient Information:

Age: 73 YR
Sex: Male
Weight: 90 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		400 MG/	Intravenous (not otherwise specified)	1 dose of 400mg once	COVID-19	06-Jun-2020	06-Jun-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA	5 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Off label use	NA

Event/Problem Narrative:

AER 2620741 is a spontaneous case, received on 11/Jun/2020 from a physician in Philippines. It concerns a 73 year old male patient who died whilst being treated with tocilizumab (Actemra) for unlabeled indication (off label use).

The patient's concurrent conditions included hypertension, diabetes. No medical history, past drugs or concomitant medications were reported.

On an unspecified date, his chest X-ray showed bronchopneumonia in both lungs, IL-6 tests were performed and COVID-19 test gave positive result. On (b) (6) the patient started therapy with intravenous (not otherwise specified) tocilizumab (lot number: not reported), 400 mg, 1 dose of 400mg once for COVID -19.He was being treated in ICU and required use of dialysis. CBC, ABG, d-dimer, SGPT, procalcitonin, urea, creatinine, uric acid and electrolyte tests were performed to evaluate clinical course of COVID-19. He was also given supplemental oxygen therapy, On (b) (6) he died due to COVID-19. It was not reported if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17890402

The physician assessed the death as not related to tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Diabetes mellitus			
Hypertension			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Coronavirus test					N
Chest X-ray					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17890402

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17890478

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ROM
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 16-Jun-2020
Mfr Rcvd Date: 11-Jun-2020
Mfr Control #: RO-ROCHE-2594390
Application #: 125276

Patient Information:

Age: 71 YR
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		400 MG/	Unknown	2 RoActemra administrations, with dose: 400 mg	COVID-19	24-Apr-2020	25-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2594390 is a spontaneous case, received on 27/Apr/2020 from a pharmacist in Romania. It concerns a 71 year old patient (gender unspecified) who administered tocilizumab (Roactemra) intentionally for unlabelled indication as off label use, death nos.

No past history and past drugs were reported. Concurrent conditions included sars-cov-2 infection, bilateral pneumonia and severe acute respiratory distress syndrome. Concomitant medications included methylprednisolone sodium succinate (Solumedrol).

On 21/Apr/2020, polymerase chain reaction test was done that revealed sars-cov-2 infection. On 22/Apr/2020, labs were performed that revealed SpO2/IH 74%. On 23/Apr/2020, labs done were; SpO2/IH 70%, IL6- 86, PCR- 152, section- 0.13, body temperature- 38.8, ferritin- 1168, platelet count- 225000, D-dimer- 0.97. On 24/Apr/2020, the patient started therapy with tocilizumab (lot number:unknown) 400mg (frequency and route not reported) (3 tocilizumab administrations with dose 400 mg) for sars-cov-2 infection (intentionally as off label use). On the same date labs were; SpO2/IH 120-180%, H score was 77, PCR- 162, section- 0.3, body temperature- 38.8, ferritin- 1050, platelet



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17890478

count- 278000, D-dimer- 3.2, TG- 257, neutrophil count- 6.73 mmm3. On 25/Apr/2020, labs were; SpO2/IH 121%, IL6- 51.1, PCR- 122, section- 0.61, body temperature- 38.4, ferritin- 1053, platelet count- 312000, D-dimer- 2.56, TG- 348, neutrophil count- 5 mmm3. On 26/Apr/2020, labs done were; PCR- 52, section- 0.44, ferritin- 1008, platelet count- 305000, D-dimer- 2.53, TG- 457, neutrophil count- 4.57 mmm3. On unspecified date, the patient died. The cause of death was not mentioned. It was not stated if autopsy was performed or not.

The reporter did not assess the causality of death with tocilizumab.

No further information was provided.

Additional information was received on 11/Jun/2020. The following information was added to the case: event death nos added. Event description updated.

Case received on 04/Jun/2020. This LRD (11/Jun/2020) captured as last closed significant version. The following information was added to this case was: dose of the suspect was added. 3 tocilizumab administrations with dose 400 mg. Narrative updated accordingly.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Pneumonia	19-Apr-2020		
COVID-19	21-Apr-2020		

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Polymerase chain reaction					N
Neutrophil count					N
Polymerase chain reaction					N
Neutrophil count					N
Polymerase chain reaction					N
Serum ferritin					N
Neutrophil count					N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17890478

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Polymerase chain reaction					N
Platelet count					N
Serum ferritin					N
Fibrin D dimer					N
Fibrin D dimer					N
Serum ferritin					N
Platelet count					N
Platelet count					N
Polymerase chain reaction					N
Serum ferritin					N
Platelet count					N
Fibrin D dimer					N
Fibrin D dimer					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	SOLUMEDROL	100 MG/QD	Unknown			23-Apr-2020	25-Apr-2020	

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17893215

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** BRA **Event Date:** **Outcomes:** DE,OT, **Application Type:** BLA

FDA Rcvd Date: 26-Jun-2020 **Mfr Rcvd Date:** 23-Jun-2020 **Mfr Control #:** BR-ROCHE-2616472 **Application #:** 125276

Patient Information:

Age: **Sex:** Female **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
COVID-19	NA
Cerebrovascular accident	NA
Intentional product use issue	NA
Off label use	NA
Sepsis	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17893215

Event/Problem Narrative:

AER 2616472 is a spontaneous case, received on 03/Jun/2020 from a physician (general practice) through roche product manager in Brazil. It concerns a female patient of unspecified age who intentionally used tocilizumab (Actemra) for unlabeled indication (off label use) and experienced trunk cerebrovascular accident.

The patient's concurrent conditions includes renal failure. No medical history, past drugs and concomitant medications were not reported.

On (b) (6) the patient started therapy with tocilizumab (lot number and dosing regimen: not reported) for COVID-19 (off label use, intentional use of actemra for unlabeled indication). She was extubated. It was reported that, 3 or 4 days after being extubated, she experienced a trunk cerebrovascular accident. It was reported that, she had an improvement after using tocilizumab, however, she presented with a neurological condition that, clinically, was diagnosed as trunk cerebrovascular accident. After the improvement, it was possible to perform a tomography scan with contrast, but, by tomography scan, the trunk cerebrovascular accident was not confirmed; therefore, diagnosis was only clinical. The physician informed that, posteriorly, she was presented with a very marked worsening, with an increase in IL-06 and procalcitonin. According to physician, after using tocilizumab, she was normal, without sepsis, with IL-06 of 25 (unit not reported). Physician reported that the confirmation of COVID-19 was done by PCR test (polymerase reaction chain) (and not serology). She underwent 3 PCR tests within 3 weeks. The first test was negative, the second was also negative, and only the third one was positive, when she was already experiencing respiratory worsening. The physician reported that the patient was initially admitted in the nursery and, after getting worse, was referred to the intensive care unit. He confirmed that the use of tocilizumab occurred in the intensive care unit, when she was already with phase 3 severity, with renal failure and on dialysis (dialysis was started early). Her creatinine was found to be 2.5. On an unspecified date, she experienced sepsis and worsening of COVID-19. Physician confirmed that the cause of death was COVID-19, since she was presented with infection worsening, even though she was covered with antibiotics for gram-positive and gram-negative bacteria. She had a septic condition that led to death.

At the time of this report, the outcome of trunk cerebrovascular accident was not reported. Therapy status with tocilizumab was not reported.

The company assessed trunk cerebrovascular accident as medically significant.

No further information was provided.

Additional information was received on 10/Jun/2020. Following information was added to the case. New event: Trunk cerebrovascular accident and event description updated accordingly.

Additional information was received on 23/Jun/2020. Following information was added to the case: Patient details(initials and date of birth). New event. Cause of death. Lab tests. Narrative updated.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17893215

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Renal failure			YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood creatinine					N
Polymerase chain reaction					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
 Sender Organization: ROCHE
 503B Compounding Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894004

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ESP **Event Date:** **Outcomes:** DE,HO,OT, **Application Type:** ANDA

FDA Rcvd Date: 18-Jul-2020 **Mfr Rcvd Date:** 16-Jul-2020 **Mfr Control #:** ES-AUROBINDO-AUR-APL-2020-029272 **Application #:** 203294

Patient Information:

Age: 72 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Azithromycin			Unknown	UNK	Pneumonia		
2	Azithromycin					COVID-19		
3	Ceftriaxone			Unknown	UNK	Pneumonia		
4	Ceftriaxone					COVID-19 pneumonia		
5	Hydroxychloroquine			Unknown	UNK	Pneumonia		
6	Hydroxychloroquine					COVID-19 pneumonia		
7	Interferon beta-1b			Subcutaneous	UNK	COVID-19 pneumonia		
8	Lopinavir/Ritonavir			Oral	UNK	Pneumonia		
9	Lopinavir/Ritonavir					COVID-19 pneumonia		
10	Methylprednisolone			Unknown	UNK	COVID-19		
11	Tocilizumab			Unknown	UNK, 3 bolus	COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Azithromycin		NA	NA				AUROBINDO	
2	Azithromycin		NA	NA				AUROBINDO	
3	Ceftriaxone		NA	NA					



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894004

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC	
4 Ceftriaxone		NA	NA						
5 Hydroxychloroquine		NA	NA						
6 Hydroxychloroquine		NA	NA						
7 Interferon beta-1b		NA	NA						
8 Lopinavir/Ritonavir		NA	NA						
9 Lopinavir/Ritonavir		NA	NA						
10 Methylprednisolone		NA	NA						
11 Tocilizumab		NA	NA						

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Cough	NA
Death	NA
Drug-induced liver injury	NA
Dyspnoea	NA
Electrocardiogram QT prolonged	NA
Hepatitis toxic	NA
Hyperbilirubinaemia	NA
Hypertransaminasaemia	NA
Ischaemia	NA
Obstructive airways disorder	NA
Off label use	NA
Peripheral arterial occlusive disease	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894004

Pyrexia	NA
Secretion discharge	NA
Thrombosis	NA

Event/Problem Narrative:

Initial report received on 11-Jun-2020: This is a spontaneous report received from Eudravigilance Database Management System (EVDMS) with ADR reference number ES-ABBVIE-20K-144-3436071-00, by physician.

This report concerned about 72-year-old male patient from Spain.

Medical history included ankle fracture, interstitial lung disease, interstitial lung disease, ill-defined disorder, appendectomy, peripheral arterial disease, dry cough, dyslipidaemia, arterial hypertension, fever, ankle fracture and dyspnea exacerbated and historical drugs of the patient were not reported.

Concomitant medications were not reported.

On an unknown date, the patient received tocilizumab at an unknown dose and frequency (3 bolus) via unknown route for COVID-19 pneumonia, azithromycin at an unknown dose and frequency via unknown route, ceftriaxone, hydroxychloroquine at an unknown dose and frequency via unknown route for bilateral pneumonia, lopinavir, ritonavir at an unknown dose and frequency via oral route all received for bilateral pneumonia and COVID-19 pneumonia and interferon beta-1b at an unknown dose and frequency via subcutaneous route for COVID-19 pneumonia, amine support medication and Methylprednisolone of unknown strength, formulation, dose, frequency and route all drugs were used for COVID-19 treatment.

On an unknown date, the patient had recurrent mucus and blood clogging (thrombosis and secretion discharge), peripheric arterial disease worsening with ischemia (ischaemia and peripheral arterial occlusive disease), toxic hepatitis, hypertransaminasemia, dyspnea worsened, airway blocking, hyperbilirubinemia worsening, prolonged QT, fever, dry cough , off label use and exitus (death).

On an unknown date, the patient died due to electrocardiogram QT prolonged and drug-induced liver injury. It was unknown whether autopsy was performed or not.

Laboratorial examinations included galactomannan antigen, blood beta-d-glucan, creatine phosphokinase, thorax x-ray, culture, fibrin d dimer, interleukin-6, lymphocytes, polymerase chain reaction, ferritin, troponin, leucocyte count with unknown results on an unknown date and treatment medications were not reported.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894004

The outcome of the events thrombosis, peripheral arterial occlusive disease, ischaemia, hepatitis toxic, hypertransaminasaemia, dyspnoea, obstructive airways disorder, secretion discharge, hyperbilirubinaemia, pyrexia, cough, off label use was unknown and death, electrocardiogram QTprolonged and drug-induced liver injury was fatal.

The case was assessed as serious (fatal, hospitalisation and medically significant for death, electrocardiogram QTprolonged and drug-induced liver injur, and only medically significant for thrombosis, peripheral arterial occlusive disease, ischaemia, hepatitis toxic, hypertransaminasaemia, dyspnoea, obstructive airways disorder, secretion discharge, hyperbilirubinaemia, pyrexia, cough, off label use).

Additional information received on 12-Jun-2020 from Eudravigilance database management system with reference number ES-ABBVIE-20K-144-3436071-00 by physician.

Indication for hydroxychloroquine, ceftriaxone and lopinavir, ritonavir was updated.

Follow-up (16-Jun-2020): This follow up report received from Eudravigilance Database Management System (EVDMS) with ADR number ES-RUBIO-2020-1471 by Physician.

Suspect drug amine support medication was added.

Event drug-induced liver injury was added.

Seriousness for the events death and QTprolonged and drug-induced liver injury was updated.

Follow-up (10-Jul-2020): This follow up report received from Eudravigilance Database Management System (EVDMS) with ADR number ES-ABBVIE-20K-144-3436071-00 by Physician.

In historical conditions dry cough, dyslipidaemia, arterial hypertension, fever, ankle fracture and dyspnea exacerbated were added.

Indication for tocilizumab and interferon beta-1b was updated.

Follow-up (16-Jul-2020): This follow up report received from Eudravigilance Database Management System (EVDMS) with ADR number ES-RUBIO-2020-1471 by Physician.

Verbatim of the event death was updated.

Dosage Text for tocilizumab was updated.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894004

Indication for amine support medication was updated.

Methylprednisolone was added as suspect drug.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Ankle fracture			
Appendectomy			
Cough			
Dyslipidaemia			
Dyspnoea			
Hypertension			
Ill-defined disorder			
Interstitial lung disease			
Peripheral arterial occlusive disease			
Pyrexia			

Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894004

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood beta-D-glucan	unknown	N/A			N
Lymphocyte count	unknown	N/A			N
Fibrin D dimer	unknown	N/A			N
Polymerase chain reaction	unknown	N/A			N
Troponin	unknown	N/A			N
Blood creatine phosphokinase	unknown	N/A			N
Aspergillus test	unknown	N/A			N
Culture	unknown	N/A			N
Interleukin level	unknown	N/A			N
Serum ferritin	unknown	N/A			N
White blood cell count	unknown	N/A			N
Chest X-ray	unknown	N/A			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: AUROBINDO

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894015

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: PAK
Event Date: 05-Jun-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 15-Jun-2020
Mfr Rcvd Date: 11-Jun-2020
Mfr Control #: PK-ROCHE-2621548
Application #: 125276

Patient Information:

Age: 63 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		480 MG/	Intravenous (not otherwise specified)	6 vials of 80 mg	COVID-19		
2	ACTEMRA					Dyspnoea		
3	ACTEMRA					Chest pain		
4	ACTEMRA					Pyrexia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				
2	ACTEMRA		NA	NA	UNKNOWN				
3	ACTEMRA		NA	NA	UNKNOWN				
4	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894015

Event/Problem Narrative:

AER 2621548 is a spontaneous case, received on 11/Jun/2020 from a consumer in Pakistan. It concerns a 63 year old male patient who died and had tocilizumab (Actemra) intentional use for unapproved indication (off label use).

The patients medical history, past drugs, concurrent conditions and concomitant medications were not reported.

On an unspecified date, the patient started therapy with intravenous tocilizumab (lot number:unknown) (frequency not reported) 6 vials of 80 mg (480 mg) for fever, difficulty in breathing, chest pain and for covid-19 (intentional use for unapproved indication - off label use). It was reported that there was a slight improvement in his health but he could not recover and he did not had any travel history. He was tested positive for COVID-19 and also had his chest X-ray done. On ^{(b) (6)} he died. It was unknown if an autopsy was performed or not.

The reporter assessed the causality of the event death as unknown with tocilizumab.

No further information was reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Computerised tomogram thorax					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894015

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894259

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: PAK
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 15-Jun-2020
Mfr Rcvd Date: 11-Jun-2020
Mfr Control #: PK-ROCHE-2621554
Application #: 125276

Patient Information:

Age: 40 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ACTEMRA		640 MG/	Intravenous (not otherwise specified)	8 vials of 80 mg	COVID-19 pneumonia			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	Unk	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2621554 is a spontaneous case, received on 11/Jun/2020 from a consumer in Pakistan. It concerns a 40 year old male patient who died due to drug use for unlabelled indication, off label use whilst being treated with tocilizumab (Actemra).

No medical history, past drug, concurrent condition and concomitant medication was reported.

On an unspecified date, the patient started therapy with intravenous tocilizumab (lot number:unknown) (strength: 8 vials of 80 mg) 640 mg (frequency not reported) for covid-19 pneumonia (fever, flu) (drug use for unlabelled indication) (off label use). On an unspecified date his covid test was positive. He was not on ventilator support. On ^{(b) (6)} he died. It was unknown if an autopsy was performed or not.

At the time of death, it was not reported if the therapy with tocilizumab was ongoing or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894259

The consumer assessed the causality as unknown between death and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894259

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894337

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: PAK
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 15-Jun-2020
Mfr Rcvd Date: 11-Jun-2020
Mfr Control #: PK-ROCHE-2621553
Application #: 125276

Patient Information:

Age:
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Off label use	NA
Product use in unapproved indication	NA

Event/Problem Narrative:

AER 2621553 is a spontaneous case, received on 11/Jun/2020 from a consumer via a company representative and digital media (twitter) in Pakistan. It concerns a male patient (age not reported) who use for unapproved indication as off label use and died whilst being treated with tocilizumab (Actemra).

Patient's medical history, concurrent condition, past drug and concomitant medication were not reported.

On an unknown date, the patient started therapy with tocilizumab (lot number: UNKNOWN, therapy regimen: not reported) for COVID-19 (tocilizumab used for unapproved indication as off label use. It was tweeted that a consumer's uncle was on tocilizumab off label for COVID 19 and he passed away. It was reported that his body was not receptive to tocilizumab injection and advised that to reconsider before giving it to any patient close to you. He died due to unknown cause on an unknown date. It was not reported if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894337

At the time of death, it was not reported, if therapy with tocilizumab was ongoing or not.

The consumer did not report a causality between death and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17894337

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17896282

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ITA
Event Date: 20-Mar-2020
Outcomes: DE,HO,OT,
Application Type: BLA
FDA Rcvd Date: 02-Jul-2020
Mfr Rcvd Date: 29-Jun-2020
Mfr Control #: IT-ROCHE-2621314
Application #: 125276

Patient Information:

Age: 47 YR
Sex: Male
Weight: 125 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ROACTEMRA		500 MG/Q12H	Intravenous (not otherwise specified)		COVID-19 pneumonia	19-Mar-2020	20-Mar-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	B2093H16,B3017 H45,B2095H10				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Blood lactate dehydrogenase increased	NA
Cardiac arrest	NA
Intentional product use issue	NA
Off label use	NA
Polymerase chain reaction positive	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17896282

Event/Problem Narrative:

AER 2621314 is a spontaneous case, received on 11/Jun/2020 from a physician in Italy. It concerns a 47 year old male patient who intentionally used tocilizumab (Roactemra) for unapproved indication (off label use) and experienced polymerase chain reaction value increased, lactate dehydrogenase increased and cardio circulatory arrest.

Patient's concurrent conditions included hypertension and obesity. Concomitant medications included ceftriaxone, lopinavir;ritonavir (Kaletra), insulin lispro (Humalog), paracetamol, amlodipine besilate (Norvasc), hydroxychloroquine sulfate (Plaquenil). No past drugs and medical history were reported.

On (b) (6), patient was admitted to their facility. On the same day, PCR was performed and test results was 127.2 mg/L (reference range: 0-8 mg/L); lactate dehydrogenase was performed and test results was 535 U/L (reference range:135-225 U/L); alanine aminotransferase was performed and test results was 75 U/L (reference range: 3-45 U/L). aspartate aminotransferase was performed and test results was 61 U/L (reference range: 5-43 U/L). On (b) (6) X-ray bilateral interstitial pneumonia with positive SARS-CoV-2 PCR. On (b) (6) chest X-ray showed COVID+ bilateral interstitial pneumonia. On (b) (6) the patient started therapy with intravenous tocilizumab (lot number: B2093H16, B3017H45, B2095H10, B3017H45), 500 mg, once in 12 hour for covid-19 pneumonia (intentional drug use for unapproved indication, off label use). On (b) (6) PCR was performed and test results was 153 mg/L (reference range: 0-8 mg/L), lactate dehydrogenase was performed and test results was 482 U/L (reference range: 135-225 U/L), aspartate aminotransferase was performed and test results was 31 U/L (reference range: 5-43 U/L), alanine aminotransferase was performed and test results was 48 U/L (reference range: 3-45 U/L). On same day, he had underwent non-invasive oxygen therapy by cpap and venturi mask. Later, he died due to cardio circulatory arrest. Autopsy was not performed. It was reported that, abnormal values for PCR, LDH, AST, ALT were linked to tocilizumab therapy. The patient presented modest alteration of AST, ALT and LDH to refer to ongoing viral infection and not of hepatic origin.

At the time of this report, the outcome of polymerase chain reaction value increased and lactate dehydrogenase increased was not reported. It was unknown if an autopsy was performed.

The reporter assessed the causality of cardio circulatory arrest, polymerase chain reaction value increased and lactate dehydrogenase increased as unrelated with tocilizumab.

No further information was provided.

Additional information received on 17/Jun/2020. The following information was added to the case: Increased ALT (Alanine aminotransferase)(48 U/L) deleted as an event, as ALT 48 U/L after tocilizumab administration is normal for CTCAE, seriousness criteria amended for increased LDH event as important medical events.

Additional information received on 22/Jun/2020. The following information was added to the case: concomitant medications added, causality of polymerase chain reaction value increased and lactate dehydrogenase increased updated from not reported to not related and event description updated (Autopsy was not performed. It was reported that, abnormal values for PCR, LDH, AST, ALT were linked to tocilizumab



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17896282

therapy).

Additional information received on 29/Jun/2020. The following information was added to the case: The patient presented modest alteration of AST, ALT and LDH to refer to ongoing viral infection and not of hepatic origin.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension			
Obesity			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	48	U/L	3	45	N
Aspartate aminotransferase	61	U/L	5	43	N
Aspartate aminotransferase	31	U/L			N
Chest X-ray					N
Alanine aminotransferase	75	U/L	3	45	N
SARS-CoV-2 test					N
Chest X-ray					N
Blood lactate dehydrogenase	482	U/L	135	225	N
Polymerase chain reaction	127.2	mg/L	0.0	8.0	N
Polymerase chain reaction	153	mg/L	0.0	8.0	N
Blood lactate dehydrogenase	535	U/L	135	225	N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17896282

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	Ceftriaxone		Unknown			18-Mar-2020		
2	HUMALOG		Unknown			18-Mar-2020	20-Mar-2020	
3	KALETRA		Unknown			19-Mar-2020	20-Mar-2020	
4	NORVASC		Unknown			18-Mar-2020	20-Mar-2020	
5	PARACETAMOL		Unknown			17-Mar-2020	19-Mar-2020	
6	PLAQUENIL [HYDROXYCHLOROQUI NE SULFATE]		Unknown			18-Mar-2020	20-Mar-2020	

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17896309

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ITA
Event Date: 17-Mar-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 02-Jul-2020
Mfr Rcvd Date: 29-Jun-2020
Mfr Control #: IT-ROCHE-2621332
Application #: 125276

Patient Information:

Age: 44 YR
Sex: Male
Weight: 101 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ROACTEMRA		800 MG/Q12H	Intravenous (not otherwise specified)		COVID-19 pneumonia	17-Mar-2020	18-Mar-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	0 Day	NA	NA	B2093H16				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Alanine aminotransferase increased	NA
Aspartate aminotransferase increased	NA
Blood lactate dehydrogenase increased	NA
Intentional product use issue	NA
Interstitial lung disease	NA
Off label use	NA
Polymerase chain reaction positive	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17896309

Event/Problem Narrative:

AER 2621332 is a spontaneous case, received on 11/Jun/2020 from a physician in Italy. It concerns a 44 year old male patient who intentionally used tocilizumab (Roactemra) for unapproved indication (off label use) and experienced increased lactate dehydrogenase, increased alanine transaminase, increased aspartate aminotransferase, abnormal polymerase chain reaction with worsening of bilateral interstitial pneumonia.

Concomitant medications included fentanyl, propofol, rocuronium, acetylcysteine (Fluimucil), esomeprazole, furosemide, hydroxychloroquine sulfate (Plaquenil), methylprednisolone, vitamins nos (Cernevit), remdesivir, piperacillin;tazobactam (Piperacilline / Tazobactam).The patients medical history, past drugs, concurrent conditions were not reported.

On 02/Mar/2020, the patient had covid-19 test positive and by chest X-ray, bilateral interstitial pneumonia was confirmed. He was give supplemental oxygen therapy and ventilator support. On 17/Mar/2020, he started therapy with intravenous tocilizumab (lot number: B2093H16), 800 mg, once in 12 hours for covid-19 pneumonia (intentional drug use for unapproved indication, off label use). On (b) (6), he was admitted to ICU from other ICU. X-ray showed bilateral interstitial pneumonia with positive severe acute respiratory syndrome-corona virus-2 pcr (SARS-CoV-2 PCR). On (b) (6) PCR was performed and result was 212.3 mg/L (reference range: 0-8 mg/L), lactate dehydrogenase test was performed and result was 813 U/L (reference range: 135-225 U/L), aspartate aminotransferase was performed and result was 75 U/L (reference range: 5-43 U/L), alanine aminotransferase test was performed and the result was 87 U/L (reference range: 3-45 U/L). On (b) (6) PCR was performed and result was 15.7 mg/L (reference range: 0-8 mg/L), lactate dehydrogenase test was performed and result was 1143 U/L (reference range: 135-225 U/L), aspartate aminotransferase was performed and result was 62 U/L (reference range: 5-43 U/L), alanine aminotransferase test was performed and the result was 82 U/L (reference range: 3-45 U/L). From the above results, he had increase in lactate dehydrogenase, aspartate aminotransferase and alanine transaminase and abnormal polymerase chain reaction. On (b) (6) he died due to worsening of bilateral interstitial pneumonia. The correlation between the abnormal values for PCR, LDH, AST, ALT (some appear to have improved but still not within the normal range, others have worsened) and tocilizumab: the evolution of these values was linked to disease progress and not to the therapy with tocilizumab. Indicate details of vasopressors or dialysis: noradrenaline - no dialysis. The reporer stated that, evaluating the case, he considered the liver enzyme alteration not related to the use of tocilizumab but to the cytonecrosis secondary to the viral infection.

At the time of this report, the outcome of increased lactate dehydrogenase, abnormal polymerase chain reaction, increased aspartate aminotransferase and increased alanine transaminase was not reported. Autopsy was not performed.

The reporter assessed the causality of worsening of bilateral interstitial pneumonia as unrelated with tocilizumab while did not report a causality of increased lactate dehydrogenase, abnormal polymerase chain reaction, increased aspartate aminotransferase and alanine transaminase with tocilizumab.

No further information was provided.

Additional information was received on 22/Jun/2020 and the following information was added to the case: concomitant medications: fentanyl,



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17896309

propofol, rocuronium, acetylcysteine, esomeprazole, furosemide, hydroxychloroquine sulfate, methylprednisolone, vitamins nos, remdesivir, piperacillin;tazobactam, autopsy not performed, additional case details and narrative updated.

Additional information was received on 29/Jun/2020 and the following information was added to the case: Narrative updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Alanine aminotransferase	87	U/L	3	45	N
Chest X-ray					N
Polymerase chain reaction	15.7	mg/L	0.0	8.0	N
Alanine aminotransferase	82	U/L	3	45	N
SARS-CoV-2 test					N
Aspartate aminotransferase	75	U/L	5	43	N
Coronavirus test					N
Blood lactate dehydrogenase	813	U/L	135	225	N
Polymerase chain reaction	212.3	mg/L	0.0	8.0	N
Blood lactate dehydrogenase	1143	U/L	135	225	N
Aspartate aminotransferase	62	U/L	5	43	N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17896309

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ESOMEPRAZOLE		Unknown			23-Mar-2020	27-Mar-2020	
2	FENTANYL		Unknown			16-Mar-2020	27-Mar-2020	1 DAY
3	FLUIMUCIL		Unknown			16-Mar-2020	27-Mar-2020	1 DAY
4	FUROSEMIDE		Unknown			17-Mar-2020	27-Mar-2020	
5	METHYLPREDNISOLON E		Unknown			20-Mar-2020	27-Mar-2020	
6	PIPERACILLINE / TAZOBACTAM		Unknown			22-Mar-2020	27-Mar-2020	
7	PLAQUENIL [HYDROXYCHLOROQUI NE SULFATE]		Unknown			16-Mar-2020	27-Mar-2020	1 DAY
8	PROPOFOL		Unknown			16-Mar-2020	27-Mar-2020	1 DAY
9	REMDESIVIR		Unknown			20-Mar-2020	26-Mar-2020	
10	ROCURONIUM		Unknown			26-Mar-2020	27-Mar-2020	

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17900139

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: MEX
Event Date:
Outcomes: DE,OT,
Application Type: BLA
FDA Rcvd Date: 16-Jun-2020
Mfr Rcvd Date: 05-Jun-2020
Mfr Control #: MX-ROCHE-2618454
Application #: 125276

Patient Information:

Age: 36 YR
Sex: Male
Weight: 110 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		560 MG/	Intravenous (not otherwise specified)	2 only doses	COVID-19	06-Jun-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Off label use	NA
Product use in unapproved indication	NA

Event/Problem Narrative:

AER 2618454 is a spontaneous case, received on 05/Jun/2020 from a physician in Mexico. It concerns a 36 year old male patient who used drug for an unapproved indication (off label use) whilst being treated with tocilizumab (Roactemra).

No medical history, past drug, concurrent condition and concomitant medication was reported.

On an unspecified date, the patient started therapy with intravenous tocilizumab (lot number: not reported) 560 mg, 2 doses (frequency not reported) for covid-19 (drug used for an unapproved indication) (off label use). The reporter was consulted for what diagnosis and he responds for covid what happens my brother in law was sick with covid, he was cased, he had been cased for 10 days, so they already put 3 doses of tocilizumab. So we need more of the medicine because he asked for it the doctor. The first 3 doses was given to my relative there in the hospital where he was hospitalized because they had it there, but since they no longer have it. It was unknown if the health authority had



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17900139

been notified to this report. On an unspecified date in (b) (6) he died due to unknown cause. It was unknown if an autopsy was performed. It was reported that his brother in law has to pay for ampoules although patient has passed away because the health sector has asked for them.

At the time of this report, it was not reported if the therapy with tocilizumab was ongoing or not.

No further information was provided.

Merger was performed. AER 2622697 was found to be duplicate of AER 2618454. All the information from AER 2622697 was added into AER 2618454 which remains the valid case.

Additional information was received on 11/Jun/2020. Following information was added to the case: New event(unknown cause of death). Dosing regimen. New reporter. Narrative updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17900139

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17901141

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: MEX
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 16-Jun-2020
Mfr Rcvd Date: 15-Jun-2020
Mfr Control #: MX-ROCHE-2622695
Application #: 125276

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2622695 is a spontaneous case, received on 15/Jun/2020 from an other health care professional in Mexico. It concerns a patient of unknown demographics who died and had tocilizumab (RoActemra) intentional use for unapproved indication (off label use).

The patients medical history, past drugs, concurrent conditions or concomitant medications were not reported.

On an unspecified date, the patient started therapy with tocilizumab (lot number: unknown) (dosing regimen not reported) for covid-19 (intentional use for unapproved indication - off label use). It was reported that the patient had received dose of tocilizumab. On an unspecified date, the patient died after the application of tocilizumab. It was not reported if an autopsy was performed or not.

The reporter did not report a causality between unknown cause of death and tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17901141

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17901141

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17907664

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: JPN Event Date: 15-Apr-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 31-Aug-2020 Mfr Rcvd Date: 26-Aug-2020 Mfr Control #: JP-ROCHE-2623252 Application #: 125276

Patient Information:

Age: 57 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	Actemra		400 MG/QD	Intravenous drip		COVID-19 pneumonia	15-Apr-2020	15-Apr-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Actemra		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1)	ReC
COVID-19	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2623252 is a spontaneous case, received at Chugai Pharmaceuticals Co. Ltd., Japan (reference number: A2020028373) on 09/Jun/2020 and at Roche on 16/Jun/2020 from a physician in Japan. It concerns a 57 year old male patient who died due to covid-19 and used tocilizumab (Actemra) as off label use.

Patient's concurrent conditions included diabetes mellitus and hypertension. Concomitant medications included avigan, ciclesonide (Alvesco), methylprednisolone, sivelestat sodium (Elaspol) and nafamostat mesilate (Futhan). No medical history and past drugs were reported.

On 15/Apr/2020, the patient started therapy with intravenous drip of tocilizumab injection (lot number: unknown) 400 mg, once in a day for covid-19 pneumonia. On 22/Mar/2020, pyrexia of 38 degrees C occurred. Contact or travel since 14 days before the onset of COVID-19 symptoms were not reported. On (b) (6) he visited Hospital A. On (b) (6) pyrexia and arthralgia occurred, and he visited Hospital B and received antibiotics. On (b) (6) as the symptoms did not improve, he visited the reporting hospital. An X-ray and chest



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17907664

computerised tomography showed ground glass opacities. A polymerase chain reaction (PCR) test showed the positive result of coronavirus. Alvesco (ciclesonide), methylprednisolone and Elaspol (sivelestat sodium hydrate) were administered. On (b) (6) oxygen inhalation at 3L was initiated. On (b) (6) Avigan (favipiravir) and futhan (nafamostat mesilate) were added. A tracheostomy was performed followed by intubation. On (b) (6) in intensive care unit, he received invasive ventilation (including artificial ventilator and extracorporeal membrane oxygenation (ECMO)). His non-invasive ventilation (including bilevel positive airway pressure [BIPAP] / non-invasive positive pressure ventilation [NPPV]), blood purification therapy (including haemodialysis/plasma exchange), administration of vasopressors and percutaneous oxygen saturation before the initiation of treatment with tocilizumab was not reported. On an unknown date in (b) (6) as an improvement tendency in the symptoms was temporarily observed, favipiravir was discontinued. On (b) (6) favipiravir was resumed because the symptoms were aggravated again, and a single dose of tocilizumab 400 mg was administered (off label use). An unspecified date in (b) (6) although the negative conversion of the CRP was noted, no other improvement was noted. On (b) (6) he died due to covid-19. It was unknown if an autopsy was performed or not.

At the time of death, therapy ongoing status of tocilizumab was unknown.

The physician assessed the death due to COVID-19 as not related to tocilizumab.

No further information was available.

Additional information was received at Chugai on 26/Aug/2020 and at Roche on 31/Aug/2020. Following information was added to the case: New reporters, reported terms changed from off label use (COVID-19 pneumonia) to off label use (viral [COVID-19] pneumonia) and COVID-19 pneumonia to death due to COVID-19. Background information, drug information, clinical course and reporter's comment.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Diabetes mellitus			YES	
Hypertension			YES	
Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17907664

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ALVESCO		Unknown	Dosage is uncertain.	COVID-19 pneumonia	Mar-2020		
2	AVIGAN		Unknown	Dosage is uncertain.	COVID-19	30-Mar-2020	01-Apr-2020	
3	AVIGAN		Unknown	Dosage is uncertain.		15-Apr-2020	26-Apr-2020	
4	ELASPOL		Unknown	Dosage is uncertain.	COVID-19 pneumonia	Mar-2020		
5	FUTHAN		Unknown	Dosage is uncertain.	COVID-19 pneumonia	30-Mar-2020		
6	METHYLPREDNISOLON E		Unknown	Dosage is uncertain.	COVID-19 pneumonia	Mar-2020		

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17907863

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: Outcomes: DE,OT, Application Type: NDA

FDA Rcvd Date: 17-Jun-2020 Mfr Rcvd Date: 16-Jun-2020 Mfr Control #: ES-ABBVIE-20K-144-3448722-00 Application #: 021906

Patient Information:

Age: 72 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	LOPINAVIR/RITONAVIR			Oral		SARS-CoV-2 infection		
2	AZITHROMYCIN			Unknown		SARS-CoV-2 infection		
3	CEFTRIAZONE			Unknown		SARS-CoV-2 infection		
4	HYDROXYCHLOROQUIN E			Unknown		SARS-CoV-2 infection		
5	INTERFERON BETA-1B			Subcutaneous		SARS-CoV-2 infection		
6	METHYLPREDNISOLONE			Unknown	(+/- 1 mg/Kg day)	SARS-CoV-2 infection		
7	METHYLPREDNISOLONE			Intravenous bolus				
8	TOCILIZUMAB			Intravenous bolus	3 bolus	SARS-CoV-2 infection		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	LOPINAVIR/RITONAVIR		Unk	NA	NOT AVAILABLE				
2	AZITHROMYCIN		Unk	NA	UNKNOWN				
3	CEFTRIAZONE		Unk	NA	UNKNOWN				
4	HYDROXYCHLOROQUIN E		Unk	NA	UNKNOWN				
5	INTERFERON BETA-1B		Unk	NA	UNKNOWN				



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FOIA Case Report Information

Case ID: 17907863

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC	
6 METHYLPREDNISOLONE		Unk	NA	UNKNOWN,UNK NOWN					
7 METHYLPREDNISOLONE		Unk	NA	UNKNOWN,UNK NOWN					
8 TOCILIZUMAB		Unk	NA	UNKNOWN					

Event Information:

Preferred Term (MedDRA Version: 23.1)

ReC

Hepatitis toxic

NA

Event/Problem Narrative:

Spontaneous report from SPAIN by a physician of a 72 year old male with an event of TOXIC HEPATITIS with LOPINAVIR/RITONAVIR.

This case was received from EMA on 16 JUN 2020 (Ref. number ES-NORMON-20201782)

On an unknown date, the patient experienced TOXIC HEPATITIS. In 2020, the patient died. It is unknown if an autopsy was performed. HYDROXYCHLOROQUINE, INTERFERON BETA-1B, AZITHROMYCIN, TOCILIZUMAB, CEFTRIAXONE and METHYLPREDNISOLONE were also considered suspect.

Reporter's comment: See case narrative.

Company comment's: Toxic hepatitis is an expected adverse reaction with Azitromicina Normon (Azithromycin, I.N.N) and Metilprednisolona Normon (Methylprednisolone, I.N.N), and an unexpected adverse reaction with Ceftriaxona Normon (Ceftriaxone, I.N.N). After reviewing all the available information and taking into account other possible alternative causes such as the administration of the other suspect drugs and the medical conditions of the patient, Laboratorios Normon,S.A. assessed the relationship between the suspect drugs and the adverse reaction as possible (Karch and Lasagna algorithm).

Primary reporter contact for lot number information was not available.

Causality for LOPINAVIR/RITONAVIR

The reporter's causality for the event(s) of TOXIC HEPATITIS with LOPINAVIR/RITONAVIR was a reasonable possibility.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17907863

Relevant Medical History:

Patient Medical History

INTENSIVE CARE
BILATERAL PNEUMONIA
RESPIRATORY DISTRESS
INTERMITTENT CLAUDICATION
HYPERTRANSAMINASAEMIA
HYPERBILIRUBINAEMIA
ARTERIAL HYPERTENSION
FIBULA FRACTURE
ISCHEMIA
QT PROLONGED
AIRWAYS OBSTRUCTION
DYSLIPIDAEMIA
PERIPHERAL ARTERIAL DISEASE
SARS-COV-2 INFECTION
APPENDICECTOMY

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Airways obstruction			
Appendicectomy			
Arterial hypertension			
Bilateral pneumonia			
Dyslipidaemia			
Fibula fracture			
Hyperbilirubinaemia			
Hypertransaminasaemia			
Intensive care			
Intermittent claudication			
Ischemia			
Peripheral arterial disease			
QT prolonged			



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17907863

Respiratory distress

SARS-CoV-2 infection

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ABBVIE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17912668

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: USA
Event Date: 24-May-2020
Outcomes: DE,OT,
Application Type: BLA
FDA Rcvd Date: 08-Jul-2020
Mfr Rcvd Date: 06-Jul-2020
Mfr Control #: US-ROCHE-2611825
Application #: 125276

Patient Information:

Age: 65 YR
Sex: Male
Weight: 85 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		100 ML/	Intravenous (not otherwise specified)	at 18:36	COVID-19 pneumonia	22-May-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	5 Day	NA	NA	MJM01507,MJM07777,MJM26089,MJM26334				

Event Information:

Preferred Term (MedDRA  Version: 23.1)	ReC
Bacteraemia	NA
Cardiac arrest	NA
Pharyngeal haemorrhage	NA
Pneumonia bacterial	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17912668

Event/Problem Narrative:

AER 2611825 is a clinical study case, received on 29/May/2020 from a physician in the USA. It concerns a 65 year old male patient (patient number: (b) (6)) who developed bacteremia, bacterial pneumonia, nasopharyngeal bleeding and fatal sudden cardiac arrest whilst enrolled in (b) (6)
(b) (6)

No medical history and past drugs were reported. Concurrent conditions included hypertension, type 2 diabetes mellitus, bradycardia, pain, and fever. Concomitant medications included chlorhexidine to rinse oral cavity, enoxaparin sodium (Lovenox) for deep vein thrombosis prophylaxis, famotidine for gastrointestinal prophylaxis, furosemide as diuretic prophylaxis, insulin aspart, methylprednisolone as standard of care for covid-19 pneumonia, ocular lubricant, carmellose sodium;sorbinate (Saliva Substitute) as oral care for intubated patients, docusate for constipation prophylaxis, insulin glargine (Lantus), senna spp. (Senna) for constipation prophylaxis, paracetamol (Acetaminophen), lactulose for constipation prophylaxis, dexmedetomidine as anesthesia for intubation, dopamine; glucose, sodium chloride for blood pressure support, hydromorphone, midazolam for sedation, multivitamin with minerals, metoprolol, rocuronium, acetaminophen and norepinephrine for blood pressure support.

(b) (6)
(b) (6) On (b) (6) he experienced non-serious event nasopharyngeal bleeding (severity grade 2). It was reported that nasopharyngeal bleeding was most likely due to trauma from repeated nasal swab collections and an estimated amount of bleeding was not documented in emergency room (EMR). There were no clinically significant lab values. No treatment medication was given, and no lab investigation was performed in response to the event. On (b) (6) his nasopharyngeal bleeding was resolved. On (b) (6) at 3:52, he was diagnosed with bacteremia (initial and most extreme severity: grade 4). On the same date, he had acute cardiac arrest at approximately 1700 per medical report. His blood culture report was positive for escherichia coli. At 4:05, he was diagnosed with bacterial pneumonia (initial and most extreme severity: grade 4). His respiratory culture was positive for klebsiella. He was treated with ipratropium; salbutamol (Albuterol; Ipratropium) 3 ml, piperacillin sodium;tazobactam sodium (Piperacilina - Tazobactam) 3.375 g, and vancomycin1500 mg. At 17:00. After 17 minutes of CPR (cardiopulmonary resuscitation), he died due to sudden cardiac arrest. An autopsy was not performed. On (b) (6) the site became aware of events and death and reported within 24 hours of being aware.

At the time of death, bacteremia and bacterial pneumonia were persisting.

The physician assessed the causality of bacterial pneumonia and bacteremia as related to blinded tocilizumab. Other suspected cause was concurrent illness. The physician assessed the fatal sudden cardiac arrest as not related to blinded tocilizumab. Other suspected cause was disease under study. The physician assessed the causality of nasopharyngeal bleeding as related to blinded tocilizumab, and other causes - procedures

The physician assessed the events of bacterial pneumonia and bacteremia to be medically significant and serious adverse events of special interest under serious and/or medically significant infection.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17912668

The physician assessed nasopharyngeal bleeding as a non serious adverse event of special interest under serious and/or medically significant bleeding events.

The company assessed the causality of bacteremia, bacterial pneumonia, and fatal sudden cardiac arrest as not related to blinded tocilizumab considering patients underlying disease of COVID-19 pneumonia is most potential cause for events as it weakens the local defences in the respiratory tract and contracts secondary bacterial infections. Additionally, the patient has received only a single dose of tocilizumab (frequency once) which is less likely to cause the events. Other contributory factors for the events are advanced age of patient (65 years), hypertension and type 2 diabetes mellitus. The event nasopharyngeal bleeding was most likely due to trauma from repeated nasal swab collections. The role of blinded tocilizumab can not be established at this point of time.

No further information was reported.

Additional information was received on 11/Jun/2020 and the following information was added to the case: New secondary reporter, therapy details of concomitant medications, treatment medications, the event worsening of COVID-19 pneumonia was amended to fatal sudden cardiac arrest, the events of bacterial pneumonia, and bacteremia upgraded to be medically significant, and the causality of the events (bacterial pneumonia, and bacteremia) was updated to be related with blinded tocilizumab (previously not related).

Additional information was received on 24/Jun/2020 and the following information was added to the case: New event (nasopharyngeal bleeding).

AER 2611822 was identified as a duplicate of AER 2611825. All the information from AER 2611822 was added to the AER 2611825, which remains the active case.

Additional information was received on 01/Jul/2020 and the following information was added to the case: End date of insulin aspart (27/May/2020), docusate (26/May/2020), lantus (25/May/2020), acetaminophen (start date 24/May/2020, end date: 27/May/2020), lactulose (24/May/2020), enoxaparin (27/May/2020), dopamine;dextrose (26/May/2020), acetaminophen (start date: 27/May/2020) and therapy details of sodium chloride 0.9% and lantus were updated.

Additional information was received on 06/Jul/2020 and the following information was added to the case: new reporter and event description (on (b) (6) the site became aware of events and death and reported within 24 hours of being aware) was updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17912668

Bradycardia	YES
Hypertension	YES
Pain	
Pyrexia	
Type 2 diabetes mellitus	YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ACETAMINOPHEN	650 MG/	Unknown	other	Pyrexia	24-May-2020		3 DAY
2	ACETAMINOPHEN	650 MG/	Unknown		Pyrexia	27-May-2020	27-May-2020	
3	CHLORHEXIDINE	15 MG/BID	Topical			21-May-2020	27-May-2020	6 DAY
4	DEXMEDETOMIDINE	400 UG/	Unknown			21-May-2020	21-May-2020	6 DAY
5	DEXTROSE;DOPAMINE	400 MG/	Unknown			23-May-2020	26-May-2020	4 DAY
6	DOCUSATE	250 MG/	Unknown			22-May-2020	26-May-2020	5 DAY
7	ENOXAPARIN	40 MG/QD	Unknown		Thrombosis prophylaxis	25-May-2020	27-May-2020	2 DAY
8	FAMOTIDINE	20 MG/BID	Unknown			21-May-2020	27-May-2020	6 DAY
9	FUROSEMIDE	20 MG/BID	Unknown			21-May-2020	27-May-2020	6 DAY
10	HYDROMORPHONE	20 MG/	Unknown		Pain	23-May-2020	27-May-2020	4 DAY



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17912668

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
11 INSULIN ASPART		Unknown		Diabetes mellitus	21-May-2020	27-May-2020	6 DAY
12 LACTULOSE	20 G/	Unknown		Constipation prophylaxis	24-May-2020	24-May-2020	3 DAY
13 LANTUS	15 IU/BID	Unknown			25-May-2020	27-May-2020	4 DAY
14 LANTUS	10 IU/QD	Unknown		Type 2 diabetes mellitus	23-May-2020	25-May-2020	4 DAY
15 LOVENOX [ENOXAPARIN SODIUM]	40 MG/	Unknown		Thrombosis prophylaxis	21-May-2020	21-May-2020	6 DAY
16 LOVENOX [ENOXAPARIN SODIUM]	80 MG/	Unknown			21-May-2020	23-May-2020	6 DAY
17 METHYLPREDNISOLON E	40 MG/	Unknown		COVID-19 pneumonia	21-May-2020	27-May-2020	6 DAY
18 METOPROLOL	5 MG/	Unknown		Hypertension	27-May-2020	27-May-2020	
19 MIDAZOLAM	2 MG/	Unknown		Sedation	23-May-2020	27-May-2020	4 DAY
20 MULTIVITAMIN WITH MINERALS	15 ML/QD	Unknown		Vitamin supplementation	25-May-2020	27-May-2020	2 DAY
21 NOREPINEPHRINE	4 MG/	Unknown			21-May-2020	27-May-2020	6 DAY
22 ROCURONIUM	50 MG/	Unknown		Sedation	27-May-2020	27-May-2020	
23 SALIVA SUBSTITUTE		Unknown	1 other		21-May-2020	27-May-2020	6 DAY
24 SENNA [SENNAL SPP.]	2 DF/	Unknown			23-May-2020	27-May-2020	4 DAY
25 SODIUM CHLORIDE 0.9%	100 ML/BID	Unknown			27-May-2020	27-May-2020	4 DAY
26 SODIUM CHLORIDE 0.9%	500 ML/	Unknown			27-May-2020	27-May-2020	4 DAY
27 SODIUM CHLORIDE 0.9%	20 MG/	Unknown		Pain	23-May-2020	27-May-2020	4 DAY

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17912668

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17913003

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 23-Mar-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 18-Jun-2020 Mfr Rcvd Date: 15-Jun-2020 Mfr Control #: IT-ROCHE-2622990 Application #: 125276

Patient Information:

Age: Sex: Female Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	TOCILIZUMAB		8 MG/KG/	Intravenous (not otherwise specified)	up to a maximum of 800mg per dose with an interval of 12 hours	COVID-19 pneumonia		13-Mar-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1) ReC
 Acute respiratory distress syndrome NA

Event/Problem Narrative:

AER 2622990 is a clinical study case, received on 15/Jun/2020 from an other health care professional in Italy. It concerns a female patient (age not reported) (patient number: (b) (6)) who developed acute respiratory distress syndrome whilst enrolled in (b) (6) (b) (6)

The patients concomitant medications included norepinephrine (Noradrenalina), clonidine hydrochloride (Catapresan), piperacillin sodium; tazobactam sodium (Tazocin), linezolid. No medical history, past drugs and concurrent conditions were reported.

(b) (6)
 (b) (6) On (b) (6), she developed acute respiratory distress syndrome (severity: grade 5) and on (b) (6) she was died for ARDS. It was unknown if an autopsy was performed or not.

At the time of this report, the outcome of event is fatal. The therapy with tocilizumab was withdrawn in response to the acute respiratory



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17913003

distress syndrome.

The other health care professional assessed the acute respiratory distress syndrome as related to tocilizumab.

The company assessed the event acute respiratory distress syndrome as not related to tocilizumab considering there is no information regarding clinical course and circumstances surrounding its supporting plausibility to establish causal relationship.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	CATAPRESAN [CLONIDINE HYDROCHLORIDE]							
2	LINEZOLID							
3	NORADRENALINA [NOREPINEPHRINE]							



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17913003

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
4 TAZOCIN							

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17914494

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: FRA
Event Date:
Outcomes: DE,HO,
Application Type:
FDA Rcvd Date: 19-Jun-2020
Mfr Rcvd Date: 17-Jun-2020
Mfr Control #: FR-CELLTRION INC.-2020FR023386
Application #:

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Rituximab (Unknown)			Unknown		Systemic scleroderma		
2	HYDROXYCHLOROQUIN E			Unknown		Systemic scleroderma		
3	TOCILIZUMAB					COVID-19 pneumonia		
4	TOCILIZUMAB					COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Rituximab (Unknown)		Unk	NA					
2	HYDROXYCHLOROQUIN E		Unk	NA					
3	TOCILIZUMAB		NA	NA					
4	TOCILIZUMAB		NA	NA					

Event Information:

Preferred Term (MedDRA  Version: 23.1)	ReC
COVID-19	NA
COVID-19 pneumonia	NA
Death	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17914494

Event/Problem Narrative:

This initial serious literature report was received via a Regulatory Authority (Reference number: FR-ROCHE-2619060) and reported by healthcare professionals from France and a healthcare professional from the United States on 17 Jun 2020 with literature article: Avouac J, Airo P, Carlier N, Matucci-Cerinic M and Allanore Y. Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. Annals of the rheumatic diseases 2020;0:1-3; and Favalli E, Agape E and Caporali R. Incidence and clinical course of COVID-19 in patients with connective tissue diseases: a descriptive observational analysis. J Rheumatol 2020.

This case refers to 32-year-old female patient who died, and also experienced COVID-19 interstitial pneumonia, COVID-19 infection, off label use, and tocilizumab intentional use for unlabeled indication following therapy with Rituximab (unknown brand name).

The patient received Rituximab (unknown) at an unspecified dose and frequency via unknown route for systemic sclerosis on unspecified therapy dates. Batch/lot number was unknown.

Co-suspect drugs included hydroxychloroquine for systemic sclerosis and tocilizumab for COVID-19 interstitial pneumonia and COVID-19 infection, both given on unspecified therapy dates at unspecified doses and frequencies via unknown routes of administration.

On unspecified dates, the patient experienced COVID-19 interstitial pneumonia, COVID-19 infection, and died. The patient also had off label use and tocilizumab intentional use for unlabeled indication. It was further reported that the patient with SSc and pulmonary involvement treated with hydroxychloroquine and Rituximab developed a severe pattern of COVID-19 interstitial pneumonia requiring hospitalization in intensive care, where, despite intubation and an attempt with tocilizumab, the patient died. Action taken with Rituximab and co-suspect drug hydroxychloroquine was unknown; while not applicable for tocilizumab. Outcome of the event described as "died" was fatal while unknown for events COVID-19 interstitial pneumonia, COVID-19 infection, off label use, and tocilizumab intentional use for unlabeled indication. It was reported that no rechallenge was done and recurrence is not applicable for the suspect drugs.

The patient's medical history included systemic sclerosis and pulmonary involvement.

Relevant laboratory test done included a positive coronavirus test.

The reporter assessed the events died (fatal), COVID-19 interstitial pneumonia and COVID-19 infection (both caused/prolonged hospitalization) as serious; while the events off label use and tocilizumab intentional use for unlabeled indication were assessed as non-serious. The reporter assessed the causality of the events COVID-19 interstitial pneumonia and COVID-19 infection as related, while for off label use and tocilizumab intentional use for unlabeled indication were assessed as not applicable. The causality of the event died was not reported.

Relevant Medical History:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17914494

Disease/Surgical Procedure

Systemic sclerosis pulmonary

Start Date

End Date

Continuing?

YES

Medical History Product(s)

Start Date

End Date

Indications

Events

Relevant Laboratory Data:

Test Name

Coronavirus test

Result

Positive

Unit

Normal Low Range

Normal High Range

Info Avail

N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: CELLTRION

**503B Compounding
Outsourcing Facility?:**

Literature Text:

Avouac J, Airo P, Carlier N, Matucci-Cerinic M and Allanore Y. Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. Annals of the rheumatic diseases. 2020;0:1-3



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17917099

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: JPN
Event Date: 25-May-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 19-Jun-2020
Mfr Rcvd Date:
Mfr Control #: JP-ROCHE-2603284
Application #: 125276

Patient Information:

Age:
Sex: Female
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		8 MG/QD	Intravenous (not otherwise specified)		COVID-19	07-May-2020	
2	AVIGAN					Cytokine storm		
3	AVIGAN			Oral		COVID-19 pneumonia	14-Apr-2020	27-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA	18 Day	NA	NA	UNKNOWN				
2	AVIGAN	41 Day	NA	NA	UNKNOWN				
3	AVIGAN	41 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1)	ReC
COVID-19	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17917099

Event/Problem Narrative:

MFR. RECEIVED DATE: 11-MAY-2020

AER 2603284 is a spontaneous case, received on 11/May/2020 from a physician in Japan via Chugai Pharmaceuticals co. Ltd (reference number: A2020023229) and at Roche on 18/May/2020. It concerns a 6 decade old female patient was intentional treated with tocilizumab for unlabeled indication (off label use) indication and died due to covid-19 whilst being treated with tocilizumab (Actemra) and favipiravir (Avigan).

The patient's concurrent conditions included acute respiratory distress syndrome (ARDS), bronchial asthma, breast cancer and panic disorder. Concomitant medications, medical history and past drugs were not reported.

On ^{(b) (6)} COVID-19 was occurred. Treatment in the intensive care unit (ICU): Present (Duration: 25 days), Invasive ventilation (including artificial ventilator and extracorporeal membrane oxygenation [ECMO]): Present (Duration: 25 days), Non-invasive ventilation (including bilevel positive airway pressure [BIPAP] / non-invasive positive pressure ventilation [NPPV]): Not reported, Blood purification therapy (including haemodialysis / plasma exchange): None, Administration of vasopressors: None, Percutaneous oxygen saturation before the initiation of treatment with tocilizumab: SpO2 94% or more. Background information (primary disease viral (COVID-19) pneumonia, cytokine storm), presence or absence of chest imaging findings: Present, Details of findings: Suggestive of extensive bilateral ground glass opacities, infiltrative shadows and acute respiratory distress syndrome (ARDS). Information regarding COVID-19, definitive diagnosis of COVID-19: Present (Procedure: Realtime reverse transcription polymerase chain reaction [rRTPCR]), Onset date of COVID-19: ^{(b) (6)}, symptom: pyrexia, severity classification of COVID-19: severe, contact or travel since 14 days before the onset of COVID-19 symptoms: Nothing noteworthy On ^{(b) (6)} Viral (COVID-19) pneumonia and cytokine storm occurred. On ^{(b) (6)} oral favipiravir (lot number and dosage details not reported) was initiated. On ^{(b) (6)} favipiravir was discontinued. On ^{(b) (6)} she started therapy with intravenous tocilizumab (lot number not reported) 8 mg, once a day for covid-19 pneumonia and cytokine storm (off label use). On ^{(b) (6)} veklury (remdesivir) intravenous drip infusion was initiated. On ^{(b) (6)} remdesivir was discontinued. On ^{(b) (6)} she died. An autopsy was not performed.

At the time of report, therapy ongoing status with tocilizumab was not reported.

No further information was provided.

Additional information received at Chugai on 12/Jun/2020 and at Roche on 18/Jun/2020. The following information was added to this case: New event (death due to covid-19), concurrent conditions included acute respiratory distress syndrome (ARDS), bronchial asthma, breast cancer and panic disorder), indication updated for suspect (covid-19 pneumonia and cytokine storm), new suspect (favipiravir (Avigan)) and narrative updated.

Relevant Medical History:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17917099

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Acute respiratory distress syndrome			YES
Asthma			YES
Breast cancer			YES
Panic disorder			YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No Sender Organization: ROCHE 503B Compounding Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17917244

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ITA **Event Date:** 19-Mar-2020 **Outcomes:** DE, **Application Type:** BLA

FDA Rcvd Date: 29-Jun-2020 **Mfr Rcvd Date:** 22-Jun-2020 **Mfr Control #:** IT-ROCHE-2621367 **Application #:** 125276

Patient Information:

Age: 61 YR **Sex:** Male **Weight:** 85 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		340 MG/Q12H	Intravenous (not otherwise specified)		COVID-19 pneumonia	19-Mar-2020	20-Mar-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	0 Day	NA	NA	B2093H16				

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
Intentional product use issue	NA
Interleukin level increased	NA
Interstitial lung disease	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17917244

Event/Problem Narrative:

AER 2621367 is a spontaneous case, received on 11/Jun/2020 from a physician in Italy. It concerns a 61 year old male patient who intentionally used tocilizumab (Roactemra) for unapproved indication (off label use) and worsening of bilateral interstitial pneumonia, IL-6 increased.

The patient's medical history, past drug and concurrent conditions were not reported. Concomitant medications included norepinephrine, lopinavir;ritonavir (Kaletra), methylprednisolone (Urbason), insulin glulisine (Apidra), piperacillin, hydroxychloroquine sulfate (Plaquenil), pantoprazole sodium sesquihydrate (Pantorc), enoxaparin sodium (Clexane), acetylcysteine (Fluimucil A), dexamethasone (Decadron), enoxaparin sodium (Clexane), furosemide, pantoprazole sodium sesquihydrate (Pantorc), cisatracurium (Cisatracurium), fentanyl, propofol and rocuronium.

On (b) (6), the patient was admitted to facility. His X-ray test showed that he was having bilateral interstitial pneumonia. On (b) (6), he was positive with severe acute respiratory syndrome-corona virus-2 polymerase chain reaction (SARS-CoV-2 PCR).COVID-19 test. On (b) (6) he started therapy with intravenous tocilizumab (lot number: B2093H16) 340 mg, once in 12 hours for covid-19 pneumonia (intentional drug use for unapproved indication, off label use). On (b) (6) he was admitted in ICU. On (b) (6), IL-6 test was performed and the result was 56.4 pg/ml. He was supplemented with oxygen therapy and ventilator support. On (b) (6) his blood culture showed positive for S. aureus. On (b) (6), he died due to worsening of bilateral interstitial pneumonia.

At the time of this report, the outcome of IL-6 increased was not reported. It was unknown if an autopsy was performed or not.

The reporter assessed a causality of worsening of bilateral interstitial pneumonia as unrelated while did not report a causality of IL-6 increased with tocilizumab.

No further information was provided.

FU on 22/Jun/2020 : Concomitant medication norepinephrine, lopinavir;ritonavir, methylprednisolone, insulin glulisine, piperacillin, hydroxychloroquine sulfate, pantoprazole sodium sesquihydrate, enoxaparin sodium, acetylcysteine, dexamethasone, enoxaparin sodium, furosemide, pantoprazole sodium sesquihydrate, cisatracurium, fentanyl, propofol, rocuronium and event description were added.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17917244

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Chest X-ray					N
Blood culture					N
Coronavirus test					N
SARS-CoV-2 test					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	APIDRA		Unknown	100 IU/ml; 3/day		27-Mar-2020	30-Mar-2020	
2	CISATRACURIUM		Unknown	(IV - 3 g/kg/min, 6.92 ml/h 2mg/ml)		30-Mar-2020	17-Apr-2020	
3	CLEXANE		Unknown	(6000 IU - 0.6ml; 1/day)		23-Mar-2020	30-Mar-2020	
4	CLEXANE		Unknown	(SC - 6000 IU x2)		23-Mar-2020	17-Apr-2020	
5	DECADRON [DEXAMETHASONE]		Unknown	(IV - 4mg x 1)		09-Apr-2020	17-Apr-2020	
6	FENTANYL		Unknown	(IV - 150 g/h 3ml/h 250 g/50ml)		30-Mar-2020	17-Apr-2020	
7	FLUIMUCIL A							
8	FUROSEMIDE		Unknown			31-Mar-2020	06-Apr-2020	
9	KALETRA		Unknown	200mg+50mg; 2/day		19-Mar-2020	24-Mar-2020	
10	NORADRENALINE [NOREPINEPHRINE]							
11	PANTORC		Unknown	(IV - 40mg x1)		19-Mar-2020	17-Apr-2020	
12	PANTORC	20 MG/QD	Unknown			19-Mar-2020	30-Mar-2020	
13	PIPERACILLIN		Unknown	4g+500; 3/day		18-Mar-2020	25-Mar-2020	1 DAY
14	PLAQUENIL [HYDROXYCHLOROQUINE SULFATE]	200 MG/QD	Unknown			18-Mar-2020	25-Mar-2020	1 DAY
15	PROPOFOL		Unknown	(IV - 3mg/kg/h 23.1 ml/h 1000mg/100ml)		30-Mar-2020	17-Apr-2020	



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17917244

Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
16 ROCURONIUM		Unknown	(IV - 0.6 mg/kg/h 4.61ml/h 10mg/ml)		05-Apr-2020	09-Apr-2020	
17 URBASON [METHYLPREDNISOLON E]	20 MG/QD	Intravenous (not otherwise specified)	(IM IV 3V 20mg+3V 1 ml; 1/day)		20-Mar-2020	30-Mar-2020	

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17917275

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** BGD **Event Date:** **Outcomes:** DE, **Application Type:** BLA

FDA Rcvd Date: 19-Jun-2020 **Mfr Rcvd Date:** 12-Jun-2020 **Mfr Control #:** BD-ROCHE-2621558 **Application #:** 125276

Patient Information:

Age: **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		
2	ACTEMRA					Lung disorder		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		Unk	NA	UNKNOWN				
2	ACTEMRA		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA Version: 23.1)	ReC
Death	NA
Off label use	NA
Product use in unapproved indication	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17917275

Event/Problem Narrative:

AER 2621558 is a spontaneous case, received on 12/Jun/2020 from a consumer via digital media in Bangladesh. It concerns a male patient (age not specified) who died while administration of actemra for unapproved indication which was off label whilst being treated with tocilizumab (Actemra).

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On an unknown date, the patient started therapy with tocilizumab (lot number: unknown) (therapy details not reported) for lung complication due to covid. On an unspecified date, it was reported that, this case report concerns a male patient (age above 50) who received treatment with off label use of tocilizumab from the attending physician for lung complication due to COVID-19 and died today. It was unknown if an autopsy was performed or not.

At the time of this report, the patient died on an unknown date. It was unknown if therapy with tocilizumab was altered or not.

The consumer did not report a causality between patient died and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17917275

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17920856

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: PAK
Event Date: 04-Jun-2020
Outcomes: DE,OT,
Application Type: BLA
FDA Rcvd Date: 22-Jun-2020
Mfr Rcvd Date: 15-Jun-2020
Mfr Control #: PK-ROCHE-2623571
Application #: 125276

Patient Information:

Age:
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		1200 MG/	Intravenous (not otherwise specified)		COVID-19		
2	ACTEMRA					Dyspnoea		
3	ACTEMRA					Pyrexia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	B2102B02				
2	ACTEMRA		NA	NA	B2102B02				
3	ACTEMRA		NA	NA	B2102B02				

Event Information:

Preferred Term (MedDRA Version: 23.1)	ReC
Condition aggravated	NA
Death	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17920856

Event/Problem Narrative:

AER 2623571 is a spontaneous case, received on 15/Jun/2020 from a consumer in Pakistan. It concerns a male patient (unspecified age) who died and experienced condition deteriorated (unk diagnosis), and used drug intentionally use for unlabelled indication (off label use) whilst being treated with tocilizumab (Actemra).

The patient's medical history, past drugs, concurrent conditions and concomitant medications were not reported.

On an unknown date, the patient started therapy with intravenous tocilizumab (lot number: B2102B02) 1200 mg for covid-19. On an unknown date, his condition deteriorated (unk diagnosis) and used drug intentionally use for unlabelled indication (off label use). He died on (b) (6). It was unknown if an autopsy was performed or not. Cause of death was due to the off label use of actemra. It was reported that before tocilizumab administration he had presented Chest CT or Chest X-ray changes and covid-19 test positive and he was on ventilator. It was informed that he was given 1200mg of tocilizumab for the treatment of Covid-19 (Fever and difficulty in breathing) after which there was slight improvement in his health and he was removed from the ventilator but 2 days later his condition deteriorated and he was again shifted to ventilator.

At the time of death, the outcome of condition deteriorated (unk diagnosis) was not reported. It was unknown if therapy with tocilizumab was altered or not in response to the condition deteriorated (unk diagnosis).

The consumer assessed the causality as unknown between death and condition deteriorated (unk diagnosis) and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17920856

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17921018

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ITA
Event Date:
Outcomes: DE,HO,
Application Type: BLA
FDA Rcvd Date: 22-Jun-2020
Mfr Rcvd Date: 08-Jun-2020
Mfr Control #: IT-ROCHE-2627033
Application #: 125276

Patient Information:

Age: 65 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		8 MG/KG/QD	Intravenous (not otherwise specified)	on day 4 and day 5	COVID-19 pneumonia		
2	METHYLPREDNISOLONE			Unknown		Prophylaxis against transplant rejection		
3	MYCOPHENOLATE MOFETIL			Unknown		Prophylaxis against transplant rejection		
4	PREDNISON			Unknown		Prophylaxis against transplant rejection		
5	TACROLIMUS			Unknown		Prophylaxis against transplant rejection		
6	THYMOGLOBULIN			Unknown		Prophylaxis against transplant rejection		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN				
2	METHYLPREDNISOLONE		NA	NA	UNKNOWN				
3	MYCOPHENOLATE MOFETIL		NA	NA	UNKNOWN				
4	PREDNISON		Unk	NA	UNKNOWN				
5	TACROLIMUS		NA	NA	UNKNOWN				
6	THYMOGLOBULIN		NA	NA	UNKNOWN				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17921018

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
COVID-19 pneumonia	NA
Enterococcal infection	NA
Intentional product use issue	NA
Off label use	NA
Pneumonia klebsiella	NA

Event/Problem Narrative:

AER 2627033 is a literature - non-interventional study case, received on 08/Jun/2020 from a physician in Italy. It concerns a 65 year old male patient (patient number: 2) who developed Enterococcus faecalis infection, Klebsiella pneumonia and died due to Corona virus disease (COVID-19) pneumonia while enrolled in a study to evaluate the effect of tocilizumab in COVID 19 positive kidney transplant recipients. The patient had hypertension, diabetes mellitus and cardiovascular disease.

The patient underwent second kidney transplant (KT) from a deceased donor in Mar/2020. A negative COVID-19 test was obtained before kidney transplant, and no positive contact with COVID-19 subjects was reported in the days before KT. Induction immunosuppressive therapy was Thymoglobulin (for three days) and methylprednisolone, and subsequent maintenance therapy included tacrolimus (TAC) (levels 10-12 ng/mL), mycophenolate mofetil (MMF) and prednisone. He also received ganciclovir for cytomegalovirus (CMV) prophylaxis (CMV IgG/donor CMV IgG+). Eight days after KT he experienced fever and cough; He was hospitalized, swab test was subsequently repeated and resulted positive. Immunosuppressive medications (TAC, MMF) were immediately stopped, except of glucocorticoids (methylprednisolone 20 mg/day). He started hydroxychloroquine (200 mg daily) and Darunavir/Ritonavir (800/100 mg daily) the day after, and remained hemodynamically stable with only slow reduction of peripheral oxygen saturation (94-95% with low-flow oxygen through nasal cannula). Laboratory tests showed C-reactive protein 90.2 mg/L, procalcitonine 0.19 mg/mL, white blood cell count 7240 per mm³, lymphocyte count 370 per mm³, lactate dehydrogenase 518 IU/L, fibrin D-dimer 707 ng/mL, ferritin 523 ng/mL and partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FiO₂) 291 mmHg. Intravenous tocilizumab (TCZ) 8 mg/kg was administered on day 4 and 5 for COVID-19 pneumonia (off label use, intentional tocilizumab use for unlabeled indication). He did not experience any adverse event with tocilizumab. On day 6 arterial pO₂ decreased and he started non-invasive ventilation (NIV); after a further deterioration of pulmonary status mechanical ventilation was needed from day 7. On day 8 blood and urinary cultures were both positive for multi-sensitive Klebsiella Pneumoniae (urinary culture was also positive for Enterococcus Faecalis) and antibiotic treatment was shifted from amoxicillin/clavulanic acid to cefepime. Three days after tocilizumab administration C-reactive protein 20.3 mg/L, procalcitonine 0.1 mg/mL, white blood cell count 6270 per mm³, lymphocyte count 310 per mm³, lactate dehydrogenase 792 IU/L, fibrin D-dimer 1497 ng/mL, ferritin 847 ng/mL and partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FiO₂) 203 mmHg. At last follow-up C-reactive protein 34.9 mg/L, procalcitonine 0.73 mg/mL, white blood cell count 11720 per mm³, lymphocyte count per 410 mm³, lactate dehydrogenase 660 IU/L, fibrin D-dimer 2032 ng/mL, ferritin 906 ng/mL and partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FiO₂) 87 mmHg. Despite progressive modifications on antibiotic therapy (with at least adoption of gentamicin, piperacillin/tazobactam and daptomycin), fluid and medication support he became oliguric (started continuous renal-replacement therapy (CRRT) from day 12) and died on day 17. It was not reported whether an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17921018

There was insufficient information regarding outcome of Enterococcus faecalis infection and Klebsiella pneumonia as well as therapy ongoing status of prednisone.

The authors stated kidney transplantation patients associated with immunosuppressive medications (mycophenolate mofetil, thymoglobulin, prednisone, methylprednisolone and tacrolimus) were high risk population for COVID-19 pneumonia, E faecalis infection and Klebsiella pneumonia.

The company assessed the causality of the event COVID-19 pneumonia as unrelated with tocilizumab and mycophenolate mofetil and rather related with other confounding risk factors like COVID -19 pandemic, advanced age, immunocompromised condition due to renal transplant and immunosuppressive medications like methylprednisolone and tacrolimus. Other risk factors include concurrent conditions like hypertension, diabetes mellitus and cardiovascular disease. The company assessed the causality of the events E faecalis infection and Klebsiella pneumonia as related with tocilizumab and mycophenolate mofetil, thymoglobulin, prednisone, methylprednisolone and tacrolimus. Though other confounding risk factors may be cause of infections but the possibility of infections due to these suspected immunosuppressive drugs could not be ruled out.

No further information was provided.

Mella A, Mingozzi S, Gallo E, Lavacca A, Rossetti M, Clari R, Randone O, Maffei S, Salomone M, Imperiale D and Biancone L
Case series of six kidney transplanted patients with COVID-19 pneumonia treated with tocilizumab.

Transplant infectious disease : an official journal of the Transplantation Society 2020; e13348. doi: 10.1111/TID.13348

This case is cross-referenced with AER's 2617472, 2627155, 2627517, 2627466 and 2627274 (same literature article).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Renal transplant	Mar-2020		
Cardiovascular disorder			
Diabetes mellitus			
Hypertension			



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17921018

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Fibrin D dimer	2032	ng/mL			N
Blood lactate dehydrogenase	518	IU/L			N
Fibrin D dimer	707	ng/mL			N
C-reactive protein	90.2	mg/L			N
Lymphocyte count	310	mm3			N
Procalcitonin	0.1	ng/mL			N
Blood lactate dehydrogenase	792	IU/L			N
Serum ferritin	906	ng/mL			N
SARS-CoV-2 test positive					N
Lymphocyte count	370	mm3			N
Lymphocyte count	410	mm3			N
Blood lactate dehydrogenase	660	IU/L			N
Procalcitonin	0.73	ng/mL			N
White blood cell count	11720	mm3			N
Blood culture					N
Procalcitonin	0.19	ng/mL			N
White blood cell count	6270	mm3			N
Culture urine					N
C-reactive protein	20.3	mg/L			N
Serum ferritin	523	ng/mL			N
Serum ferritin	847	ng/mL			N
Fibrin D dimer	1497	ng/mL			N
C-reactive protein	34.9	mg/L			N
White blood cell count	7240	mm3			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	GANCICLOVIR							



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17921018

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

**503B Compounding
Outsourcing Facility?:**

Literature Text: Mella A, Mingozzi S, Gallo E, Lavacca A, Rossetti M, Clari R, Randone O, Maffei S, Salomone M, Imperiale D and Biancone L Case series of six kidney transplanted patients with COVID-19 pneumonia treated with tocilizumab. Transplant infectious disease : an official journal of the Transplantation Society 2020 Jun 05;:e13348-.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17923666

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ESP
Event Date: 30-Mar-2020
Outcomes: DE,HO,
Application Type: BLA
FDA Rcvd Date: 22-Jun-2020
Mfr Rcvd Date: 15-Jun-2020
Mfr Control #: ES-ROCHE-2622388
Application #: 125276

Patient Information:

Age: 62 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		600 MG/	Intravenous (not otherwise specified)		COVID-19	29-Mar-2020	29-Mar-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	13 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Hypocoagulable state	NA
Hypofibrinogenaemia	NA
Pulmonary embolism	NA

Event/Problem Narrative:

AER 2622388 is a spontaneous case, received on 15/Jun/2020 from a physician in Spain via health authority (reference number: ES-AEMPS-632938) and the European Medicines Agency (EMA). It concerns a 62 year old male patient who developed embolism pulmonary, hypofibrinogenemia and hypocoagulable state whilst being treated with tocilizumab (Roactemra).

The patient's concomitant medications included enoxaparin sodium (Enoxaparina). No medical history, past drugs and concurrent conditions were reported.

On 29/Mar/2020, the patient started therapy with intravenous tocilizumab (lot number: unknown) 600 mg once in 24 hours for sars-cov-2 acute respiratory disease. On 30/Mar/2020, he developed hypocoagulable state. On 03/Apr/2020, he developed hypofibrinogenemia. On (b) (6) he developed embolism pulmonary and was hospitalised. On an unknown date, died due to embolism pulmonary. It was not



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17923666

reported if an autopsy was performed or not.

At the time of the report, hypofibrinogenemia and hypocoagulable state was persisting. Therapy with tocilizumab was withdrawn.

The physician did not report a causality between embolism pulmonary, hypofibrinogenemia and hypocoagulable state with tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ENOXAPARINA	40 MG/Q12H	Subcutaneous	40MG CADA 12 HORAS	Thrombosis prophylaxis	30-Mar-2020		12 DAY

Reporter Source:

Study Report?: No
Sender Organization: ROCHE
503B Compounding Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17923666

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17925339

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: FRA
Event Date: 12-Apr-2020
Outcomes: DE,HO,LT,
Application Type:
FDA Rcvd Date: 25-Jun-2020
Mfr Rcvd Date: 19-Jun-2020
Mfr Control #: FR-CELLTRION INC.-2020FR023393
Application #:

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Rituximab (Unknown)			Intravenous drip	500 mg/8 months, last infusion on /Jun/2019	Systemic scleroderma	Jan-2015	Jun-2019
2	TOCILIZUMAB					COVID-19 pneumonia		
3	TOCILIZUMAB		8 MG/KG/	Intravenous (not otherwise specified)	8 milligram/kilogram	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Rituximab (Unknown)		Unk	NA					
2	TOCILIZUMAB		NA	NA					
3	TOCILIZUMAB		NA	NA					

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
COVID-19	NA
COVID-19 pneumonia	NA
Condition aggravated	NA
Intentional product use issue	NA
Intentional product use issue	NA
Off label use	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17925339

Sepsis

NA

Event/Problem Narrative:

This initial serious spontaneous literature report was received via regulatory authority (reference number: FR-ROCHE-2618449) and reported by two health professionals in France on 17 Jun 2020: Avouac J, Airo P, Carlier N, Matucci-Cerinic M and Allanore Y. Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. *Annals of the rheumatic diseases*. 2020;:1-3.

This case refers to an 84-year-old female patient who experienced COVID-19 infection, COVID-19 pneumonia, off label use, intentional use for unlabeled indication with tocilizumab, and intentional use for unlabeled indication with rituximab following therapy with rituximab (trade name: unknown).

From Jan 2015 to Jun 2019, the patient received rituximab with dosing described as "500 mg/8 months, last infusion on /Jun/2019" via IV drip for cutaneous systemic sclerosis. Batch/lot number was unknown.

Co-suspect drugs as per eudravigilance report included prednisone at 5 mg/day via unknown route for cutaneous systemic sclerosis, and tocilizumab at 8 milligram per kilogram with unspecified frequency via intravenous route for COVID-19 infection and COVID-19 pneumonia; both on unspecified therapy dates. Batch/lot numbers were unknown.

On 12 Apr 2020, the patient experienced COVID-19 infection; and on an unspecified date, the patient experienced the events COVID-19 pneumonia, off label use, intentional use for unlabeled indication with tocilizumab, and intentional use for unlabeled indication with rituximab. The events COVID-19 infection (first symptoms: fever, diarrhea, cough) and COVID-19 pneumonia resulted to hospitalization. Corrective treatment for events COVID-19 infection and COVID-19 pneumonia included ventilatory support by high-flow nasal cannula and four subcutaneous daily injections of anakinra in association with lopinavir. Despite this treatment, rapid respiratory deterioration led to the use of intravenous corticosteroid pulses (120 mg) for 3 days and tocilizumab (1 infusion of 8 mg/kg). Action taken with rituximab and co-suspect prednisone was unknown, while not applicable for tocilizumab. Outcome of all reported events was unknown.

Patient's relevant history included long-lasting limited Cutaneous Systemic Sclerosis (SSc) with recurrent digital ulcers and inflammatory arthritis as the main disease manifestations; Chronic renal insufficiency in 2002; and Pulmonary embolism in 2008.

Laboratory tests included body mass index (unspecified date) of 20 kg/m²; Chest CT Scan on unspecified date which demonstrated typical bilateral interstitial pneumonia related to COVID-19 but no pre-existing systemic sclerosis-associated interstitial lung disease; Confirmation of COVID-19 diagnosis by reverse transcription (RT)-PCR from nasopharyngeal swab specimens (positive result) on unspecified date; and Gamma globulin with result of 12.9 g/L on Feb 2020. Furthermore, B-cell depletion (with rituximab therapy) was reported complete on Feb 2020 for this patient.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17925339

Past medications and concomitant therapy were not reported.

The reporters assessed the events COVID-19 infection and COVID-19 pneumonia as serious (hospitalization) while the events off label use, intentional use for unlabeled indication with tocilizumab, and intentional use for unlabeled indication with rituximab as non-serious. Reporter's causality with rituximab was related for events COVID-19 infection and COVID-19 pneumonia. It was also reported that the routine rituximab regimen with a complete B-cell depletion confirmed at least 2 months before COVID-19 (B-cell depletion was reported complete on Feb 2020 for this patient) might have been an additional risk of infection. The reporters assessed the causality of events off label use, intentional use for unlabeled indication with tocilizumab, and intentional use for unlabeled indication with rituximab as not applicable.

This follow-up serious spontaneous literature report was received via a Regulatory Authority (reference number: FR-ROCHE-2618449) and reported by a physician and a health care professional in France on 19 Jun 2020: Avouac J, Airo P, Carlier N, Matucci-Cerinic M and Allanore Y Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. Annals of the rheumatic diseases 2020;:1-3. It was reported that the patient died due to septic complications, unknown diagnosis (sepsis). Death date was not reported. It was unknown if autopsy was done. At the time of this report, no adverse event is being reported with fatal outcome. Hence, additional event of "septic complications (unk diagnosis)" was captured in this case considering that cause of death was provided. The reporter did not describe the added event. Seriousness (death) was captured for additional event due to fatal outcome.

Case comment: Causality of event COVID-19 infection (Listed, Serious) is Related based on temporal relationship and known safety profile. Causality of event COVID-19 Pneumonia (Listed, Serious) is Not Related, event attributed to COVID-19 infection. Causality of event Intentional use for unlabeled indication and Off label use (Unlisted, Non-serious) is Not Applicable, event due to HCPs prescribing practice.

Case comment for follow up information dated 19 Jun 2020: Update on event details and additional event noted. Causality of the event Sepsis (listed, serious) is not assessable in the absence of a clear event onset date that will establish a temporal relationship between the event and Rituximab use. Causality of the event COVID-19 (listed, serious) is related based on established temporal relationship and known drug safety profile. Causality of the event COVID-19 pneumonia (listed, serious) is not related as the event is attributed to the COVID-19 infection. Causality of the event Intentional product use issue -- Tocilizumab intentional use for unlabeled indication (unlisted, non-serious) is not applicable as the event is attributed to a non-company drug. Causality of the events Intentional product use issue -- Rituximab intentional use for unlabeled indication and Off label use (unlisted, non-serious) is not applicable as the events are attributed to the prescribing HCP's practice.

This case is for nullification. A copy of this case, active case 2020FR023571, has been created to reflect the correct order of the receipt dates to allow appropriate submission of this report. All subsequent follow-up information will be reported under active case 2020FR023571.

Relevant Medical History:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17925339

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Chronic kidney disease	2002		
Pulmonary embolism	2002	2008	
Pulmonary embolism	2008		
Chronic kidney disease			YES
Systemic scleroderma			YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Polymerase chain reaction	Positive				Y
Body mass index	20 kg/m2				N
Immunoglobulins	12.9 g/L				N
Computerised tomogram thorax	NA				Y

Concomitant Products:

#	Product Name	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	PREDNISONE	5 MG/	Unknown	5 mg/day	Product used for unknown indication			
2	PREDNISONE				Systemic scleroderma			

Reporter Source:

Study Report?: No

Sender Organization: CELLTRION

503B Compounding Outsourcing Facility?:

Literature Text: Avouac J, Airo P, Carlier N, Matucci-Cerinic M and Allanore Y. Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. Annals of the rheumatic diseases. 2020;1-3



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17925741

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ITA
Event Date:
Outcomes: DE,HO,
Application Type: BLA
FDA Rcvd Date: 23-Jun-2020
Mfr Rcvd Date: 08-Jun-2020
Mfr Control #: IT-ROCHE-2627517
Application #: 125276

Patient Information:

Age: 62 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		8 MG/KG/QD	Intravenous (not otherwise specified)	day 16	COVID-19 pneumonia		
2	MYCOPHENOLATE MOFETIL			Unknown		Prophylaxis against transplant rejection		
3	TACROLIMUS			Unknown		Prophylaxis against transplant rejection		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB		NA	NA	UNKNOWN				
2	MYCOPHENOLATE MOFETIL		NA	NA	UNKNOWN				
3	TACROLIMUS		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
COVID-19 pneumonia	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17925741

Event/Problem Narrative:

AER 2627517 is a literature - non-interventional study case, received on 08/Jun/2020 from a physician in Italy. It concerns a 62 year old male patient (patient number: 4) who died due to COVID-19 pneumonia and tocilizumab used intentionally for unlabeled indication whilst enrolled in a study to evaluate the effect of tocilizumab in COVID 19 positive kidney transplant recipients.

The patient concurrent condition included hypertension and cardiovascular disease. The patient had negative hepatitis C virus (HCV)-ribonucleic acid (RNA) in after eradication.

The patient underwent second kidney transplantation (KT) on 2007. Immunosuppressive therapy was composed by tacrolimus (TAC), mycophenolate mofetil (MMF) and steroids. On 22/Mar/2020, he experienced fever, dyspnea and diarrhea and then tested positive for COVID-19. TAC and MMF were immediately discontinued. Hydroxychloroquine 200 mg daily, methylprednisolone 20 mg daily and piperacillin-tazobactam, in association to fluconazole, were started. A rapid worsening of respiratory status was observed from day 1 after diagnosis, needed mechanical ventilation. Before tocilizumab administration C-reactive protein 32 mg/L, procalcitonine 0.12 mg/mL, white blood cell count 13660 per mm³, lymphocyte count 230 per mm³, lactate dehydrogenase 704 IU/L, fibrin D-dimer 3188 ng/mL, ferritin 830 ng/mL, interleukin-6 465 pg/mL (normal range: 2-29) and partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FiO₂) 300 mmHg. Intravenous TCZ was administered (8 mg/kg) on day 16 for COVID-19 pneumonia (off label use, intentional use for unlabeled indication); respiratory status showed no improvement. Three days after tocilizumab administration C-reactive protein 12 mg/L, procalcitonine 0.13 mg/mL, white blood cell count 21790 per mm³, lymphocyte count 400 per mm³, lactate dehydrogenase 565 IU/L, fibrin D-dimer 2873 ng/mL, ferritin 637 ng/mL, interleukin-6 564.5 pg/mL and partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FiO₂) 111 mmHg. At last follow-up C-reactive protein 10 mg/L, procalcitonine 0.15 mg/mL, white blood cell count 36890 per mm³, lymphocyte count per 800 mm³, lactate dehydrogenase 814 IU/L, fibrin D-dimer 2842 ng/mL, ferritin 840 ng/mL, interleukin-6 1077.6 pg/mL and partial pressure of oxygen/fraction of inspired oxygen (PaO₂/FiO₂) 170 mmHg. He was deceased on day^{(b) (6)}. No autopsy information was reported.

The authors stated kidney transplantation patients associated with immunosuppressive medications (mycophenolate mofetil, tacrolimus and unspecified steroids) were high risk population for fatal COVID-19 pneumonia. The authors did not assess causality of COVID-19 pneumonia with tocilizumab.

The company assessed the event fatal COVID-19 pneumonia as not related with tocilizumab considering insufficient evidence to conclude a reasonable possibility that the event is attributed to suspect drug. The role of underlying illness cannot be excluded. The causality will be reassessed as per updated information is received.

No further information was provided.

Mella A, Mingozzi S, Gallo E, Lavacca A, Rossetti M, Clari R, Randone O, Maffei S, Salomone M, Imperiale D and Biancone L
Case series of six kidney transplanted patients with COVID-19 pneumonia treated with tocilizumab.

Transplant infectious disease : an official journal of the Transplantation Society 2020;: e13348. doi: 10.1111/TID.13348



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17925741

This case is cross-referenced with AERs 2617472, 2627033, 2627155, 2627517, 2627466 and 2627274 (same literature article).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Renal transplant	2007		
Cardiovascular disorder			
Hepatitis C			
Hypertension			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Fibrin D dimer	2873	ng/mL			N
White blood cell count	13660	mm3			N
White blood cell count	21790	mm3			N
C-reactive protein	32	mg/L			N
SARS-CoV-2 test positive					N
Serum ferritin	830	ng/mL			N
Serum ferritin	840	ng/mL			N
Procalcitonin	0.13	ng/mL			N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17925741

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Lymphocyte count	400	mm3			N
Lymphocyte count	800	mm3			N
Blood lactate dehydrogenase	814	IU/L			N
Fibrin D dimer	2842	ng/mL			N
Procalcitonin	0.12	ng/mL			N
Lymphocyte count	230	mm3			N
Blood lactate dehydrogenase	704	IU/L			N
Blood lactate dehydrogenase	565	IU/L			N
Fibrin D dimer	3188	ng/mL			N
Procalcitonin	0.15	ng/mL			N
White blood cell count	36890	mm3			N
C-reactive protein	12	mg/L			N
Serum ferritin	637	ng/mL			N
C-reactive protein	10	mg/L			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	FLUCONAZOLE							
2	HYDROXYCHLOROQUIN E		Unknown					
3	METHYLPREDNISOLON E		Unknown		Prophylaxis against transplant rejection			
4	PIPERACILLIN/TAZOBAC TAM							

Reporter Source:

Study Report?: No Sender Organization: ROCHE 503B Compounding Outsourcing Facility?:

Literature Text: Mella A, Mingozzi S, Gallo E, Lavacca A, Rossetti M, Clari R, Randone O, Maffei S, Salomone M, Imperiale D and Biancone L Case series of six kidney transplanted patients with COVID-19 pneumonia treated with tocilizumab. Transplant infectious disease : an official journal of the Transplantation Society 2020 Jun 05;:e13348-.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17926239

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ESP Event Date: 31-Mar-2020 Outcomes: DE,HO, Application Type: BLA
 FDA Rcvd Date: 23-Jun-2020 Mfr Rcvd Date: 15-Jun-2020 Mfr Control #:ES-ROCHE-2622391 Application #: 125276

Patient Information:

Age: 58 YR Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ROACTEMRA		600 MG/1X	Intravenous (not otherwise specified)		COVID-19	30-Mar-2020		
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	2 Day	Yes	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Hypofibrinogenaemia	NA
Off label use	NA
Product use in unapproved indication	NA

Event/Problem Narrative:

AER 2622391 is a spontaneous case, received on 15/Jun/2020 from a physician in Spain via health authority and European medicine agency (EMA). It concerns a 58 year old male patient who developed hypofibrinogenemia whilst being treated with tocilizumab (Roactemra).

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On 30/Mar/2020, the patient started receiving therapy with intravenous tocilizumab infusion (lot number: UNKNOWN) 600 mg once total for SARS-COV-2 acute respiratory disease. On ^{(b) (6)} he developed hypofibrinogenemia and was hospitalized. Therapy with tocilizumab was withdrawn. On ^{(b) (6)} the hypofibrinogenemia resolved. On ^{(b) (6)} he died due to COVID-19 pneumonia. It was unknown if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17926239

The physician did not report causality between hypofibrinogenemia and tocilizumab.

The physician assessed the seriousness of the event hypofibrinogenemia was medically significant.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17926239

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17926454

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: PAK
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 22-Jun-2020
Mfr Rcvd Date: 16-Jun-2020
Mfr Control #: PK-ROCHE-2626173
Application #: 125276

Patient Information:

Age: 61 YR
Sex: Male
Weight: KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		400 MG/	Intravenous (not otherwise specified)	frequency once	COVID-19 pneumonia	06-Jun-2020	06-Jun-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	82092801				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Cardio-respiratory arrest	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2626173 is a spontaneous case, received on 16/Jun/2020 from a pharmacist in Pakistan. It concerns a 61 year old male patient who developed fatal cardio respiratory arrest whilst being treated intentionally with tocilizumab (Actemra) for unlabeled indication.

Patient's concurrent conditions included diabetes mellitus (DM) and hypertension (HTN). No medical history, past drug or concomitant medication was reported.

On ^{(b) (6)} the patient started therapy with intravenous tocilizumab (lot number: 82092801) 400 mg once for COVID-19 pneumonia as intentionally used for unlabeled indication (off-label use). Prior to the administration of Actemra, the infection duration was reported as 9 days, he had presented Chest CT or Chest X-ray changes (Bilateral Infiltrates), COVID-19 test positive and IL-6 test performed. He was treated in the ICU with supplemental oxygen therapy. He was not in ventilator support nor needed vasopressors or dialysis. On ^{(b) (6)} he died



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17926454

due to cardio respiratory arrest. It was not reported if an autopsy was performed or not.

The pharmacist did not report a causality between cardio respiratory arrest and tocilizumab.

No further information was reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Diabetes mellitus			
Hypertension			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17926454

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17930403

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: BEL
Event Date: 17-Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 07-Jul-2020
Mfr Rcvd Date: 06-Jul-2020
Mfr Control #: BE-ROCHE-2626440
Application #: 125276

Patient Information:

Age: 81 YR
Sex: Female
Weight: KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		600 MG/1X	Intravenous (not otherwise specified)		COVID-19	01-Apr-2020	01-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	16 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Asthenia	NA
Colectomy	NA
Colitis ischaemic	NA
Melaena	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17930403

Event/Problem Narrative:

AER 2626440 is a spontaneous case, received on 18/Jun/2020 from a physician in Belgium via health authority (Belgium, FAMHPDH (Federal Agency for Medicines and Health Products), BEFAMHPDHHN202074607) and the European Medicines Agency (EMA). It concerns a 81 year old female patient who died due to melena, asthenia, transverse colectomy, left hemicolectomy and colitis ischemic whilst being treated with tocilizumab (Roactemra).

No medical history, past drug, concurrent condition and concomitant medication were reported.

On 01/Apr/2020, the patient started receiving therapy with intravenous tocilizumab (lot number: unknown) at 600 mg total for covid-19. On 17/Apr/2020, she developed melena. On an unspecified date, she developed asthenia, transverse colectomy, left hemicolectomy and colitis ischemic. On ^{(b) (6)} she died due to melena, asthenia, transverse colectomy, left hemicolectomy and colitis ischemic. It was unknown if an autopsy was performed or not.

The physician assessed melena, asthenia, transverse colectomy, left hemicolectomy, colitis ischemic as related to tocilizumab.

No further information was available.

Additional information was received on 06/Jul/2020 via European Medicines Agency (EMA) and the following information was added to the case: Causality of events changed to related from not reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
COVID-19			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17930403

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17930404

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ITA Event Date: 01-Apr-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 23-Jun-2020 Mfr Rcvd Date: 18-Jun-2020 Mfr Control #: IT-ROCHE-2626726 Application #: 125472

Patient Information:

Age: 76 YR Sex: Female Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ROACTEMRA		324 MG/	Subcutaneous		COVID-19 pneumonia	31-Mar-2020	31-Mar-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	1 Day	Unk	NA	B1125B12				

Event Information:

Preferred Term (MedDRA @ Version: 23.1) ReC
 Respiratory failure NA

Event/Problem Narrative:

AER 2626726 is a spontaneous case received on 18/Jun/2020 from a physician via health authority Agenzia Italiana del Farmaco (AIFA) (Italy: IT-MINISAL02-620992) and the European Medicines Agency (EMA). It concerns a 76 year old female patient who developed respiratory failure aggravated whilst being treated with tocilizumab (Roactemra).

Past drugs included metformin hydrochloride (Zuglimet), atorvastatin calcium trihydrate, bisoprolol fumarate (Cardicor), pantoprazole sodium sesquihydrate, acetylsalicylic acid (Acido Acetilsalicilico), furosemide (Lasix), allopurinol (Zyloric), potassium chloride (Kcl Retard) and canrenone (Luvion). Concurrent conditions included IHD, diabetes. Concomitant medications included sitagliptin (Januvia) and ramipril (Triatec (Italy)). No medical history was reported.

On 31/Mar/2020, the patient started receiving therapy with subcutaneous tocilizumab (lot number: B1125B12) 324 mg (frequency not reported) for covid-19 pneumonia. On 01/Apr/2020, she developed respiratory failure aggravated. On (b) (6) she died due to respiratory failure aggravated. It was unknown if an autopsy was performed or not. Reporter commented that for some years in therapy also with glargin insulin and lispro insulin.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17930404

It was not reported if therapy with tocilizumab was altered or not in response to the respiratory failure aggravated.

The physician did not report a causality between respiratory failure aggravated with tocilizumab.

No further information was available.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Diabetes mellitus	05-Dec-2003		UNKNOWN	
Myocardial ischaemia	17-Jun-2011		UNKNOWN	
Medical History Product(s)	Start Date	End Date	Indications	Events
LASIX	11-May-2013	28-Feb-2020		
ATORVASTATIN CALCIUM TRIHYDRATE	11-May-2013	28-Feb-2020		
LUVION	11-May-2013	12-Jun-2018		
ZYLORIC	11-May-2013	28-Feb-2020		
PANTOPRAZOLE SODIUM SESQUIHYDRATE	11-May-2013	28-Feb-2020		
ACIDO ACETILSALICILICO	11-May-2013	28-Feb-2020		
CARDICOR	11-May-2013	28-Feb-2020		
ZUGLIMET	08-May-2018	28-Feb-2020		
KCL RETARD	11-May-2013	08-May-2018		



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17930404

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	JANUVIA [SITAGLIPTIN]		Unknown			08-May-2018	14-May-2020	694 DAY
2	TRIATEC [RAMIPRIL]		Unknown			11-May-2013		7 YR

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17932524

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** IND **Event Date:** **Outcomes:** DE, **Application Type:** BLA

FDA Rcvd Date: 23-Jun-2020 **Mfr Rcvd Date:** 18-Jun-2020 **Mfr Control #:** IN-ROCHE-2626089 **Application #:** 125276

Patient Information:

Age: 46 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		400 MG/	Unknown	Single dose	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Drug ineffective	NA
Off label use	NA
Product use in unapproved indication	NA
Respiratory distress	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17932524

Event/Problem Narrative:

AER 2626089 is a spontaneous case, received on 18/Jun/2020 from an other health care professional in India. It concerns a 46 year old male patient who developed acute respiratory distress, drug could not improve his health (captured as no improvemnt (drug ineffective)), who was given tocilizumab for COVID-19 (captured as actemra used for unapproved indication) which was off label use whilst being treated with tocilizumab (Actemra).

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On an unknown date, the patient received therapy with tocilizumab (lot number: unknown) 400 mg (single dose) (route and frequency not reported) for COVID-19. On an unspecified date, it was reported that in article irregular supply hits treatment. (b) (6) run hospitals ask patients to procure expensive tocilizumab drug on their own mentioned that the he developed fever and cough earlier this month, he was admitted to (b) (6) hospital. He was shifted to (b) (6) hospital after his condition deteriorated. The doctor said he requires tocilizumab urgently for treatment, but the hospital had no stock. He asked us to arrange it. Since he was critical we had little choice in the matter a FDA official said family of him, who worked as a clerk borrowed money from relatives and started reaching out to suppliers. On (b) (6) they finally purchased a single dose of 400 mg of the drug from (b) (6) for Rs 31,000. It was administered to him on the same day. But by then his condition had become bad. Even the drug could not improve his health, the FDA official said. He died at 10.30 pm monday night after being breathless for several days, he suffered acute respiratory distress. It was unknown if an autopsy was performed or not.

At the time of this report, on an unspecified date he died. It was unknown if therapy with tocilizumab was altered or not in response to the acute respiratory distress.

The other health care professional assessed the drug could not improve his health as related to tocilizumab while did not report a causality between acute respiratory distress and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17932524

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17932932

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ESP **Event Date:** **Outcomes:** DE,OT, **Application Type:** NDA

FDA Rcvd Date: 21-Jul-2020 **Mfr Rcvd Date:** 17-Jul-2020 **Mfr Control #:** ES-PFIZER INC-2020239071 **Application #:** 050670

Patient Information:

Age: 72 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	AZITHROMYCIN				UNK	Bilateral pneumonia		
2	CEFTRIAZONE				UNK	COVID-19 pneumonia		
3	HYDROXYCHLOROQUIN E				UNK	COVID-19 pneumonia		
4	INTERFERON BETA-1B			Subcutaneous	UNK	COVID-19 pneumonia		
5	LOPINAVIR/RITONAVIR			Oral	UNK	COVID-19 pneumonia		
6	TOCILIZUMAB				UNK	COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	AZITHROMYCIN		NA	NA				PFIZER	
2	CEFTRIAZONE		NA	NA					
3	HYDROXYCHLOROQUIN E		NA	NA					
4	INTERFERON BETA-1B		NA	NA					
5	LOPINAVIR/RITONAVIR		NA	NA					
6	TOCILIZUMAB		NA	NA					



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17932932

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
Disease progression	NA
Electrocardiogram QT prolonged	NA
Hepatitis toxic	NA
Hyperbilirubinaemia	NA
Hypertransaminasaemia	NA
Ischaemia	NA
Obstructive airways disorder	NA
Off label use	NA
Peripheral arterial occlusive disease	NA
Secretion discharge	NA
Thrombosis	NA

Event/Problem Narrative:

This is a spontaneous report from a contactable physician downloaded from the European Medicines Agency (EMA) EudraVigilance-WEB and based on information received from another manufacturer, ABBIVE (manufacturer control number: ES-ABBVIE-20K-144-3436071-00).

A 72-year-old male patient started to receive azithromycin (MANUFACTURER UNKNOWN), via an unspecified route of administration from an unspecified date at an unspecified dose for bilateral pneumonia; interferon beta-1b (MANUFACTURER UNKNOWN), subcutaneous from an unspecified date at an unspecified dose for COVID-19 pneumonia; hydroxychloroquine (MANUFACTURER UNKNOWN) via an unspecified route of administration from an unspecified date at an unspecified dose for COVID-19 pneumonia; ceftriaxone (MANUFACTURER UNKNOWN) via an unspecified route of administration from an unspecified date at an unspecified dose for COVID-19 pneumonia; lopinavir/ritonavir (MANUFACTURER UNKNOWN), oral from an unspecified date at an unspecified dose for COVID-19 pneumonia; tocilizumab (MANUFACTURER UNKNOWN) via an unspecified route of administration from an unspecified date at an unspecified dose for COVID-19 pneumonia. Medical history included interstitial lung disease, peripheral arterial disease, ill-defined disorder (as reported), appendectomy, ankle fracture, ill-defined disorder (as reported), dry cough, Dyslipidaemia, Arterial hypertension, Fever, Dyspnea exacerbated. The patient concomitant medications were not reported. On unknown dates, the patient experienced prolonged QT, hypertransaminasemia, peripheral arterial disease worsening with ischemia, dyspnea worsened, recurrent mucus and blood clogging, airway blocking, toxic hepatitis, fever, dry cough, and hyperbilirubinemia worsening; all reported as serious for being medically significant. On unknown dates, the patient underwent lab tests and procedures which included Galactomannan antigen, blood beta-d-glucan, creatine phosphokinase, X-ray of thorax, culture, fibrin d dimer, interleukin-6 level, lymphocyte count, polymerase chain reaction (performed 4 times), serum ferritin, troponin (performed 3 times), and leukocyte count; all with unknown results. On an unknown date, the patient died due to an unknown cause of death. It was not reported if an autopsy was performed. As of 17Jul2020, it was reported that the events Off label use,



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17932932

hepatitis toxic, hyperbilirubinemia, peripheral arterial disease, airways obstruction, QT prolonged, Mucus discharge, clot blood, ischemia, hypertransaminasemia results in death. It was also reported that fever, dyspnea exacerbated and dry cough were part of the patient's relevant medical history. The action taken in response to the events for azithromycin, interferon beta-1b, hydroxychloroquine, ceftriaxone, lopinavir/ritonavir, and tocilizumab were not applicable. The clinical outcomes of prolonged QT, hypertransaminasemia, peripheral arterial disease worsening with ischemia, recurrent mucus and blood clogging, airway blocking, toxic hepatitis, and hyperbilirubinemia worsening were fatal at the time of death. The outcome of other events was unknown.

Pfizer is the Marketing Authorization Holder of azithromycin in the country of incidence or the country where the product was purchased (if different). This may be a duplicate report if another Marketing Authorization Holder of azithromycin has submitted the same report to the regulatory authorities.

No follow-up attempts possible. No further information is expected.

Follow-up (17Jul2020): New information downloaded from the European Medicines Agency (EMA) EudraVigilance-WEB ES-ABBVIE-20K-144-3436071-00 included: patient details (added relevant medical history and death details), product details (added indication of interferon beta-1b and tocilizumab) and event details (updated outcome of events prolonged QT, hypertransaminasemia, peripheral arterial disease worsening with ischemia, recurrent mucus and blood clogging, airway blocking, toxic hepatitis, and hyperbilirubinemia worsening to fatal; events fever, dry cough and dyspnea exacerbated were deleted as adverse events as reported under relevant medical history. Additional event off label use. Unknown cause of death was deleted as adverse event).

No follow-up attempts possible. No further information is expected.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Ankle fracture			
Appendectomy			
Arterial hypertension			
Dry cough			
Dyslipidaemia			
Dyspnea exacerbated			
Fever			



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17932932

Ill-defined disorder

Interstitial lung disease

Peripheral arterial disease

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Galactomannan antigen	unknown results				N
Thorax X-ray	unknown results				N
Fibrin D dimer	unknown results				N
Ferritin	unknown results				N
Lymphocytes	unknown results				N
PCR	unknown results				N
Culture	unknown results				N
Leucocyte count	unknown results				N
Blood beta-D-glucan	unknown results				N
Troponin	unknown results				N
Creatine phosphokinase	unknown results				N
QT interval	prolonged				N
Interleukin-6	unknown results				N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: PFIZER

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17939291

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: IDN
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 25-Jun-2020
Mfr Rcvd Date: 21-Jun-2020
Mfr Control #: ID-ROCHE-2627800
Application #: 125276

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Off label use	NA
Product use in unapproved indication	NA

Event/Problem Narrative:

AER 2627800 is a spontaneous case, received on 21/Jun/2020 from a physician in Indonesia. It concerns a patient of unknown demographics who died and had tocilizumab (Actemra) used for unapproved indication (off-label use).

The patients medical history, past drugs, concurrent conditions or concomitant medications were not reported.

On an unspecified date, the patient started therapy with tocilizumab (lot number: unknown) (dosing regimen not reported) for covid-19 (used for unapproved indication - off-label use). On an unspecified date, the patient received tocilizumab in combination with immunoglobulin. On an unspecified date, the patient died. It was not reported if an autopsy was performed or not.

The reporter did not report causality between unknown cause of death and tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17939291

No further information was provided.

This case is cross-referenced with AER 2627861 (same reporter).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17939291

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17939900

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: USA Event Date: 19-Apr-2020 Outcomes: DE,OT, Application Type: BLA

FDA Rcvd Date: 12-Nov-2020 Mfr Rcvd Date: 30-Oct-2020 Mfr Control #: US-SA-2020SA116278 Application #: 761037

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	SARILUMAB		200 MG/1X	Intravenous (not otherwise specified)	200 mg, 1X	COVID-19	17-Apr-2020	17-Apr-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	SARILUMAB	2630 MINUTES	No	NA				SANOFI	

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
Cardiac arrest	NA
Transaminases increased	NA

Event/Problem Narrative:

On 20-May-2020, event AKI was upgraded from SAE to serious AESI due to site confirmation that the event is an AESI due to ALT and AST increase.

Initial information received on 27-Apr-2020 regarding a solicited valid serious case received from (LP) REGENERON-USA GSA-PCP under reference RGN MCN: 2020-34719 on 27-Apr-2020 and transmitted to Sanofi, in the scope of company sponsored study ^{(b) (6)}

Patient ID: ^{(b) (6)} Center ID: ^{(b) (6)} Country: United States

Study title: ^{(b) (6)}
^{(b) (6)}



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17939900

Cardiac arrest due to consequence of respiratory failure (initially reported as Cardiac arrest) [Cardiac arrest]: Death; Onset date: (b) (6)
Severity: Grade 5; Outcome: Fatal; Event ended on: (b) (6)

Elevated AST & ALT [Transaminases increased] (previously reported as Elevated AST [Aspartate aminotransferase increased], initially reported as AKI [Acute kidney injury]): Medically significant; Serious AESI (ALT / AST increase); Onset date: (b) (6) Severity: Grade 3; Outcome: Not Recovered / Not Resolved; Event resolved on: Ongoing

A 79-year-old, Hispanic, female patient with severe or critical COVID-19 was enrolled in study (b) (6)

(b) (6)

(b) (6)

(b) (6)

The patient experienced above-referenced serious AESI on (b) (6) and SAE on (b) (6) after receiving study drug.

Relevant medical history included hypertension and hyperlipidaemia.

Relevant concomitant medications included hydroxychloroquine.

On (b) (6) the patient started experiencing earliest symptoms of pneumonia. Evidence of pneumonia was present based on historical X-ray chest scan, rales/crackles were present on lung auscultation at baseline and fever was documented in medical record. Patient's condition required use of invasive mechanical ventilation and treatment in ICU (intensive care unit).

On (b) (6) chest X-ray possibly reflected viral or bacterial multifocal pneumonia or acute respiratory distress syndrome. The patient was tested positive for SARS-CoV-2 Virus.

The highest temperature recorded within 24 hours prior to dosing was 99.7°F.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17939900

On (b) (6) peripheral oxygen saturation (SpO₂) was 90%, and the patient was receiving supplemental oxygen via invasive mechanical ventilation. Temperature was 36.9°C, blood pressure was 146/70, and pulse 87 bpm. Alanine aminotransferase (ALT) was 44 U/L (reference range: 9-50), aspartate aminotransferase (AST) was 56 U/L (10-37), creatinine was 1.31 mg/dl (0.5-0.95), total bilirubin was 0.2 mg/dl (0.2-1.3). Haematology results were as follows: platelets 245 x10³/L (167-374), white blood cells (WBC) 13.87 x10³/L (3.48-9.42), and neutrophils (absolute) 12.03 (units and reference range were not reported).

On (b) (6) creatinine phosphokinase was 3700.0 U/L (64-499).

On (b) (6) at 11:50 i.e. (b) (6) (b) (6) hrs 50 min after the first investigational product (IP) administration, the patient experienced Elevated AST and ALT [transaminases increased]. ALT increased to 106, AST increased to 255, WBC was 11.01 and creatinine decreased to 1.2. AST and ALT were elevated because of acute kidney injury. The event was assessed as medically significant and adverse event of special interest (AESI). Corrective treatment included monitoring with fluids and avoidance of nephrotoxins. On the same day, blood pressure decreased to 149/66 mmHg, pulse increased to 99 bpm, respiratory rate was 25 rpm, total bilirubin was 0.2, temperature was 37.2, SpO₂ was 96, platelets were 223, and neutrophils were 10.46.

On (b) (6) ALT increased to 242 and AST increased to 619. On the same day, electrical cardioversion and transthoracic echo were performed.

On (b) (6) WBC increased to 21.25, temperature decreased to 34.9, and creatinine increased to 2.74. Creatine phosphokinase increased to 61272.0, neutrophils were 16.58, blood pressure was 107/60, pulse was 112, SpO₂ was 90, and platelets were 368.

On (b) (6) the patient developed respiratory failure, requiring intubation and ventilator support. Condition of patient worsened until the patient developed shock and multi-organ failure. Despite all efforts, at 12:08 the same day i.e. (b) (6) days 20 hrs 8 min after the first IP administration, the patient experienced cardiac arrest and passed away. Autopsy was not performed.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17939900

On (b) (6) treatment assignment was unblinded for regulatory reporting purposes.

Study drug was continued in response to the event of Elevated AST & ALT. Study drug was discontinued in response to the event of Cardiac arrest.

Outcome for the other event was not recovered.

Causality assessment is as follows:

(b) (6)

Cardiac arrest: Severity = Grade 5; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Not related as the patient was in critical condition related to COVID infection. Other suspected causes included respiratory failure as a result of septic shock, COVID-19 pneumonia and renal failure.

Company causality rationale: A 79-year-old, female patient enrolled in the trial experienced cardiac arrest due to consequence of respiratory failure, which ended fatally (b) (6) days after receiving the study drug. Patient's relevant medical history of hypertension and hyperlipidaemia, along with underlying COVID-19 infection and invasive mechanical ventilation further aggravated by patient's advanced age confounds causality. Therefore, the event is assessed as not related to study drug or any clinical trial procedure.

Transaminases increased: Investigator Causality = Not Related; Company Causality = Related

Investigator causality rationale: Not related as patient is in critical care. AKI (acute kidney injury) related to critical clinical status and elevated AST/ALT is a result of AKI. Other suspected causes include critical illness. AKI occurred as a result of COVID-19 infection, respiratory failure and shock. Elevated AST/ALT as a result of AKI.

Company causality rationale: A 79-year-old, female patient enrolled in the trial experienced elevated AST and ALT (b) (6) days after receiving the study drug. Patient's baseline AST and ALT levels were above reference range and ALT increased two times while AST increased up to four



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17939900

times more than on baseline, (b) (6) days after study drug administration. Based on a plausible temporal association between study drug administration and the reported event, and considering known potential effect of study drug on the functional liver enzymes, causality for the event is assessed as related to study drug and not related to any clinical trial procedure. Underlying critical COVID 19 disease confounds causality.

Causality assessment for previously reported event term Elevated AST:

Elevated AST: Severity = Grade 3; Investigator Causality = Not Related; Company Causality = Related

Investigator causality rationale: Not related as patient is in critical care. AKI (acute kidney injury) related to critical clinical status and elevated AST is a result of AKI. Other suspected causes include critical illness.

Company causality rationale: A 79-year-old, female patient enrolled in the trial experienced elevated AST level after receiving study drug. Patient's baseline AST level was above reference range and increased up to four times more than on baseline, two days after study drug administration. Based on a plausible temporal association between study drug administration and the reported event, and considering known potential effect of study drug on the functional liver enzymes, causality for the event is assessed as related to study drug and not related to any clinical trial procedure.

Causality assessment for initially reported event term Acute kidney injury:

(b) (6)

Acute kidney injury: Severity = Grade 3; Investigator Causality = Not Related; Company Causality = Not Related

Investigator causality rationale: Not related as acute kidney injury was related to critical clinical status. It occurred as a result of COVID-19 infection, respiratory failure and shock.

Company causality rationale: A 79-year-old female patient with severe or critical COVID-19 infection and worsening pneumonia experienced acute kidney injury (b) (6) days after receiving the study drug. During hospitalization the patient developed respiratory failure and shock. Previously mentioned condition (b) (6) in addition to patient's advanced age and severe or critical COVID-19 with pneumonia could provide plausible cause for acute kidney injury in this patient. Therefore, the event is assessed as not related to the study drug or to any clinical trial procedure.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17939900

Relationship to study conduct or study procedure: The Investigator assessed the events as not related to study conduct or study procedure.

Follow up: 01-May-2020

The Investigator provided the following updates: new event Cardiac arrest added, clinical course updated.

Follow up: 20-May-2020

The Investigator provided the following updates: AESI criterion confirmed.

Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Follow-up: 28-May-2020

The Investigator provided the following updates: event term updated from AKI (acute kidney injury) to Elevated AST, cause of death, medical history and clinical course updated.

Follow-up: 10-Jun-2020, 12-Jun-2020 and 15-Jun-2020 (processed together)

The investigator provided the following updates: event terms updated for both events, seriousness criterion of hospitalization removed for Elevated AST & ALT, relevant tests and clinical course updated.

Follow-up: 15-Oct-2020



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17939900

The investigator provided the following updates: event outcome, event stop date, concomitant medications, relevant concomitant medication and clinical course updated.

Upon medical review, the follow-up information was assessed as not medically significant and does not alter the medical interpretation of the reported events.

Expectedness Assessment per current IB (version 14):
Cardiac arrest due to consequence of respiratory failure: unexpected
Elevated AST & ALT: unexpected

(b) (6)

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Hyperlipidemia			YES	
Hypertension			YES	
Peptic ulcer disease			YES	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood pressure measurement	146/70	mmHg			N
Heart rate	87	beats/min			N
Heart rate	112	beats/min			N
Oxygen saturation	90	%			N
Aspartate aminotransferase	255	U/L	10	37	N
Oxygen saturation	96	%			N
White blood cell count	13.87	10 ³ /uL	3.48	9.42	N
White blood cell count	11.01	10 ³ /uL	3.48	9.42	N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17939900

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood bilirubin	0.2	mg/dL	0.2	1.3	N
Creatine phosphokinase	61272.0	U/L	64	499	N
Creatinine	1.31	mg/dL	0.5	0.95	N
Neutrophil count	10.46	UNK			Y
SARS-CoV-2 test					N
Alanine aminotransferase	44	U/L	9	50	N
Blood bilirubin	0.2	mg/dL	0.2	1.3	N
Creatine phosphokinase	3700.0	U/L	64	499	N
Chest X-ray					Y
Platelet count	223	10*3/uL	167	374	N
Aspartate aminotransferase	56	U/L	10	37	N
Creatinine	2.74	mg/dL	0.5	0.95	N
Blood pressure measurement	149/66	mmHg			N
Body temperature	36.9	Cel			N
Heart rate	99	beats/min			N
Neutrophil count	12.03	UNK			Y
Platelet count	368	10*3/uL	167	374	N
Respiratory rate	25	breaths/min			N
Alanine aminotransferase	106	U/L	9	50	N
Body temperature	37.2	Cel			N
Oxygen saturation	90	%			N
Creatinine	1.2	mg/dL	0.5	0.95	N
Blood pressure measurement	107/60	mmHg			N
Body temperature	34.9	Cel			N
White blood cell count	21.25	10*3/uL	3.48	9.42	N
Alanine aminotransferase	242	U/L	9	50	N
Aspartate aminotransferase	619	U/L	10	37	N
Neutrophil count	16.58	UNK			Y
Platelet count	245	10*3/uL	167	374	N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	AMLODIPINE	2.5 MG/QD	Oral	2.5 mg, qd	Hypertension	2000	23-Apr-2020	
2	AZITHROMYCIN	250 MG/QD		250 mg, qd		09-Apr-2020	09-Apr-2020	23768 MIN



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17939900

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
3	AZITHROMYCIN	500 MG/QD	Oral	500 mg, qd	COVID-19	07-Apr-2020	08-Apr-2020	23768 MIN
4	HYDROXYCHLOROQUIN E	400 MG/QD	Oral	400 mg, qd		09-Apr-2020	12-Apr-2020	22328 MIN
5	HYDROXYCHLOROQUIN E	600 MG/Q12H	Oral	600 mg, bid	COVID-19	08-Apr-2020	08-Apr-2020	22328 MIN
6	METOPROLOL TARTRATE	50 MG/Q12H	Oral	50 mg, bid	Hypertension	2000	23-Apr-2020	
7	OMEPRAZOLE				Peptic ulcer disease			
8	OMEPRAZOLE	20 MG/QD	Oral	20 mg, qd		2000	23-Apr-2020	
9	SIMVASTATIN	20 MG/QD	Oral	20 mg, qd	Hyperlipidaemia	2000	23-Apr-2020	

Reporter Source:

Study Report?: No

Sender Organization: SANOFI AVENTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17940899

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** FRA **Event Date:** 22-Apr-2020 **Outcomes:** DE,LT,OT, **Application Type:** NDA

FDA Rcvd Date: 24-Jun-2020 **Mfr Rcvd Date:** 22-Jun-2020 **Mfr Control #:** FR-PFIZER INC-2020241020 **Application #:** 021446

Patient Information:

Age: 72 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	PREGABALIN				UNK		17-Apr-2020	
2	SARILUMAB		400 MG/QD	Intravenous (not otherwise specified)	400 mg, 1x/day	COVID-19	18-Apr-2020	18-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	PREGABALIN	21 Day	Unk	NA	Unknown			PFIZER	
2	SARILUMAB	20 Day	NA	NA	Unknown				

Event Information:

Preferred Term (MedDRA  Version: 23.1)	ReC
Bacterial sepsis	NA
Neutropenia	NA
Respiratory distress	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17940899

Event/Problem Narrative:

This is a Non-Interventional Study titled (b) (6)
(b) (6)

(b) (6)
(u) (b)
(b) (6) Medical history included ongoing chronic obstructive pulmonary disease, foot fracture from Jul2014, peripheral arterial occlusive disease, ongoing cirrhosis alcoholic, ongoing type 2 diabetes mellitus, colon neoplasm from May2015, ongoing chronic alcoholism, ongoing polyneuropathy. Concomitant medication included lansoprazole (LANSOPRAZOLE), melatonin (MELATONINE), piperacillin sodium, tazobactam sodium (TAZOCILLINE), insulin (INSULIN), bromazepam (BROMAZEPAM), fluticasone propionate, salmeterol xinafoate (SERETIDE), acetylsalicylic acid (ASPIRIN), enoxaparin (ENOXAPARIN). The patient experienced death secondary to respiratory distress on (b) (6) Severe sepsis to GNB which was life threatening on 05May2020 with outcome of recovered 07May2020, neutropenia which was medically significant on 22Apr2020 with outcome of recovered 27Apr2020. The patient underwent lab tests and procedures which included blood culture on an unknown date positive to Citrobacter koseri on probably urinary entry point. The action taken in response to the event for pregabalin was unknown, for sarilumab was not applicable. The patient died on (b) (6) It was not reported if an autopsy was performed. The reporter considered the events were related to pregabalin.

Pfizer is a marketing authorization holder of pregabalin. This may be a duplicate report if another marketing authorization holder of pregabalin has submitted the same report to the regulatory authorities.

Sanofi company comment: for follow-up dated 08-Jun-2020: The follow-up information does not alter the previous assessment of the case. This case involves 72 years old male patient who experienced event of the Gram- negative bacteria and neutropenia, after receiving sarilumab. The causal role of the suspect product sarilumab can be excluded for event owing to the contributory role of co-suspect drug, concomitant drugs, medical history and patients underlying condition of COVID-19.

No FU attempts are possible. no further information is expected.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Fractured toe	Jul-2014		UNKNOWN
Colon neoplasm NOS	May-2015		UNKNOWN
Alcoholic cirrhosis			YES



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17940899

Chronic alcoholism	YES
Chronic obstructive pulmonary disease	YES
Peripheral arterial occlusive disease	
Polyneuritis	YES
Type 2 diabetes mellitus	YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood culture	positive to Citrobacter koseri				Y

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ASPIRIN [ACETYLSALICYLIC ACID]							
2	BROMAZEPAM							
3	ENOXAPARIN							
4	INSULIN							
5	LANSOPRAZOLE							
6	MELATONINE							
7	SERETIDE							
8	TAZOCILLINE							



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17940899

Reporter Source:

Study Report?: No

Sender Organization: PFIZER

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17942818

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: FRA
Event Date: 12-Apr-2020
Outcomes: DE,HO,LT,
Application Type:
FDA Rcvd Date: 24-Jun-2020
Mfr Rcvd Date: 15-Jun-2020
Mfr Control #: FR-CELLTRION INC.-2020FR023571
Application #:

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Rituximab (Unknown)			Intravenous drip	500 mg/8 months, last infusion on /Jun/2019	Systemic sclerosis	Jan-2015	Jun-2019
2	PREDNISON		5 MG/	Unknown	5 mg/day	Systemic sclerosis		
3	TOCILIZUMAB					COVID-19 pneumonia		
4	TOCILIZUMAB		8 MG/KG/	Intravenous (not otherwise specified)	8 milligram/kilogram	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Rituximab (Unknown)		Unk	NA					
2	PREDNISON		Unk	NA					
3	TOCILIZUMAB		NA	NA					
4	TOCILIZUMAB		NA	NA					

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
COVID-19	NA
COVID-19 pneumonia	NA
Condition aggravated	NA
Intentional product use issue	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17942818

Off label use

NA

Sepsis

NA

Event/Problem Narrative:

This initial serious literature report was received from a health professional in France on 15 Jun 2020: Avouac J., Airo P., Carlier N., Matucci-Cerinic M., Allanore Y. et. Al. Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. Annals of the rheumatic diseases. 2020; 1-3.

This case refers to an 84-year-old female patient with body mass index of 20 kg/m2 who was affected by COVID-19 and experienced a late clinical worsening to severe pneumonia following therapy with Rituximab (unknown brand).

The patient was treated with Rituximab (unknown brand) 500mg every 8 months via parenteral route for systemic sclerosis (off label use) from Jan 2015. The last infusion was in Jun 2019. Batch/lot numbers were not reported.

On 12 Apr 2020 (day 0), the patient presented typical COVID-19 first symptoms (fever, diarrhoea, cough). The patient had confirmation of COVID-19 diagnosis by reverse transcription (RT)-PCR from nasopharyngeal swab specimens. Chest high-resolution CT was performed and demonstrated typical bilateral interstitial pneumonia. The patient experienced secondary clinical worsening on day ^{(b) (6)} and sudden respiratory failure requesting emergency hospitalisation. The patient requested ventilatory support by high-flow nasal cannula.

As corrective treatment, the patient received four subcutaneous daily injections of anakinra in association with lopinavir. Despite this treatment, rapid respiratory deterioration led to the use of intravenous corticosteroid pulses (120 mg) for 3 days and tocilizumab (1 infusion of 8 mg/kg). These treatments were associated with improved clinical outcome, characterised by decreased oxygen support requirement. No thromboembolism and bacterial secondary infection were observed on heparin (therapeutic dosing) and antibiotic therapies. Moreover, microangiopathy was not progressive. Action taken with Rituximab was not reported. The outcome reported was favourable (improved clinical outcome), coded as recovering. The patient was still in the general ward at the time of reporting.

Concomitant medication included prednisone (5mg/day) via unknown route for unknown indication.

Patient medical history included long-lasting limited cutaneous systemic sclerosis with recurrent digital ulcers and inflammatory arthritis as the main disease manifestations for 18 years, chronic renal insufficiency and history of pulmonary embolism (in 2002 and 2008). The patient had a complete B-cell depletion from Feb 2020 and gammaglobulin at 12.9 g/dL in Feb 2020. The patient had not interstitial lung disease and primary or secondary heart involvement.

The reporter assessed the events Covid -19 pneumonia and coronavirus aggravated as serious (life threatening and hospitalization) while



FDA - Adverse Event Reporting System (FAERS)

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causality was not reported. Seriousness and causality assessments of events off label use and intentional product use issue were not reported.

Authors comment: Given the frequent presence of interstitial lung disease and concurrent immunosuppressive treatment, patients with systemic sclerosis may be considered at risk for a more severe disease course and higher mortality when they develop SARS-CoV-2 virus infection. Importantly, the patient had no pre-existing interstitial lung disease that may have favoured the severity of the infection. On the other hand, the potential implication of age and comorbidities, as well as immunosuppressors including long-lasting RITUXIMAB therapy, need to be taken in consideration.

RITUXIMAB and long-term corticosteroid use, may have initially but insufficiently limited the cytokine storm, leading to a delayed worsening. The impairment of antiviral humoral response, more specifically observed with rituximab, might also have contributed to this secondary worsening. The routine RITUXIMAB regimen with a complete B-cell depletion in FEB-2020 (confirmed at least 2 months before COVID-19), but without severe hypogammaglobulinemia (gammaglobulin at 12.9 g/dL in FEB-2020), might have been an additional risk of infection. Although the impact of RITUXIMAB on infectious events remains to be clarified. However, this observation of severe and life-threatening form of COVID-19 support the continuous attention of patients with systemic sclerosis under immunosuppressants.

Event "rituximab is often used off-label in patients with systemic sclerosis" was captured as off label use and intentional product use issue as reported on source.

Follow up serious spontaneous literature report was received via regulatory authority (reference number: FR-ROCHE-2618449) and reported by two health professionals in France on 17 Jun 2020: Avouac J, Airo P, Carlier N, Matucci-Cerinic M and Allanore Y. Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. Annals of the rheumatic diseases. 2020. 1-3.

Rituximab 500 mg/8 months was given via IV drip for cutaneous systemic sclerosis from Jan 2015 with last infusion in Jun 2019. Batch/lot number was unknown.

Tocilizumab was reported as co-suspect drug at a dose of 8mg/kg via intravenous infusion for Covid-19 infection and Covid-19 pneumonia on unspecified therapy date. Batch/lot number was unknown. Previously reported concomitant prednisone was updated as co-suspect drug for systemic sclerosis.

Additional events were reported. On 12 Apr 2020, the patient experienced Covid-19 infection (coded to Covid-19). On unspecified date, the patient had tocilizumab intentional use for unlabeled indication (coded to Intentional use for unlabeled indication). Action taken with rituximab and co-suspect prednisone was unknown while not applicable for tocilizumab. Re-challenge was not done for rituximab and outcome was not applicable. Outcome of events was unknown.

The reporters assessed the events Covid-19 infection and Covid-19 pneumonia as serious (hospitalization) while the events off label use, tocilizumab intentional use for unlabeled indication and rituximab intentional use for unlabeled indication as non-serious. Causality of events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17942818

Covid-19 infection and Covid-19 pneumonia was related whereas not applicable for events off label use, tocilizumab intentional use for unlabeled indication and rituximab intentional use for unlabeled indication.

This follow-up serious spontaneous literature report was received via a Regulatory Authority (reference number: FR-ROCHE-2618449) and reported by a physician and a health care professional in France on 19 Jun 2020: Avouac J, Airo P, Carlier N, Matucci-Cerinic M and Allanore Y Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. Annals of the rheumatic diseases 2020. 1-3.

It was reported that the patient died due to septic complications (unknown diagnosis). Death date was not reported and it was unknown if autopsy was performed. Treatment for the event septic complications was not reported. Action taken with rituximab was unknown. Outcome of event was fatal. Septic complications (unknown diagnosis) was captured as event as it was reported as cause of death but was not reported as event in this latest follow up report. This new event was not described by the reporter in this follow up.

Case comment for initial information dated 15 Jun 2020 and follow up information dated 17 & 19 JUN 2020: Causality of event Sepsis (Listed, Serious) is Not Assessable in the absence of therapy and event dates that establishes temporal relationship. Causality of event COVID-19 (Listed, Serious) is Related based on temporal relationship and known safety profile. Causality of event COVID-19 Pneumonia (Listed, Serious) is Not Related, event attributed to COVID-19 infection. Causality of events Off label use, Intentional use for unlabeled indication (Unlisted, Non-serious) is Not Applicable, event due to HCPs prescribing practice.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Chronic kidney disease	2002		YES
Pulmonary embolism	2008		
Systemic scleroderma			YES

Medical History Product(s)	Start Date	End Date	Indications	Events



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FOIA Case Report Information

Case ID: 17942818

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Computerised tomogram thorax	NA				Y
Immunoglobulins	12.9 g/L				N
Body mass index	20 kg/m2				N
Polymerase chain reaction	Positive				Y

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: CELLTRION

503B Compounding
Outsourcing Facility?:

Literature Text: Avouac J, Airo P, Carlier N, Matucci-Cerinic M and Allanore Y. Severe COVID-19-associated pneumonia in 3 patients with systemic sclerosis treated with rituximab. Annals of the rheumatic diseases. 2020;1-3



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17942975

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: PAK
Event Date: 16-Jun-2020
Outcomes: DE,OT,
Application Type: BLA
FDA Rcvd Date: 25-Jun-2020
Mfr Rcvd Date: 19-Jun-2020
Mfr Control #: PK-ROCHE-2627675
Application #: 125276

Patient Information:

Age: 38 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		320 MG/	Intravenous (not otherwise specified)	Frequency stat	COVID-19	16-Jun-2020	16-Jun-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA	0 Day	Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Cardiac arrest	NA
Chest pain	NA
Diarrhoea	NA
Intentional product use issue	NA
Off label use	NA
Oxygen saturation decreased	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17942975

Event/Problem Narrative:

AER 2627675 is a spontaneous case, received on 19/Jun/2020 from a consumer in Pakistan. It concerns a 38 year old male patient who experienced reduced oxygen saturation, chest pain, diarrhea and died due to cardiac arrest whilst being treated with tocilizumab (Actemra) for unlabeled indication (off label use).

No medical history, past drugs, concurrent conditions or concomitant medications were reported.

On 12/Jun/2020, it was reported that the patient was not much affected with COVID but the symptoms of COVID appeared. On (b) (6) he was diagnosed with COVID via test. He was admitted in (b) (6) hospital in Isolation ward 3 and not in the ICU and was not on ventilator. His oxygen saturation level was 90-95 and had no medical history of any disease and was in perfect health previously. On (b) (6) he started therapy with intravenous tocilizumab (lot number: not reported), 320 mg, Frequency STAT for COVID-19 (off label use). After the Actemra injection patient experienced some pain in chest and requested his brother to punch his back. His oxygen level was dropped to 55 (captured as: reduced oxygen saturation) within 8 hours. The reporter informed that after tocilizumab administration he also experienced severe motion (captured as: diarrhea). The frequency of motion was not provided. Also due to his condition and severe symptoms he was shifted to CCU and during his shifting to CCU he expired due to cardiac arrest. It was not reported if an autopsy was performed or not.

At the time of this report, the outcome of reduced oxygen saturation, chest pain, diarrhea and cardiac arrest was fatal.

The reporter did not assess the causality of reduced oxygen saturation, chest pain, diarrhea and cardiac arrest with tocilizumab.

The reporter and company assessed reduced oxygen saturation, chest pain, diarrhea and cardiac arrest as medically significant (fatal).

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Coronavirus test					N



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17942975

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17943117

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: IDN Event Date: Outcomes: DE, Application Type: BLA

FDA Rcvd Date: 25-Jun-2020 Mfr Rcvd Date: 21-Jun-2020 Mfr Control #: ID-ROCHE-2627854 Application #: 125276

Patient Information:

Age: Sex: Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2627854 is a spontaneous case, received on 21/Jun/2020 from a physician in Indonesia. It concerns a patient of unknown demographics who died whilst being treated intentionally with tocilizumab (Actemra) for an unlabeled indication (off-label use).

No medical history, past drug, concurrent condition or concomitant medication was reported.

On an unknown date, the patient started therapy with tocilizumab (lot number: unknown; dosing regimen not reported) for COVID-19 as Actemra intentionally used for unlabeled indication (off-label use) in combination with immunoglobulin. On an unknown date, several days after the therapy, the patient died due to an unknown cause. It was not reported if an autopsy was performed or not.

The physician did not report a causality between death and tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17943117

No further information was reported.

Follow up is not possible as no consent was given.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17943117

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17943910

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: EGY
Event Date: 21-Jun-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 25-Jun-2020
Mfr Rcvd Date: 22-Jun-2020
Mfr Control #: EG-ROCHE-2629510
Application #: 125276

Patient Information:

Age: 54 YR
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		400 MG/	Unknown		COVID-19	11-Jun-2020	12-Jun-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2629510 is a spontaneous case, received on 22/Jun/2020 from a consumer in Egypt. It concerns a 54 year old patient (gender unspecified) who actemra intentionally used for unlabeled indication as an off label use and died whilst being treated with tocilizumab (Actemra).

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On 11/Jun/2020 the patient received one vial of tocilizumab 400 on 11/Jun/2020 and another vial of tocilizumab 400 on 12th June (lot number: not provided) for covid 19 intentionally used for unlabeled indication as an off label used, It is reported that patient passed away on (b) (6) It was not reported if an autopsy was performed or not.

At the time of death It was unknown if therapy with tocilizumab was altered or not in response to the death.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17943910

The reporter did not report a causality between death and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17943910

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17943996

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ZAF
Event Date: 20-Jun-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 25-Jun-2020
Mfr Rcvd Date: 23-Jun-2020
Mfr Control #: ZA-ROCHE-2630816
Application #: 125276

Patient Information:

Age: 56 YR
Sex: Male
Weight: KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ACTEMRA		400 MG/	Intravenous (not otherwise specified)		COVID-19 pneumonia	19-Jun-2020	19-Jun-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA	1 Day	NA	NA	B2096B207				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2630816 is a spontaneous case, received on 23/Jun/2020 from a pharmacist (pharmacy) in South Africa. It concerns a 56 year old male patient being treated with tocilizumab (Actemra) for unapproved indication and died (reported as patient demised).

The patiet's concurrent conditions included diabetic. Concomitant medications included furosemide (Lasix), ascorbic acid (Vitamin C), thiamine , methylprednisolone, hydrocortisone, rocuronium bromide (Esmeron). No past history and past drug was not reported.

It was reported that clinical course prior to tocilizumab was a chest cat tomography or chest x-ray a covid 19 test which was reported as non positive, treated in intensive care unit, ventilator support and he was needed vasopressors or other dialysis (no specified). On 19/Jun/2020, he started therapy with intravenous (IV) tocilizumab (lot number: B2096B207)400 mg STAT for covid-19 pneumonia, which was given for unapproved indication (off label use). There was no change noted after administration of tocilizumab. On (b) (6) he died. It was



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17943996

unknown if an autopsy was performed or not.

The pharmacist did not report a causality between death and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Diabetes mellitus			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ESMERON	50 G/	Unknown					
2	HYDROCORTISONE	50 UG/	Intravenous (not otherwise specified)	6 hour				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17943996

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
3	LASIX [FUROSEMIDE]	500 UG/	Unknown	50ml				
4	METHYLPREDNISOLON E	100 MG/	Intravenous (not otherwise specified)	over 1 hour				
5	THIAMINE	100 UG/	Unknown					
6	VITAMIN C [ASCORBIC ACID]	1.8 G/	Unknown					

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944026

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ESP **Event Date:** 25-May-2020 **Outcomes:** DE, **Application Type:** BLA

FDA Rcvd Date: 25-Jun-2020 **Mfr Rcvd Date:** 18-Jun-2020 **Mfr Control #:** ES-ROCHE-2627644 **Application #:** 125276

Patient Information:

Age: 67 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		600 MG/Q12H	Intravenous (not otherwise specified)	20 mg/ml	COVID-19 pneumonia	08-May-2020	09-May-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	18 Day	NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1) **ReC**

Intestinal perforation NA

Event/Problem Narrative:

AER 2627644 is a spontaneous case, received on 18/Jun/2020 from a pharmacist via Spain health authority (reference number: ES-AEMPS-636148) and European Medical Agency (EMA). It concerns a 67 year old male patient who experienced fatal intestinal perforation whilst being treated with tocilizumab (Roactemra).

The patient's concomitant medications included azithromycin (Azitromicina), methylprednisolone (Metilprednisolona), dexamethasone (Dexametasona), hydroxychloroquine sulfate (Hidroxicloroquina), ruxolitinib (Ruxolitinib), amoxicillin trihydrate;clavulanate potassium (Amoxicillin + Clavulanic Acid), anakinra and doxycycline (Doxiciclina). No medical history, past drugs and concurrent conditions were reported.

On 08/May/2020, the patient started therapy with intravenous tocilizumab 20 mg/ml (lot number: not reported) infusion at 600 mg every 12 hours for coronavirus pneumonia. On 25/May/2020, he experienced intestinal perforation. On an unknown date, he was died due to intestinal perforation. It was not reported if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944026

At the time of this report, therapy with tocilizumab was withdrawn in response to the intestinal perforation.

The reporter and health authority did not report a causality between intestinal perforation and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	AMOXICILLIN + CLAVULANIC ACID				Coronavirus infection			
2	ANAKINRA		Unknown		Coronavirus infection	07-May-2020		18 DAY
3	AZITROMICINA				Coronavirus infection			
4	DEXAMETASONA [DEXAMETHASONE]							



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944026

	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
5	DOXICICLINA [DOXYCYCLINE]				Coronavirus infection			
6	HIDROXICLOROQUINA SULFATO				Coronavirus infection			
7	METILPREDNISOLONA [METHYLPREDNISOLON E]	500 MG/QD	Unknown			15-May-2020		20 DAY
8	METILPREDNISOLONA [METHYLPREDNISOLON E]	500 MG/QD	Unknown		Coronavirus infection	05-May-2020	10-May-2020	20 DAY
9	RUXOLITINIB	5 MG/Q12H	Unknown		Coronavirus infection			

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944035

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ESP
Event Date: 05-Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 25-Jun-2020
Mfr Rcvd Date: 22-Jun-2020
Mfr Control #: ES-ROCHE-2628216
Application #: 125276

Patient Information:

Age: 52 YR
Sex: Male
Weight: KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	ROACTEMRA		600 MG/	Intravenous (not otherwise specified)		COVID-19 pneumonia	28-Mar-2020	28-Mar-2020	
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	9 Day	NA	NA	B3017H39				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)
ReC
Intestinal perforation
NA

Event/Problem Narrative:

AER 2628216 is a spontaneous case received on 22/Jun/2020 from a pharmacist via health authority Agencia Espanola de Medicamentos y Productos Sanitarios (AEMPS) (Spain: ES-AEMPS-636129) and the European Medicines Agency (EMA). It concerns a 52 year old male patient who developed intestinal perforation while being treated with tocilizumab (Roactemra).

Concomitant medications included lopinavir;ritonavir, hydroxychloroquine sulfate (Hidroxicloroquina Sulfato) and interferon beta. No medical history, past drugs and concurrent conditions were reported

On 28/Mar/2020, the patient started therapy with intravenous tocilizumab (lot number: B3017H39) 600 mg (frequency not reported) for COVID-19 pneumonia. On 05/Apr/2020, he developed intestinal perforation. Therapy with tocilizumab was withdrawn in response to the intestinal perforation. On an unknown date, he died. It was unknown if an autopsy was performed or not.

The pharmacist did not report a causality between intestinal perforation with tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944035

No further information was available.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	HIDROXICLOROQUINA SULFATO				COVID-19			
2	INTERFERON BETA				COVID-19			
3	LOPINAVIR;RITONAVIR				COVID-19			



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944035

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944049

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ROM
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 25-Jun-2020
Mfr Rcvd Date: 22-Jun-2020
Mfr Control #: RO-ROCHE-2629338
Application #: 125276

Patient Information:

Age:
Sex:
Weight: KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		1600 MG/	Unknown	total dose: 3200 mg	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Off label use	NA

Event/Problem Narrative:

AER 2629338 is a spontaneous case, received on 22/Jun/2020 from a physician in Romania. It concerns a 61 year old patient (gender unspecified) who had (off label use) and death whilst being treated with tocilizumab (Roactemra).

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On an unknown date, the patient started receiving therapy with tocilizumab (lot number not reported) 1600 mg (total dose)for 2 days for sars-cov 2 infection. On an unknown date, the patient died (death) (off label use) due to unknown cause. It was not stated if autopsy was performed or not.

The reporter did not report the causality of death with tocilizumab.

No further information was provided.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944049

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944529

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: DZA
Event Date: 05-Jun-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 02-Nov-2020
Mfr Rcvd Date: 27-Oct-2020
Mfr Control #: DZ-ROCHE-2615785
Application #: 125276

Patient Information:

Age: 75 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	
1	Actemra			Intravenous (not otherwise specified)		COVID-19			
#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Actemra		NA	NA	ASKED BUT UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2615785 is a spontaneous case, received on 04/Jun/2020 from a physician in Algeria. It concerns a 75 year old male patient who intentionally used drug for unlabeled indication (off label use) and later he died whilst being treated with tocilizumab (Actemra).

Patient's concurrent conditions included high blood pressure. Concomitant medication, past drugs and medical history was not reported.

A patient with COVID-19 was admitted to the hospital and was intubated due to a decrease of oxygen saturation. On an unknown date, the patient started therapy with intravenous tocilizumab (lot number: requested but not available) for COVID-19 (drug intentional use for unlabeled indication, off label use). The intensive care physician (resuscitator) has administered tocilizumab with maintaining the intubation. The perfusion of tocilizumab went well and he was stable for the moment. Later, on ^{(b) (6)} he died due to unknown cause. It was unknown if an autopsy was performed or not. Was not able to reach the reporter for batch number once it will possible the information will be provided.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944529

At the time of this report, therapy status with tocilizumab was not reported.

The physician did not report a causality between death and tocilizumab.

No further information was provided.

Additional information was received on 19/Jun/2020. Following information was added to the case: New event (death) added, product trade name added. case narrative updated.

Additional information was received on 27/Oct/2020. The following information was added to the case: Updated lot number (from unknown to asked but unknown).

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Hypertension			

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944529

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944967

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ROM
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 26-Jun-2020
Mfr Rcvd Date: 22-Jun-2020
Mfr Control #: RO-ROCHE-2629612
Application #: 125276

Patient Information:

Age:
Sex:
Weight: 90 KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		2400 MG/	Unknown	in the first day patient received 1600 mg and next day received 800 mg	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2629612 is a spontaneous case, received on 22/Jun/2020 from a physician via company representative in Romania. It concerns a 68 year old patient (gender unspecified) who had tocilizumab (Roactemra) intentionally used for unapproved indication (off label use) and experienced death nos.

The patient's past drug, medical history, concomitant medication and concurrent condition was not reported.

On an unknown date, the patient started therapy with tocilizumab (lot number: unknown, route and frequency: not reported), 2400 mg, in the first day the patient received 1600 mg and next day received 800 mg for SARS-COV 2 infection as an off label use (drug intentionally used for unapproved indication). On an unspecified date, it was reported that, the patient the patient died. The exact cause of death was not mentioned. It was not reported if an autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944967

The physician did not assess a causality of death nos with tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
SARS-CoV-2 test					N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17944967

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17945414

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ESP
Event Date: 31-Mar-2020
Outcomes: DE,
Application Type: NDA
FDA Rcvd Date: 25-Jun-2020
Mfr Rcvd Date: 22-Jun-2020
Mfr Control #: NVSC2020ES176754
Application #: 013422

Patient Information:

Age: 26 YR
Sex: Female
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	DEXAMETHASONE		20 MG/QD	Intravenous (not otherwise specified)	20 mg, QD	Product used for unknown indication	28-Mar-2020	
2	AZITHROMYCIN		500 MG/QD	Oral	500 mg, QD	COVID-19 pneumonia	23-Mar-2020	24-Mar-2020
3	DEXKETOPROFEN "SANDOZ"		25 MG/Q8H	Intravenous (not otherwise specified)	25 mg, Q8H	Product used for unknown indication	27-Mar-2020	
4	ENOXAPARIN		40 MG/QD	Subcutaneous	40 mg, QD	Product used for unknown indication	27-Mar-2020	
5	HYDROXYCHLOROQUIN E		400 MG/QD	Oral	400 mg, QD	COVID-19 pneumonia	23-Mar-2020	
6	TOCILIZUMAB		600 MG/	Intravenous (not otherwise specified)	600 mg, ONCE/SINGLE	Severe acute respiratory syndrome	29-Mar-2020	29-Mar-2020
7	TOCILIZUMAB					COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	DEXAMETHASONE	4 Day	NA	NA				NOVARTIS	
2	AZITHROMYCIN	9 Day	NA	NA					
3	DEXKETOPROFEN "SANDOZ"	5 Day	NA	NA					
4	ENOXAPARIN	5 Day	NA	NA					
5	HYDROXYCHLOROQUIN E	9 Day	NA	NA					



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17945414

Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text		Indications(s)		Start Date	End Date
Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC	
6 TOCILIZUMAB	3 Day	NA	NA						
7 TOCILIZUMAB	3 Day	NA	NA						

Event Information:

Preferred Term (MedDRA Version: 23.1)

ReC

Coagulopathy

NA

Event/Problem Narrative:

Case number# NVSC2020ES176754, is an initial spontaneous report received from a physician on 22 Jun 2020 from European Medicines Agency. This report refers to a 26-year-old female patient. Historical conditions were not reported. The patient underwent C-section on (b) (6). Current condition included Severe acute respiratory syndrome. Concomitant medication was not reported.

The patient received dexamethasone (manufacturer unknown) for the treatment of an unknown indication from 28 Mar 2020 at a dose of 20 mg, QD (intravenous).

The patient received hydroxychloroquine (manufacturer unknown) for the treatment of cCOVID-19 pneumonia from 23 Mar 2020 at a dose of 400 mg, QD (oral).

The patient received azithromycin (manufacturer unknown) for the treatment of cCOVID-19 pneumonia from 23 Mar 2020 to 24 Mar 2020 at a dose of 500 mg, QD (oral).

The patient received Dexketoprofen "Sandoz" (dexketoprofen trometamol) for the treatment of an unknown indication from 27 Mar 2020 at a dose of 25 mg, Q8H (intravenous).

The patient received enoxaparin (manufacturer unknown) for the treatment of an unknown indication from 27 Mar 2020 at a dose of 40 mg, QD (subcutaneous).

The patient received tocilizumab (manufacturer unknown) for the treatment of severe acute respiratory syndrome and sras covid 19 from 29 Mar 2020 to 29 Mar 2020 at a dose of 600 mg, ONCE/SINGLE (intravenous).

On 31 Mar 2020, 9 days after the first dose of the suspect drug, the patient developed coagulopathy. The outcome of the event coagulopathy was reported as fatal. The patient died on (b) (6). The death was due to coagulopathy. It was unknown if an autopsy was performed. The causality of coagulopathy with dexamethasone was reported as not assessable. The causality of coagulopathy with hydroxychloroquine was reported as not assessable. The causality of coagulopathy with azithromycin was reported as not assessable. The causality of coagulopathy with Dexketoprofen "Sandoz" was reported as not assessable.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17945414

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Caesarean section	(b) (6)	(b) (6)	
Severe acute respiratory syndrome			YES

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: NOVARTIS

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17947493

Case Information:

Case Type: EXPEDITED (15-DAY) eSub: Y HP: Country: ARG Event Date: 21-Jun-2020 Outcomes: DE, Application Type: BLA
 FDA Rcvd Date: 26-Jun-2020 Mfr Rcvd Date: 22-Jun-2020 Mfr Control #:AR-ROCHE-2628818 Application #: 125276

Patient Information:

Age: Sex: Male Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19	20-Jun-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2628818 is a spontaneous case, received on 22/Jun/2020, from a consumer in Argentina. It concerns a male patient (age not reported) who had intentional use of actemra for an unapproved indication which is covid-19 (off label use) and unknown cause of death whilst being treated with tocilizumab (Actemra).

No medical history, past drugs, concurrent conditions and concomitant medications were reported.

On (b) (6) patient was hospitalized with a diagnosis of COVID-19 and required intubation and as his situation did not improved. On 20/Jun/2020, he started therapy with tocilizumab (lot number, dosage regimen not reported) for covid-19. On an unknown date, he intentional used tocilizumab for an unapproved indication which was covid-19 (off label use). On (b) (6) he died due to unknown cause. Province: (b) (6)



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17947493

At the time of death, therapy ongoing status with tocilizumab was not reported.

The reporter did not report the causality of unknown cause of death with tocilizumab.

No further information was reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17947493

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17948725

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ITA
Event Date: 13-Apr-2020
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 26-Jun-2020
Mfr Rcvd Date: 16-Jun-2020
Mfr Control #: IT-ROCHE-2623644
Application #: 125472

Patient Information:

Age: 60 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ROACTEMRA		324 MG/	Subcutaneous		COVID-19 pneumonia	27-Mar-2020	27-Mar-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ROACTEMRA	17 Day	Unk	NA	B1125B12				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Off label use	NA
Product use in unapproved indication	NA
Respiratory failure	NA

Event/Problem Narrative:

AER 2623644 is a spontaneous case, received on 16/Jun/2020 from a physician in Italy. This case was received via the European Medicines Agency (EMA). It concerns a 60 year old male patient who had use Product for unapproved indication and developed respiratory failure aggravated and died whilst being treated with tocilizumab (Roactemra).

The patient's medical history included intubation. Past drugs, concurrent conditions, and concomitant medications were not reported.

On 27/Mar/2020, the patient started therapy with subcutaneous tocilizumab (lot number: B1125B12) 324 mg for COVID-19 pneumonia (frequency not reported) as off label use for an unapproved indication. On 13/Apr/2020, he developed respiratory failure aggravated. He died on (b) (6) It was unknown if an autopsy was performed or not.

At the time of death, It was not reported if therapy with tocilizumab was ongoing or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17948725

The physician did not report a causality between respiratory failure aggravated and tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Endotracheal intubation	(b) (6)	(b) (6)	UNKNOWN

Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17948725

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17950145

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** ITA **Event Date:** **Outcomes:** DE,HO, **Application Type:** ANDA

FDA Rcvd Date: 26-Jun-2020 **Mfr Rcvd Date:** 23-Jun-2020 **Mfr Control #:** NVSC2020IT179355 **Application #:** 065379

Patient Information:

Age: 57 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	MYCOPHENOLATE MOFETIL			Unknown	UNK	Prophylaxis against transplant rejection		
2	TOCILIZUMAB					COVID-19 pneumonia		
3	TOCILIZUMAB		8 MG/KG/	Intravenous (not otherwise specified)	8 mg/kg	Acute respiratory distress syndrome		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	MYCOPHENOLATE MOFETIL		NA	NA				NOVARTIS	
2	TOCILIZUMAB		NA	NA					
3	TOCILIZUMAB		NA	NA					

Event Information:

Preferred Term (MedDRA Ⓐ Version: 23.1)	ReC
Acute respiratory distress syndrome	NA
Bacterial sepsis	NA
COVID-19	NA
COVID-19 pneumonia	NA
Intentional product use issue	NA
Off label use	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17950145

Event/Problem Narrative:

Case number# NVSC2020IT179355, is an initial literature case report received from an author via health authority (European Medicines Agency) (HA reference number: IT-ROCHE-2598288) on 23 Jun 2020 cited in an article Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A et.al, A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. Kidney international 2020; 1-6. This report refers to a 57-year-old male patient. Historical conditions were not reported. Current condition included Kidney transplant in Aug 2018. Concomitant medication was not reported. The patient received mycophenolate mofetil (manufacturer unknown) for the treatment of prophylaxis against renal transplant rejection from an unknown start date at an unknown dose and frequency (route: unknown). The patient received tocilizumab (manufacturer unknown) solution for infusion for the treatment of acute respiratory distress syndrome and Covid-19 pneumonia from an unknown start date at a dose of 8 mg/kg (intravenous). On an unknown date, the patient developed bacterial sepsis, covid 19 infection (covid-19), covid-19 pneumonia, acute respiratory distress syndrome, tocilizumab intentional use for unlabeled indication (intentional product use issue) and off label use. The patient was hospitalized on an unknown date for the event of covid-19, covid-19 pneumonia, acute respiratory distress syndrome. The following significant lab tests were recorded: On an unknown date, creatinine was 282 umol/l, coronavirus test was positive and estimated glomerular filtration rate was 16 millilitre per minute per 1.73 square metre. The action taken with suspect drugs was not applicable. The patient fully recovered from covid-19, covid-19 pneumonia and acute respiratory distress syndrome on an unknown date. The outcome of the events intentional product use issue and off label use was unknown. The outcome of the event bacterial sepsis was reported as fatal. The patient died on an unknown date. The death was due to bacterial sepsis. It was unknown if an autopsy was performed. The diagnosed event bacterial sepsis (death) was considered as serious by the health authority. The diagnosed events covid-19, covid-19 pneumonia and acute respiratory distress syndrome were considered as serious (hospitalization) by the health authority. The diagnosed events intentional product use issue and off label use were considered non-serious by the health authority. The causality of covid-19, covid-19 pneumonia and acute respiratory distress syndrome with mycophenolate mofetil was reported as suspected. The causality of bacterial sepsis, intentional product use issue and off label use with mycophenolate mofetil was reported as not reported. The causality of acute respiratory distress syndrome with tocilizumab was reported as not suspected. The causality of covid-19, covid-19 pneumonia, bacterial sepsis, intentional product use issue and off label use with tocilizumab was not reported.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?
Renal transplant	Aug-2018		

Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17950145

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Glomerular filtration rate	16	millilitre per minute per 1.73 squa			N
Coronavirus test					N
Blood creatinine	282	umol/l			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: NOVARTIS

503B Compounding
Outsourcing Facility?:

Literature Text: Alberici F, Delbarba E, Manenti C, Econimo L, Valerio F, Pola A et.al.. A single center observational study of the clinical characteristics and short-term outcome of 20 kidney transplant patients admitted for SARS-CoV2 pneumonia. KIDNEY INTERNATIONAL. 2020;1-6



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17951119

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** FRA **Event Date:** 22-Apr-2020 **Outcomes:** DE,LT,OT, **Application Type:** ANDA

FDA Rcvd Date: 26-Jun-2020 **Mfr Rcvd Date:** 17-Jun-2020 **Mfr Control #:** FR-MYLANLABS-2020M1058140 **Application #:** 091228

Patient Information:

Age: 72 YR **Sex:** Male **Weight:**

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	PREGABALIN				UNK	Product used for unknown indication	17-Apr-2020	
2	SARILUMAB		400 MG/	Intravenous (not otherwise specified)	400 mg, 1X	COVID-19	18-Apr-2020	18-Apr-2020

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	PREGABALIN	21 Day	NA	NA					
2	SARILUMAB	20 Day	NA	NA				MYLAN	

Event Information:

Preferred Term (MedDRA Version: 23.1)	ReC
Bacterial sepsis	NA
Neutropenia	NA
Respiratory distress	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17951119

Event/Problem Narrative:

This Regulatory Authority with Study report was sent to Mylan on 17-Jun-2020 via the French Regulatory Authority (Company Number: FR-SA-2020SA131229)

The patient participated in (b) (6)

This case, received from physician in France, involved a 72-years-old male patient who reportedly experienced respiratory distress, bacterial sepsis, neutropenia while receiving pregabalin.

Medical history included foot fracture, peripheral arterial occlusive disease, colon neoplasm.

Current condition included chronic obstructive pulmonary disease, cirrhosis alcoholic, type 2 diabetes mellitus, alcoholism, polyneuropathy, COVID-19.

Concomitant medications were lansoprazole, melatonin, Tazocilline (piperacillin sodium, tazobactam sodium), insulin, bromazepam, Seretide (fluticasone propionate, salmeterol xinafoate), aspirin, enoxaparin.

Non-company suspect medication included sarilumab.

Unknown Date: Laboratory data included blood culture was positive to citrobacter koseri on probably urinary entry point.

17-Apr-2020: The patient initiated pregabalin capsule at an unknown dose, unit and frequency via unknown route for unknown indication.

(b) (6)

(b) (6)

22-Apr-2020: The patient experienced neutropenia. The event neutropenia was considered medically significant.

27-Apr-2020: The outcome of event neutropenia was resolved.

05-May-2020: The patient experienced severe sepsis to GNB. The event bacterial sepsis was considered life-threatening.

07-May-2020: The outcome of event bacterial sepsis was resolved.

(b) (6) The patient had died secondary to respiratory distress.

The patient died on (b) (6) and the cause of death was respiratory distress. It was unknown if the autopsy was performed or not.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17951119

Company Comment:

Serious: Respiratory distress (fatal) and bacterial sepsis are unlisted events whereas neutropenia is a listed event as per company RSI of pregabalin. Causality of the reported events respiratory distress, bacterial sepsis, neutropenia assessed as unassessable due to lack of information regarding familial history, dates, therapy and event details. However, the patient's elderly age with underlying colon neoplasm , diabetes, COVID, chronic obstructive pulmonary disease and alcoholism may confound the causality of events respiratory distress, bacterial sepsis and neutropenia.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Foot fracture	Jul-2014		NO	
Colon neoplasm	May-2015		NO	
Alcoholism			YES	
COVID-19			YES	
Chronic obstructive pulmonary disease			YES	
Cirrhosis alcoholic			YES	
Peripheral arterial occlusive disease			NO	
Polyneuropathy			YES	
Type 2 diabetes mellitus			YES	
Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17951119

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Blood culture					Y

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	ASPIRIN /00002701/			UNK				
2	BROMAZEPAM			UNK				
3	ENOXAPARIN			UNK				
4	INSULIN			UNK				
5	LANSOPRAZOLE			UNK				
6	MELATONINE			UNK				
7	SERETIDE			UNK				
8	TAZOCILLINE			UNK				

Reporter Source:

Study Report?: No

Sender Organization: MYLAN

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17954076

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: IDN
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 29-Jun-2020
Mfr Rcvd Date: 21-Jun-2020
Mfr Control #: ID-ROCHE-2627861
Application #: 125276

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA			Unknown		COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		NA	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

Initial information for this spontaneous case received on 21 June 2020 from company representative originating from physician concerning a patient with unknown identifier who received off-label use of Actemra for COVID-19 and experienced unknown cause of death.

Patient received off label use of Actemra in combination with imunoglobulin. Patient died several days after that.

The reporter did not provide seriousness and causality assessment for the events.

The company assessed Off-label use as non serious while unknown cause of death as serious.

Follow up is not possible as no consent.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17954076

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No Sender Organization: ROCHE 503B Compounding Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17954786

Case Information:

Case Type: EXPEDITED (15-DAY) **eSub:** Y **HP:** **Country:** BRA **Event Date:** 30-Apr-2020 **Outcomes:** DE, **Application Type:** BLA

FDA Rcvd Date: 20-Aug-2020 **Mfr Rcvd Date:** 17-Aug-2020 **Mfr Control #:** BR-ROCHE-2627595 **Application #:** 125276

Patient Information:

Age: **Sex:** Male **Weight:** KG

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	Actemra		600 MG/	Unknown		COVID-19	13-Apr-2020	

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	Actemra	17 Day	Unk	NA	B2083B06				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Acute kidney injury	NA
Alanine aminotransferase increased	NA
Aspartate aminotransferase increased	NA
Gamma-glutamyltransferase increased	NA
Intentional product use issue	NA
Interleukin level increased	NA
Off label use	NA
Respiratory gas exchange disorder	NA
Septic shock	NA



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17954786

Event/Problem Narrative:

AER 2627595 is a spontaneous case, received on 18/Jun/2020 from a pharmacist via company representative in Brazil. It concerns a male patient (age not reported) who developed actemra off label use, intentional use of actemra for unlabeled indication, septic shock, acute renal injury, gammaglutamyltransferase increased, alanine aminotransferase increased, respiratory gas exchange disorder, interleukin-6 increased, glutamic oxalacetic transaminase increased, pyruvic glutamic transaminase increased whilst being treated with tocilizumab (Actemra).

Concomitant medication included chloroquine. No medical history, past drug, concurrent condition were reported.

On 13/Apr/2020, the patient presented with internal viral pneumonia (covid-19). On same day, he received therapy with tocilizumab (lot number: B2083B06, route and frequency: not reported) at a dose of 600 mg, for covid-19 (intentional use for unlabeled indication, off label use). On 18/Apr/2020, his symptoms worsened. On 18/Apr/2020, gammaglutamyltransferase: 41 (unit and normal range not reported). On 19/Apr/2020, alanine aminotransferase: 56 (unit and normal range not reported). On 27/Apr/2020, interleukin-6 result: 63.3 pg/mL (test done on (b) (6) results not provided). On 28/Apr/2020, glutamic oxalacetic transaminase: 23, pyruvic glutamic transaminase: 38 (unit and normal range not reported). On same day, he received another 600 mg infusion of tocilizumab. On 30/Apr/2020, the was in serious situation as he presented hemodynamic worsening due to septic shock, acute renal failure with indication for hemodialysis and worsening of gas exchange (worsening of respiratory gas exchange disorder) gammaglutamyltransferase increased, alanine aminotransferase increased, interleukin-6 increased, glutamic oxalacetic transaminase increased. On (b) (6) glutamic oxalacetic transaminase: 2832, pyruvic glutamic transaminase: 1573, gammaglutamyltransferase: 117, alanine aminotransferase: 74 (unit and normal range not reported). Later on the same day, after (b) (6) days of use, he presented worsening in the performed exams, including liver enzymes, and he died on (b) (6). It was unknown if an autopsy was performed or not. He was not neutropenic at the time of the infectious event, as the result provided on (b) (6) was 29980 /mm³. In addition, the infection was not related to absolute neutrophil count less than 1000. It was also reported that, he did not present any risk factor such as diabetes mellitus, HIV infection, felty syndrome, rheumatoid arthritis, splenomegaly, low leukocyte count, splenectomy, permanence catheter nor previous infection. He did not use methotrexate, biological medicines, anti-inflammatories nor corticosteroids, however he used chloroquine before being hospitalized at the hospital where the reporter has been working. As corrective treatment, he used antibiotic regimen (unspecified) and mechanical ventilation. It was also specified, due to the context of the (b) (6) submission, that the questionnaire was regarding infections.

At the time of death, it was not reported if therapy with tocilizumab and ceftriaxone sodium was altered or not in response to the septic shock, acute renal injury, respiratory gas exchange disorder, interleukin-6 increased, glutamic oxalacetic transaminase increased, pyruvic glutamic transaminase increased, gammaglutamyltransferase increased, alanine aminotransferase increased.

The pharmacist assessed the septic shock, acute renal injury as related to tocilizumab, ceftriaxone sodium. The pharmacist did not report a causality for the gammaglutamyltransferase increased, alanine aminotransferase increased, respiratory gas exchange disorder, interleukin-6 increased, glutamic oxalacetic transaminase increased, pyruvic glutamic transaminase increased with tocilizumab, ceftriaxone sodium.

No further information was provided.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17954786

Additional information was received on 10/Aug/2020 and the following information was added to the case: Updated reporter details, start date of tocilizumab and updated event description accordingly.

Additional information was received on 17/Aug/2020 and the following information was added to the case: Event description: As corrective treatment, he used antibiotic regimen (unspecified) and mechanical ventilation. It was also specified, due to the context of the (b) (6) submission, that the questionnaire was regarding infections, case received from pharmacist via company representative and event description updated accordingly.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail
Aspartate aminotransferase					N
Alanine aminotransferase					N
Alanine aminotransferase					N
Aspartate aminotransferase					N
Gamma-glutamyltransferase					N
Interleukin level	63.3	pg/mL			N

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event
1	CHLOROQUINE				COVID-19			



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17954786

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17955137

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: ESP
Event Date: 04-Apr-2020
Outcomes: DE,HO,OT,
Application Type: BLA
FDA Rcvd Date: 29-Jun-2020
Mfr Rcvd Date: 15-Jun-2020
Mfr Control #: ES-ROCHE-2621971
Application #: 125276

Patient Information:

Age: 66 YR
Sex: Male
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	TOCILIZUMAB		600 MG/1X	Intravenous (not otherwise specified)		COVID-19	01-Apr-2020	01-Apr-2020
2	ENOXAPARINA		20 MG/QD	Unknown			03-Apr-2020	10-Apr-2020
3	ENOXAPARINA		80 MG/Q12H	Unknown		Product used for unknown indication	11-Apr-2020	22-Apr-2020
4	ENOXAPARINA		40 MG/Q12H	Unknown			01-Apr-2020	02-Apr-2020
5	TOCILIZUMAB					COVID-19 pneumonia		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	TOCILIZUMAB	15 Day	Yes	NA	UNKNOWN				
2	ENOXAPARINA	15 Day	NA	NA	UNKNOWN,UNKNOWN,UNKNOWN				
3	ENOXAPARINA	15 Day	NA	NA	UNKNOWN,UNKNOWN,UNKNOWN				
4	ENOXAPARINA	15 Day	NA	NA	UNKNOWN,UNKNOWN,UNKNOWN				
5	TOCILIZUMAB	15 Day	Yes	NA	UNKNOWN				



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17955137

Event Information:

Preferred Term (MedDRA ® Version: 23.1)	ReC
Hypofibrinogenaemia	NA
Intentional product use issue	NA
Off label use	NA
Wound haemorrhage	NA

Event/Problem Narrative:

AER 2621971 is a spontaneous case, received on 15/Jun/2020 from a physician in Spain. This case was received via the European Medicines Agency (EMA). It concerns a 66 year old male patient who uses tocilizumab as intentional for unlabeled indication and developed wound hemorrhage and hypofibrinogenemia whilst being treated with enoxaparin sodium (Enoxaparina) and tocilizumab.

The patient's medical history, past drugs, concurrent conditions, and concomitant medications were not reported. Background information, previous diseases: influenza A with admission in the hospital, no high blood pressure, diabetes, mellitus or dyslipidemia, ex-smoker, no known drug allergies not specified vertigo. No other relevant disease was referred. Previous surgery: head cysts 58 years ago, low limbs varices 10 years ago (possible intern saphenectomy from the groin).

On ^{(b) (6)} the patient was admitted to an emergency room and the reason for consultation was cough. Referred by primary care physician due to 24-48 hours of symptoms which consist of cough without expectoration. The Dyspnea feeling was denied. Fever of 38.5 grades persisting despite paracetamol. He denied other level symptoms. Physical examinations: Temperature (C): 36.4, systolic pressure (mmHg): 105, diastolic pressure (mmHg): 72, heart rate (bpm): 40 pul/min, oxygen saturation in nasal cannula (%) 94, flux l/min: 4, oxygen saturation with mask (%) 96, oxygen concentration with mask (%) 100, oxygen saturation with non-invasive ventilation (%): 95, oxygen flux non-invasive ventilation (l/min) 15, capillary blood glucose (mg/dl) 101. When he comes, he was in alert stage, oriented, without subjective dyspnea or tachypnea appearance. His O2: 96 % with reservoir, analytic 215 C-reactive protein (CRP), 129 IL-6, 1235 Ferritin, increased transaminases, severe lymphopenia, increased acute phase reactants. Laboratory. blood analytic on ^{(b) (6)} hemoglobin 16.9 g/dl (12.5-17.2), leucocytes 6.27x10e3/mcl (3.6-10.5), neutrophils 88.3% (42-77), 1.2 INR (0.8-1.2), neutrophils 965 mg/dl (150-450), fibrinogen 176 IU/l (0-40) ASAT/GOT, 100 IU/L (0-35) ALAT/GPT, total bilirubin 0.85 mg/dl (0.3-1.2), C reactive protein 215.8 mg/l (0-5), ferritin 1235 ng/ml (22-322), interleukin-6 129.0 pg/ml (0-3.4). Imagen: Chest x-ray: PA and lateral chest imagen was performed. No previous imagen was available for comparison. Lung parenchyma had alveolar opacities with subpleural region predominance, of the right upper lobe and middle and lower bilateral lobes. Greater right hemithorax involvement. COVID-19 Bronchopneumonia compatible findings. Radiological findings of COPD. Cardiothoracic ration conserved. Aortic enlargement. Degenerative changes of the spinal cord. Other tests, vital signs 37.1 C, 126/77, Heart rate 83 bpm, O2 sat. 95% with a reservoir (15l). Regular general status. He presented respiratory worsening despite the reservoir, so they started tocilizumab. On ^{(b) (6)} He started therapy with enoxaparin sodium (lot number and route not reported) 40 mg every 12 hours for unknown indication, intravenous tocilizumab (lot number not reported) 600 mg every day for SARS-COV-2 acute respiratory disease as off label unlabeled indication. Tocilizumab therapy was started due to worsening despite the reservoir (young patient without comorbidities. ICU candidate and progressed respiratory failure despite the reservoir. Increased IL-6 and ferritin. Normal PCT. No other alternative diagnosis



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17955137

to COVID-19. No treatment contraindication). Evening turn, vital signs: O2 saturation with non-invasive mechanical ventilation (%): 94, O2 flux with noninvasive mechanical ventilation (l/min): 100. He was clinical and hemodynamically stable. Without any issue during the turn. Tocilizumab was scheduled in the morning. Analytic: 215 CRP, 129 il-6, 1235 ferritin, increased transaminases, severe lymphopenia, increased acute phase reactants. Chest X-ray: bilateral pneumonia compatible with COVID-19. COVID PCR: positive, clinical judgment, moderate COVID-19 pneumonia. Treatment, hydroxichloroquine+ azithromycin+ceftriaxone. Plan: admission at general internal medicine. O2: 94 % with reservoir. Analytic: 215 CRP, 129 IL-6, 1235 ferritin, increased transaminases, severe lymphopenia, increased acute phase reactants. Control analytic (b) (6) pending, SARS-CoV2 Treatment: hydroxichloroquine. Antibiotic: azithromycin. Clinical Judgement: mild-moderate COVID-19 Pneumonia, prior to evening turn, he had a desaturation of 86 % with reservoir so ICU was warned, who assessed the patient. At 16.30, he had O2 saturation improvement: 94% with reservoir, oxygen flux 100%. Tocilizumab was started at 17.30h. Plan to admission in the charge of general internal medicine. Given that he presented symptoms since less than 5 days, it was decided to keep azithromycin. It was decided ceftriaxone discontinuation due to acute phase reactants results: PCT 0.11 (215 CRP could be explained because of COVID-19 pneumonia). Analytic at admission (b) (6) 10:14:00: Red cells: red blood cells 5.08 x10e6/uL (4 - 5.65), hemoglobin 15.5 g/dL (12.5 - 17.2), hematocrit 46.7 % (37 - 49), mean cell volume (MCV). 92.0 fL (80 - 101), mean corpuscular hemoglobin (MCH). 30.5 pg (27 - 34), mean corpuscular hemoglobin concentration (MCHC) 33.2 g/dL (31.5 - 36), red cell distribution width (RDW). 13.3 % (11.5 - 14.7), white cells leucocytes 7.53 x10e3/uL (3.6 - 10.5), neutrophils 84.4 % (42 - 77), lymphocytes 9.7 % (20 - 44), monocytes 2.8 % (2 - 9.5), eosinophils 2.0 % (0.5 - 5.5), basophils 0.2 % (0 - 1.8), LUC 1.0 % (0 - 6), neutrophils 6.36 x10e3/uL (1.5 - 7.7), lymphocytes 0.73 x10e3/uL (1.1 - 4.5), monocytes 0.21 x10e3/uL (0.1 - 0.9), eosinophils 0.15 x10e3/uL (0.02 - 0.65), basophils 0.02 x10e3/uL (0 - 0.2), LUC 0.08x10e3/uL, platelets, platelets 286 x10e3/uL (150 - 370), MPV. 9.8 fL (5.9 - 9.9), prothrombin time 13.1 seg, prothrombin activity 62 % (70 - 120), INR 1.2 (0.8 - 1.2), fibrinogen 1136 mg/dL (150 - 450), Kaolin cephalin clotting time 25.0 seg, RATIO cephalin times 0.94 (0.8 - 1.2), D DIMER 16555 ng/mL (0 - 500), serum glucose 92 mg/dL (74 - 106), total cholesterol 122 mg/dL (0 - 200), triglycerides 188 mg/dL (0 - 150), Serum creatinine 0.67 mg/dL (0.7 - 1.3), glomerular filtration (CKD-EPI) 90 mL/min/1.73m2 (45 - 999999), serum urea 41 mg/dL (11 - 49), serum sodium 139 mmol/L (136 - 145), serum potassium 3.7 mmol/L (3.5 - 5.1), serum chloride 102 mmol/L (99 - 109), allen scholarship cum admission test (ASAT)/GOT 89 IU/L (0 - 40), alanine aminotransferase (ALAT) / serum glutamic pyruvic transaminase (SGPT) 77 IU/L (0 - 35), lactate dehydrogenase (LDH) 618 IU/L (100 - 190), GGT 110 IU/L (0 - 73), total bilirubin 0.61 mg/dL (0.3 - 1.2), CPK 82 IU/L (40 - 280), Serum total proteins 6.3 g/dL (6.4 - 8.3), serum albumin 3.5 g/dL (2.9 - 5.2), C reactive protein 276.8 mg/L (0 - 5), procalcitonin 0.12 ng/mL (0 - 0.5), ferritin 2034 ng/mL (22 - 322), Indication: left ear heart, troponin I (hs-TnI) 8.7 ng/L (0 - 53.5), interleukin-6 1000 pg/mL (0 - 3.4). On (b) (6) he started therapy with enoxaparin sodium (lot number and route not reported) 20 mg every day for unknown indication. Intensive medicine (b) (6) cause of consultation, respiratory failure Bad prognosis analytic factors; lymphopenia 0.73, D dimer 16500, LDH 618, ferritin 2300. IL-6 1000, Pneumonia: yes, bilateral serious pneumonia CURB-65: 1, oxygen: 89% with the mask with reservoir ventilation. He admitted to the hospital floor of internal medicine due to desaturation. At assessment work of breathing with refractory hypoxemia. He was admitted in the unit, and orotracheal intubation with rapid sequence intubation with rocuronium, etomidate, and fentanyl. Cormack I. Central venous cannulation via the left jugular vein and left radial artery without issues. On (b) (6) he developed hypofibrinogenemia. Analytic, (b) (6) Leucocytes 14,01 x10e3/u (3,60-10,50), Red blood cells 4,59 x10e6/uL (4,00-5,65), Hemoglobin 14,1 g/dL (12,5-17,2), Hematocrit 42,6 % (37,0-49,0), Platelets 194 x10e3/uL (150-370), Neutrophils 89,3 % (42,0-77,0) neutrophils 12,51 x10e3/uL (1,50-7,70), Lymphocytes 4,3 % (20,0-44,0) Lymphocytes 0,60 x10e3/uL (1,10-4,50), Monocytes 4,8 % (2,0-9,5) Monocytes 0,67 x10e3/uL (0,10-0,90), Eosinophils 0,1 % (0,5-5,5), Eosinophils 0,01 x10e3/uL (0,02-0,65), Basophils 0,1 % (0,0-1,8) Basophils 0,01 x10e3/uL



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17955137

(0,00-0,20), LUC 1,3 % (0,0-6,0) LUC 0,18 x10e3/uL coagulation, prothrombin time 15,5 seg, prothrombin activity 46 % (70-120), INR 1,5 (0,8-1,2), functional fibrinogen 76 mg/dL (150-450), cephalin time 22,6 seg, ratio cephalin time 0,85 (0,80-1,20), D dimer 26408 ng/mL (0-500). On (b) (6) leucocytes 17,05 x10e3/u (3,60-10,50), Red blood cells 4,87 x10e6/uL (4,00-5,65), Hemoglobin 15,1 g/dL (12,5-17,2), Hematocrit 45,7 % (37,0-49,0), Platelets 400 x10e3/uL (150-370), Neutrophils 82,9 % (42,0-77,0) Neutrophils 14,13 x10e3/uL (1,50-7,70), Lymphocytes 10,1 % (20,0-44,0) Lymphocytes 1,72 x10e3/uL (1,10-4,50), coagulation, prothrombin time 13,1 seg, prothrombin activity 62 % (70-120), INR 1,2 (0,8-1,2), derived fibrinogen 304 mg/dL (150-450), cephalin time 24,7 seg, ratio del cephalin time 0,93 (0,80-1,20), D dimer 9680 ng/mL (0-500). On (b) (6) the hypofibrinogenemia was resolved. Therapy with tocilizumab was withdrawn. On (b) (6) he started therapy with enoxaparin sodium (lot number not reported) 80 mg every 12 hours for unknown indication. On (b) (6) he developed wound hemorrhage. On an unspecified date, wound hemorrhage was resolving. On (b) (6) Leucocytes 12,51 x10e3/u (3,60-10,50), Red blood cells 3,83 x10e6/uL (4,00-5,65), Hemoglobin 11,6 g/dL (12,5-17,2), Macrocytosis + Hematocrit 37,5 % (37,0-49,0), Platelets 333 x10e3/uL (150-370), Neutrophils 74,9 % (42,0-77,0) Neutrophils 9,37 x10e3/uL (1,50-7,70), Lymphocytes 9,5 % (20,0-44,0) Lymphocytes 1,19 x10e3/uL (1,10-4,50), coagulation, prothrombin time 11,9 seg, prothrombin activity 78 % (70-120), INR 1,1 (0,8-1,2), derived fibrinogen 1200 mg/dL (150-450), cephalin time 30,5 seg, ratio cephalin time 1,14 (0,80-1,20), D dimer 4190 ng/mL (0-500). On (b) (6) Leucocytes 10,59 x10e3/u (3,60-10,50), Red blood cells 3,87 x10e6/uL (4,00-5,65), Hemoglobin 12,0 g/dL (12,5-17,2), Hematocrit 37,2 % (37,0-49,0), Platelets 338 x10e3/uL (150-370), Neutrophils 57,7 % (42,0-77,0) Neutrophils 6,11 x10e3/uL (1,50-7,70), Lymphocytes 14,5 % (20,0-44,0) Lymphocytes 1,54 x10e3/uL (1,10-4,50), coagulation, prothrombin time 11,2 seg, prothrombin activity 91 % (70-120), INR 1,0 (0,8-1,2), derived fibrinogen 1012 mg/dL (150-450), cephalin time 28,5 seg, ratio cephalin time 1,07 (0,80-1,20). He died on (b) (6) due to an unknown cause of death.

At the time of death, therapy with enoxaparin sodium was ongoing.

The physician did not report a causality between wound hemorrhage, hypofibrinogenemia, and enoxaparin sodium, tocilizumab.

No further information was provided.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17955137

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:

Literature Text:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17959552

Case Information:

Case Type: EXPEDITED (15-DAY)
eSub: Y
HP:
Country: BOL
Event Date:
Outcomes: DE,
Application Type: BLA
FDA Rcvd Date: 29-Jun-2020
Mfr Rcvd Date: 12-Jun-2020
Mfr Control #: BO-ROCHE-2623751
Application #: 125276

Patient Information:

Age:
Sex:
Weight:

Suspect Products:

#	Product Name	Compounded Drug ?	Dose/Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date
1	ACTEMRA		400 MG/	Unknown	2 doses	COVID-19		

#	Product Name	Interval 1st Dose to Event	DeC	ReC	Lot#	Exp Date	NDC #	MFR/Labeler	OTC
1	ACTEMRA		Unk	NA	UNKNOWN				

Event Information:

Preferred Term (MedDRA @ Version: 23.1)	ReC
Death	NA
Intentional product use issue	NA
Off label use	NA

Event/Problem Narrative:

AER 2623751 is a spontaneous case, received on 12/Jun/2020 from a consumer in Bolivia, Plurinational State Of. It concerns a patient of unknown demographics who intentional use of actemra for an unapproved indication (off label use), unknown cause of death whilst being treated with tocilizumab (Actemra).

No medical history, past drug, concurrent condition and concomitant medication were reported.

On an unreported date, the patient received tocilizumab (lot number: unknown), 400 mg, 2 doses (route and frequency not reported) for COVID-19 (off label use). Patient did not experienced any adverse event. It is reported that the patient died while being treated with tocilizumab for the off-label use of COVID. It was unknown if an autopsy was performed or not.

The consumer did not report the causality for the unknown cause of death with tocilizumab.



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17959552

No further information was reported.

Additional information was received on 26/Jun/2020 and the following information was added to the case (source id: 1572020): new event: unknown cause of death and narrative updated.

Relevant Medical History:

Disease/Surgical Procedure	Start Date	End Date	Continuing?	
Medical History Product(s)	Start Date	End Date	Indications	Events

Relevant Laboratory Data:

Test Name	Result	Unit	Normal Low Range	Normal High Range	Info Avail

Concomitant Products:

#	Product Name	Dose/ Frequency	Route	Dosage Text	Indications(s)	Start Date	End Date	Interval 1st Dose to Event

Reporter Source:

Study Report?: No

Sender Organization: ROCHE

503B Compounding
Outsourcing Facility?:



FDA - Adverse Event Reporting System (FAERS)

FOIA Case Report Information

Case ID: 17959552

Literature Text:

Printer: CDPEDQ5

User: STEPPERH

Date - Time: 12-Nov-2020 04:11 PM

Total Number of Cases (Non-Esub): 10

Total Number of Pages: 64

Print Job Number: 23304

Disclaimers:

Submission of a safety report does not constitute an admission that medical personnel, user facility, importer, distributor, manufacturer or product caused or contributed to the event. The information in these reports has not been scientifically or otherwise verified as to a cause and effect relationship and cannot be used to estimate the incidence of these events.

Data provided in the Quarterly Data Extract (QDE) or a FAERS FOIA report are a snapshot of FAERS at a given time. There are several reasons that a case captured in this snapshot can be marked as inactive and not show up in subsequent reports. Manufacturers are allowed to electronically delete reports they submitted if they have a valid reason for deletion. FDA may merge cases that are found to describe a single event, marking one of the duplicate reports as inactive. The data marked as inactive are not lost but may not be available under the original case number.

Processed Case Id's for Images:

17745001 17751095 17769604 17769605 17802678 17802947 17845062 17861011
17935068 17949779

Failed Case Id's for Images:

Total Failed Cases: 0

All dates displayed in the report are in EST(GMT-05:00) time zone

Basic Details			
Company Unit	CDER-CTU	Originating Account	FAERS
Source Medium	MWO (Drug)	Source Form Type	E2B XML 3500
Priority	Urgent		
Override Auto Calculation Rule	No		
FDA Received Date	04-May-2020	CTU Received Date	04-May-2020
CTU Triage Date		CTU Data Entry Date	
Report Type	Spontaneous	Report Classification	Drug
Assign To	User		
User/Group			
Forward to Department	☒ CDER (CDER-OSE-RSS-CTU@fda.hhs.gov) (E2B)		
Case Priority	Direct		

Contact				
Case Reporter	First Name	Last Name	Email Address	Phone
☒	(b) (6)	(b) (6)	(b) (6)	(b) (6)

A. PATIENT INFORMATION	
Patient Identifier (In Confidence)	(b) (6)
Age	65 Year(s)
Date of Birth	
Gender	Female
Weight	80 kg
Ethnicity (Check single best answer)	Hispanic/Latino
Race (Check all that apply)	☐ Asian ☐ American Indian or Alaskan Native ☐ Black or African American ☐ White ☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM	
Type of Report (check all that apply)	☒ Adverse Event ☐ Product Use/Medication Error ☐ Product Problem (e.g., defects/malfunctions) ☐ Problem with Different Manufacturer of Same Medicine
Serious	Yes
Outcome Attributed to Adverse Event (Check all that apply)	☒ Death ☐ Life Threatening ☐ Hospitalization (initial or prolonged) ☐ Other Serious or Important Medical Events ☐ Disability or Permanent Damage ☐ Congenital Anomaly/Birth Defects ☐ Required Intervention to Prevent Permanent Impairment/Damage

Date of Death	(b) (6)
Date of Event	27-Apr-2020
Date of this Report	04-May-2020

Describe Event, Problem or Product Use Error

Describe Event, Problem, or Product Use Error: Hydroxychloroquine Sulfate treatment under Emergency Use Authorization (EUA):

Relevant Test/Laboratory Data 1 of 1

Test Name	COVID 19	Test Date	18-Apr-2020
Test Result	Positive	Test Unit	
Low Test Range		High Test Range	
More Information Available?			

Additional Comments

Other Relevant History, Including Preexisting Medical Conditions

Covid-19

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)	No
Returned to Manufacturer on	
Do you have a picture of the product? (check yes if you are including a picture)	No

D. PRODUCT(S) 1 of 2

Suspect	Yes
Does this report involve cosmetic, dietary supplement or food/medical food?	Yes
Primary?	Yes
Type	Drug/Biologic
Product Name	Hydroxychloroquine
Strength	200 mg milligram(s) If Other
Manufacturer/Compounder	Actavis
NDC# or Unique ID	00591-3041-01
Product Type(check all that apply)	☐ OTC

	☐ Compounded ☒ Generic ☐ Biosimilar	
Event Abated After Use Stopped or Dose Reduced?	Doesn't Apply	
Event Reappeared after Reintroduction ?	Doesn't Apply	

Drug Therapy 1 of 1

Dose or Amount	400 mg milligram(s)	If Other	
Frequency	Daily	If Other	
Route	Oral	If Other	
Dosage Form			
Start	19-Apr-2020		
Stop	23-Apr-2020		
Therapy Duration		If Other	
Is therapy still on-going?	No		
Lot Number	1385969A		
Expiration Date	31-Jul-2021		

Diagnosis for Use (indication) 1 of 1

Covid-19

D. PRODUCT(S) 2 of 2

Suspect	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Actemra		
Strength	400 mg milligram(s)	If Other	
Manufacturer/Compounder	Genetec		
NDC# or Unique ID	50242-0137-01		
Product Type(check all that apply)	☐ OTC ☒ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?	Doesn't Apply		
Event Reappeared after Reintroduction ?	Doesn't Apply		

Drug Therapy 1 of 1

Dose or Amount	400 mg milligram(s)	If Other	
Frequency	Other	If Other	x1
Route	Intravenous bolus	If Other	

Dosage Form		
Start	27-Apr-2020	
Stop	27-Apr-2020	
Therapy Duration		If Other
Is therapy still on-going?	No	
Lot Number	B2097B01	
Expiration Date	30-May-2022	

Diagnosis for Use (indication)		1 of 1
Covid-19		

E. SUSPECT MEDICAL DEVICE

Brand Name	
Common Device Name	
Procode	
Manufacturer Name	
City	
State	
Model #	
Lot #	
Catalog #	
Expiration Date	
Serial #	
Unique Identifier (UDI)#	
Operator of Device	☐ Health Professional ☐ Patient/Consumer ☐ Other
Other	
If Implanted, Give Date	
If Explanted, Give Date	
Is this a single-use device that was reprocessed and reused on a patient?	
If Yes for the above field, Enter Name and Address of Reprocessor	
Was this device serviced by a third party?	

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

CONCOMITANT MEDICAL PRODUCT DESCRIPTION

G. REPORTER 1 of 1

Primary?	Yes	
Reporter is Patient?		
Title		
Last Name	(b) (6)	
Middle Name		
First Name	(b) (6)	
Address	(b) (6)	
City	(b) (6)	
State/Province/Region	(b) (6)	
Country	UNITED STATES	If Other
ZIP/Postal Code	(b) (6)	
Phone	(b) (6)	
Email	(b) (6)	
Fax		
Reporter Organization		
Department		
Reporter Speciality		
Health Professional?	Yes	
Occupation	Pharmacist	If Other
Also Reported to	☐ Manufacturer/Compounder ☒ User Facility ☐ Distributor/Importer	
If you do NOT want your identity disclosed to the manufacturer, please mark this box (Confidentiality Requested):	Yes	

All dates displayed in the report are in EST(GMT-05:00) time zone

Basic Details			
Company Unit	CDER-CTU	Originating Account	FAERS
Source Medium	MWO (Drug)	Source Form Type	E2B XML 3500
Priority	High		
Override Auto Calculation Rule	No		
FDA Received Date	06-May-2020	CTU Received Date	06-May-2020
CTU Triage Date		CTU Data Entry Date	
Report Type	Spontaneous	Report Classification	Drug
Assign To	User		
User/Group			
Forward to Department	☒ CDER (CDER-OSE-RSS-CTU@fda.hhs.gov) (E2B)		
Case Priority	Direct		

Contact				
Case Reporter	First Name	Last Name	Email Address	Phone
☒	(b) (6)	(b) (6)	(b) (6)	(b) (6)

A. PATIENT INFORMATION

Patient Identifier (In Confidence)	(b) (6)
Age	
Date of Birth	(b) (6)
Gender	Male
Weight	145.7 kg
Ethnicity (Check single best answer)	Not Hispanic/Latino
Race (Check all that apply)	☐ Asian ☐ American Indian or Alaskan Native ☒ Black or African American ☐ White ☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM

Type of Report (check all that apply)	☒ Adverse Event ☐ Product Use/Medication Error ☐ Product Problem (e.g., defects/malfunctions) ☐ Problem with Different Manufacturer of Same Medicine
Serious	Yes
Outcome Attributed to Adverse Event (Check all that apply)	☒ Death ☒ Life Threatening ☒ Hospitalization (initial or prolonged) ☐ Other Serious or Important Medical Events ☐ Disability or Permanent Damage ☐ Congenital Anomaly/Birth Defects ☐ Required Intervention to Prevent Permanent Impairment/Damage

Date of Death	(b) (6)	
Date of Event	01-May-2020	
Date of this Report	06-May-2020	

Describe Event, Problem or Product Use Error

Describe Event, Problem, or Product Use Error: Received off-label sarilumab for treatment of lab-confirmed COVID-19 while intubated in the ICU (requiring 100% FiO2) on (b) (6). Risks and benefits discussed with patient prior to initiation, and he gave his consent which was documented in the medical record. On (b) (6) the patient suffered an ST elevation myocardial infarction and underwent cardiac cath. He later developed secondary bacterial pneumonia on (b) (6) growing *Serratia marcescens* from sputum on (b) (6) (treated with cefepime, and de-escalated to ceftriaxone and then levofloxacin) and MRSA from sputum on (b) (6) (treated with vancomycin x1, followed by linezolid). On (b) (6) he developed progressive lactic acidosis (>17). There was also concern for ischemic bowel (but no obvious perforation) given elevated liver enzymes and rising lactic acid, but the patient was too hemodynamically unstable to travel for CTA. He later died that same day of cardiac arrest. Additional Meds from this hospitalization (wouldn't fit in section below): hydrocortisone, hydroxychloroquine, insulin glargine, insulin lispro, insulin regular, iopamidol, ipratropium/albuteral neb, ketamine, lactulose, levofloxacin, linezolid, lorazepam, magnesium sulfate, melatonin, meropenem, metoprolol tartrate, metronidazole, micafungin, midazolam, morphine, multivitamin, norepinephrine, ondansetron, oxycodone, pantoprazole, polyethylene glycol, potassium chloride, propofol, quetiapine, senna, senna/docusate, sodium bicarbonate, ticagrelor, vancomycin, vasopressin, vitamin B1, zinc sulfate

Relevant Test/Laboratory Data 1 of 7

Test Name	FERRITIN	Test Date	(b) (6)
Test Result	1106	Test Unit	NANOGRAMS PER MILLILITRE
Low Test Range		High Test Range	
More Information Available?			

Relevant Test/Laboratory Data 2 of 7

Test Name	C-REACTIVE PROTEIN	Test Date	(b) (6)
Test Result	23.2	Test Unit	MILLIGRAMS PER DECILITRE
Low Test Range		High Test Range	
More Information Available?			

Relevant Test/Laboratory Data 3 of 7

Test Name	LACTIC ACID	Test Date	(b) (6)
Test Result	>17	Test Unit	MILLIMOLES PER LITRE
Low Test Range		High Test Range	
More Information Available?			

Relevant Test/Laboratory Data 4 of 7

Test Name	AST	Test Date	(b) (6)
Test Result	3045	Test Unit	
Low Test Range		High Test Range	
More Information Available?			

Relevant Test/Laboratory Data 5 of 7

Test Name	ALT	Test Date	(b) (6)
Test Result	731	Test Unit	
Low Test Range		High Test Range	

More Information Available?	

Relevant Test/Laboratory Data 6 of 7

Test Name	TOTAL BILIRUBIN	Test Date	(b) (6)
Test Result	5.4	Test Unit	MILLIGRAMS PER DECILITRE
Low Test Range		High Test Range	
More Information Available?			

Relevant Test/Laboratory Data 7 of 7

Test Name	DIRECT BILIRUBIN	Test Date	(b) (6)
Test Result	3.9	Test Unit	MILLIGRAMS PER DECILITRE
Low Test Range		High Test Range	
More Information Available?			

Additional Comments

Units/L for AST and ALT above

Other Relevant History, Including Preexisting Medical Conditions

Hypertension

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)	No
Returned to Manufacturer on	
Do you have a picture of the product? (check yes if you are including a picture)	No

D. PRODUCT(S) 1 of 22

Suspect	Yes
Does this report involve cosmetic, dietary supplement or food/medical food?	
Primary?	Yes
Type	Drug/Biologic
Product Name	Sarilumab
Strength	200 mg milligram(s) If Other
Manufacturer/Compounder	Regeneron
NDC# or Unique ID	0024-5910-01
Product Type(check all that apply)	☐ OTC

	☐ Compounded ☐ Generic ☐ Biosimilar
Event Abated After Use Stopped or Dose Reduced?	Doesn't Apply
Event Reappeared after Reintroduction ?	Doesn't Apply

Drug Therapy 1 of 1

Dose or Amount	200 mg milligram(s)	If Other	
Frequency	Other	If Other	Once
Route	Intravenous bolus	If Other	
Dosage Form			
Start	06-Apr-2020		
Stop	06-Apr-2020		
Therapy Duration		If Other	
Is therapy still on-going?	No		
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

Adjunctive therapy for COVID-19 in a critically ill patient.

D. PRODUCT(S) 2 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Acetaminophen		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	

Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication)			1 of 1

D. PRODUCT(S) 3 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Adenosine		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID	-		
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 4 of 22

Concomitant	Yes	
Does this report involve cosmetic, dietary supplement or food/medical food?		
Primary?		
Type	Drug/Biologic	
Product Name	Albumin	
Strength		If Other
Manufacturer/Compounder		
NDC# or Unique ID		
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar	
Event Abated After Use Stopped or Dose Reduced?		
Event Reappeared after Reintroduction ?		

Drug Therapy 1 of 1

Dose or Amount		If Other
Frequency		If Other
Route		If Other
Dosage Form		
Start		
Stop		
Therapy Duration		If Other
Is therapy still on-going?		
Lot Number		
Expiration Date		

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 5 of 22

Concomitant	Yes	
Does this report involve cosmetic, dietary supplement or food/medical food?		
Primary?		

Type	Drug/Biologic		
Product Name	Albuterol		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 6 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Amiodarone		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		

Event Abated After Use Stopped or Dose Reduced?		
Event Reappeared after Reintroduction ?		

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 7 of 22

Concomitant	Yes
Does this report involve cosmetic, dietary supplement or food/medical food?	
Primary?	
Type	Drug/Biologic
Product Name	Aspirin
Strength	
Manufacturer/Compounder	
NDC# or Unique ID	
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar
Event Abated After Use Stopped or Dose Reduced?	
Event Reappeared after Reintroduction ?	

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			

Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 8 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Atorvastatin		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 9 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Azithromycin		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 10 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Bivalirudin		
Strength		If Other	
Manufacturer/Compounder			

NDC# or Unique ID	
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar
Event Abated After Use Stopped or Dose Reduced?	
Event Reappeared after Reintroduction ?	

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 11 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Calcium gluconate		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	

Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 12 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Cefepime		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 13 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Ceftriaxone		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 14 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			

Type	Drug/Biologic		
Product Name	Dexmedatomidine		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 15 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Diltiazem		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		

Event Abated After Use Stopped or Dose Reduced?	
Event Reappeared after Reintroduction ?	

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 16 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Docusate		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			

Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 17 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Enoxaparin		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 18 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Epinephrine		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 19 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Eptifibatide		
Strength		If Other	
Manufacturer/Compounder			

NDC# or Unique ID	
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar
Event Abated After Use Stopped or Dose Reduced?	
Event Reappeared after Reintroduction ?	

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 20 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Fentanyl		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	

Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 21 of 22

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Furosemide		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start			
Stop			
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 22 of 22

Concomitant	Yes	
Does this report involve cosmetic, dietary supplement or food/medical food?		
Primary?		
Type	Drug/Biologic	
Product Name	Heparin	
Strength		If Other
Manufacturer/Compounder		
NDC# or Unique ID		
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar	
Event Abated After Use Stopped or Dose Reduced?		
Event Reappeared after Reintroduction ?		

Drug Therapy 1 of 1

Dose or Amount		If Other
Frequency		If Other
Route		If Other
Dosage Form		
Start		
Stop		
Therapy Duration		If Other
Is therapy still on-going?		
Lot Number		
Expiration Date		

Diagnosis for Use (indication) 1 of 1

E. SUSPECT MEDICAL DEVICE

Brand Name	
Common Device Name	
Procode	
Manufacturer Name	

City	
State	
Model #	
Lot #	
Catalog #	
Expiration Date	
Serial #	
Unique Identifier (UDI)#	
Operator of Device	☐ Health Professional ☐ Patient/Consumer ☐ Other
Other	
If Implanted, Give Date	
If Explanted, Give Date	
Is this a single-use device that was reprocessed and reused on a patient?	
If Yes for the above field, Enter Name and Address of Reprocessor	
Was this device serviced by a third party?	

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

CONCOMITANT MEDICAL PRODUCT DESCRIPTION

G. REPORTER 1 of 1

Primary?	Yes
Reporter is Patient?	
Title	
Last Name	(b) (6)
Middle Name	
First Name	(b) (6)
Address	(b) (6)
City	(b) (6)
State/Province/Region	(b) (6)
Country	UNITED STATES If Other
ZIP/Postal Code	(b) (6)
Phone	(b) (6)
Email	(b) (6)
Fax	
Reporter Organization	

Department			
Reporter Speciality			
Health Professional?	Yes		
Occupation	Pharmacist	If Other	
Also Reported to	☐ Manufacturer/Compounder ☒ User Facility ☐ Distributor/Importer		
If you do NOT want your identity disclosed to the manufacturer, please mark this box (Confidentiality Requested):	No		

All dates displayed in the report are in EST(GMT-05:00) time zone

Basic Details			
Company Unit	CDER-CTU	Originating Account	FAERS
Source Medium	MWO (Drug)	Source Form Type	E2B XML 3500
Priority	High		
Override Auto Calculation Rule	No		
FDA Received Date	11-May-2020	CTU Received Date	11-May-2020
CTU Triage Date		CTU Data Entry Date	
Report Type	Spontaneous	Report Classification	Drug
Assign To	User		
User/Group			
Forward to Department	☒ CDER (CDER-OSE-RSS-CTU@fda.hhs.gov) (E2B)		
Case Priority	Direct		

Contact				
Case Reporter	First Name	Last Name	Email Address	Phone
☒	(b) (6)	(b) (6)	(b) (6)	

A. PATIENT INFORMATION	
Patient Identifier (In Confidence)	Unspecified
Age	56 Year(s)
Date of Birth	
Gender	Male
Weight	95.8 kg
Ethnicity (Check single best answer)	Not Hispanic/Latino
Race (Check all that apply)	☐ Asian ☐ American Indian or Alaskan Native ☐ Black or African American ☒ White ☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM	
Type of Report (check all that apply)	☒ Adverse Event ☐ Product Use/Medication Error ☐ Product Problem (e.g., defects/malfunctions) ☐ Problem with Different Manufacturer of Same Medicine
Serious	Yes
Outcome Attributed to Adverse Event (Check all that apply)	☒ Death ☐ Life Threatening ☒ Hospitalization (initial or prolonged) ☐ Other Serious or Important Medical Events ☐ Disability or Permanent Damage ☐ Congenital Anomaly/Birth Defects ☐ Required Intervention to Prevent Permanent Impairment/Damage
Date of Death	09-May-2020

Date of Event	10-Apr-2020
Date of this Report	11-May-2020

Describe Event, Problem or Product Use Error

Describe Event, Problem, or Product Use Error: Tocilizumab for COVID-19: 56 yo M with PMH of smoking/vaping, COPD, and T2DM presented on (b) (6) with SOB, fever, and malaise. Pt was found to be COVID positive. On (b) (6), pt received Tocilizumab 400mg IV x 1 dose for COVID pneumonia. On (b) (6) pt developed MSSA and pseudomonas aeruginosa pneumonia and bacteremia. Also found to have empyema. Pt's received antibiotics however clinical course continued to worsen and required prolonged ventilatory support. Family opted for comfort care on (b) (6) and pt passed on (b) (6)

Relevant Test/Laboratory Data				1 of 5
Test Name	COVID-19 CORONAVIRUS PCR	Test Date	(b) (6)	
Test Result	Positive	Test Unit		
Low Test Range		High Test Range		
More Information Available?				

Relevant Test/Laboratory Data				2 of 5
Test Name	CULTURE SPUTUM	Test Date	(b) (6)	
Test Result	Staphylococcus aureus (MSSA)	Test Unit		
Low Test Range		High Test Range		
More Information Available?				

Relevant Test/Laboratory Data				3 of 5
Test Name	CULTURE SPUTUM	Test Date	(b) (6)	
Test Result	Pseudomonas aeruginosa	Test Unit		
Low Test Range		High Test Range		
More Information Available?				

Relevant Test/Laboratory Data				4 of 5
Test Name	CULTURE BLOOD VENIPUNCTURE	Test Date	(b) (6)	
Test Result	Pseudomonas aeruginosa	Test Unit		
Low Test Range		High Test Range		
More Information Available?				

Relevant Test/Laboratory Data				5 of 5
Test Name	CULTURE PLEURAL FLUID	Test Date	(b) (6)	
Test Result	Staphylococcus aureus (MSSA), Pseudomonas aeruginosa	Test Unit		
Low Test Range		High Test Range		
More Information Available?				

Additional Comments

Other Relevant History, Including Preexisting Medical Conditions

	Smoking, vaping, COPD, T2DM, occasional alcohol use

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)	No
Returned to Manufacturer on	
Do you have a picture of the product? (check yes if you are including a picture)	No

D. PRODUCT(S) 1 of 1

Suspect	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?	Yes		
Type	Drug/Biologic		
Product Name	Tocilizumab		
Strength	400 mg milligram(s)	If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☒ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?	Doesn't Apply		
Event Reappeared after Reintroduction ?	Doesn't Apply		

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency	Other	If Other	Once
Route	Intravenous (Not otherwise specified)	If Other	
Dosage Form			
Start	10-Apr-2020		
Stop	10-Apr-2020		
Therapy Duration		If Other	
Is therapy still on-going?	No		

Lot Number	
Expiration Date	
Diagnosis for Use (indication) 1 of 1	
COVID-19	

E. SUSPECT MEDICAL DEVICE

Brand Name	
Common Device Name	
Procode	
Manufacturer Name	
City	
State	
Model #	
Lot #	
Catalog #	
Expiration Date	
Serial #	
Unique Identifier (UDI)#	
Operator of Device	☐ Health Professional ☐ Patient/Consumer ☐ Other
Other	
If Implanted, Give Date	
If Explanted, Give Date	
Is this a single-use device that was reprocessed and reused on a patient?	
If Yes for the above field, Enter Name and Address of Reprocessor	
Was this device serviced by a third party?	

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

CONCOMITANT MEDICAL PRODUCT DESCRIPTION	

G. REPORTER 1 of 1

Primary?	Yes
Reporter is Patient?	
Title	

Last Name	(b) (6)	
Middle Name		
First Name	(b) (6)	
Address	(b) (6)	
City	(b) (6)	
State/Province/Region	(b) (6)	
Country	UNITED STATES	If Other
ZIP/Postal Code	(b) (6)	
Phone		
Email	(b) (6)	
Fax		
Reporter Organization		
Department		
Reporter Speciality		
Health Professional?	Yes	
Occupation	Pharmacist	If Other
Also Reported to	☐ Manufacturer/Compounder ☐ User Facility ☐ Distributor/Importer	
If you do NOT want your identity disclosed to the manufacturer, please mark this box (Confidentiality Requested):	Yes	

All dates displayed in the report are in EST(GMT-05:00) time zone

Basic Details			
Company Unit	CDER-CTU	Originating Account	FAERS
Source Medium	MWO (Drug)	Source Form Type	E2B XML 3500
Priority	High		
Override Auto Calculation Rule	No		
FDA Received Date	11-May-2020	CTU Received Date	11-May-2020
CTU Triage Date		CTU Data Entry Date	
Report Type	Spontaneous	Report Classification	Drug
Assign To	User		
User/Group			
Forward to Department	☒ CDER (CDER-OSE-RSS-CTU@fda.hhs.gov) (E2B)		
Case Priority	Direct		

Contact				
Case Reporter	First Name	Last Name	Email Address	Phone
☒	(b) (6)	(b) (6)	(b) (6)	

A. PATIENT INFORMATION	
Patient Identifier (In Confidence)	Unspecified
Age	54 Year(s)
Date of Birth	
Gender	Female
Weight	95.3 kg
Ethnicity (Check single best answer)	Hispanic/Latino
Race (Check all that apply)	☐ Asian ☐ American Indian or Alaskan Native ☐ Black or African American ☐ White ☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM	
Type of Report (check all that apply)	☒ Adverse Event ☐ Product Use/Medication Error ☐ Product Problem (e.g., defects/malfunctions) ☐ Problem with Different Manufacturer of Same Medicine
Serious	Yes
Outcome Attributed to Adverse Event (Check all that apply)	☒ Death ☐ Life Threatening ☒ Hospitalization (initial or prolonged) ☐ Other Serious or Important Medical Events ☐ Disability or Permanent Damage ☐ Congenital Anomaly/Birth Defects ☐ Required Intervention to Prevent Permanent Impairment/Damage
Date of Death	(b) (6)

Date of Event	10-Apr-2020
Date of this Report	11-May-2020

Describe Event, Problem or Product Use Error

Describe Event, Problem, or Product Use Error: Tocilizumab for COVID-19: 54 yo F with PMH of anemia, HLD, peripheral neuropathy, HTN and DM presented on (b) (6) with productive cough and vomiting x 3 days. Pt was confirmed to have COVID-19. On (b) (6) pt received Tocilizumab 400mg IV x 1 dose for COVID pneumonia. Due to increased oxygen requirements, pt was also intubated on (b) (6). On (b) (6) sputum and BCx x 2 with MSSA. Pt treated with cefazolin x 2 weeks. However persistent MSSA noted in sputum on (b) (6) with fevers and leukocytosis and antibiotics were resumed. Pt was extubated on (b) (6) and pt passed on (b) (6).

Relevant Test/Laboratory Data 1 of 4

Test Name	COVID-19 CORONAVIRUS PCR	Test Date	(b) (6)
Test Result	Positive	Test Unit	
Low Test Range		High Test Range	
More Information Available?			

Relevant Test/Laboratory Data 2 of 4

Test Name	CULTURE BLOOD VENIPUNCTURE	Test Date	(b) (6)
Test Result	Staphylococcus aureus (MSSA)	Test Unit	
Low Test Range		High Test Range	
More Information Available?			

Relevant Test/Laboratory Data 3 of 4

Test Name	CULTURE SPUTUM	Test Date	(b) (6)
Test Result	Staphylococcus aureus (MSSA)	Test Unit	
Low Test Range		High Test Range	
More Information Available?			

Relevant Test/Laboratory Data 4 of 4

Test Name	CULTURE SPUTUM	Test Date	(b) (6)
Test Result	Staphylococcus aureus (MSSA)	Test Unit	
Low Test Range		High Test Range	
More Information Available?			

Additional Comments

Other Relevant History, Including Preexisting Medical Conditions

Anemia, type 2 diabetes, hyperlipidemia, hypertension, peripheral neuropathy, former smoker (quit 03/2014)

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)	No
Returned to Manufacturer on	
Do you have a picture of the product? (check yes if you are including a picture)	No

D. PRODUCT(S) 1 of 1

Suspect	Yes
Does this report involve cosmetic, dietary supplement or food/medical food?	
Primary?	Yes
Type	Drug/Biologic
Product Name	Tocilizumab
Strength	400 mg milligram(s) If Other
Manufacturer/Compounder	
NDC# or Unique ID	
Product Type(check all that apply)	☐ OTC ☐ Compounded ☒ Generic ☐ Biosimilar
Event Abated After Use Stopped or Dose Reduced?	Doesn't Apply
Event Reappeared after Reintroduction ?	Doesn't Apply

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency	Other	If Other	once
Route	Intravenous (Not otherwise specified)	If Other	
Dosage Form			
Start	10-Apr-2020		
Stop	10-Apr-2020		
Therapy Duration		If Other	
Is therapy still on-going?	No		
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

COVID-19

E. SUSPECT MEDICAL DEVICE

Brand Name	
Common Device Name	
Procode	
Manufacturer Name	
City	
State	
Model #	
Lot #	
Catalog #	
Expiration Date	
Serial #	
Unique Identifier (UDI)#	
Operator of Device	☐ Health Professional ☐ Patient/Consumer ☐ Other
Other	
If Implanted, Give Date	
If Explanted, Give Date	
Is this a single-use device that was reprocessed and reused on a patient?	
If Yes for the above field, Enter Name and Address of Reprocessor	
Was this device serviced by a third party?	

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

CONCOMITANT MEDICAL PRODUCT DESCRIPTION

G. REPORTER 1 of 1

Primary?	Yes
Reporter is Patient?	
Title	
Last Name	(b) (6)
Middle Name	
First Name	(b) (6)

Address	(b) (6)	
City	(b) (6)	
State/Province/Region	(b) (6)	
Country	UNITED STATES	If Other
ZIP/Postal Code	(b) (6)	
Phone		
Email	(b) (6)	
Fax		
Reporter Organization		
Department		
Reporter Speciality		
Health Professional?	Yes	
Occupation	Pharmacist	If Other
Also Reported to	☐ Manufacturer/Compounder ☐ User Facility ☐ Distributor/Importer	
If you do NOT want your identity disclosed to the manufacturer, please mark this box (Confidentiality Requested):	Yes	

CTU #: FDA-CDER-CTU-2020-49257 | Department: CDER | RCT #: RCT-811349 | CTU Triage Date: 19-May-2020 | AER #: 17802678 |

Report Form

U.S. Department of Health and Human Services
Food and Drug Administration

For VOLUNTARY reporting of
adverse events, product problems
and product use/medication errors

Form Approved: OMB No. 0910-0281, Expires: 11-30-2021
See PRA statement on reverse.

MEDWATCH

FORM FDA 3500 (2/20) The FDA Safety Information and Adverse Event Reporting Program

FDA USE ONLY	
Triage unit sequence #	
FDA Rec. Date	

Note: For date prompts of "dd-mmm-yyyy" please use 2-digit day, 3-letter month abbreviation, and 4-digit year; for example, 01-Jul-2018.

A. PATIENT INFORMATION			
1. Patient Identifier (b) (6)	2. Age ☐ Year(s) ☐ Month(s) ☐ Week(s) ☐ Day(s)	3. Gender (check one) ☐ Female ☒ Male ☐ Intersex ☐ Transgender ☐ Prefer not to disclose	4. Weight 99.7 ☐ lb ☒ kg
or Date of Birth (e.g., 08 Feb 1925) (b) (6)			

5. Ethnicity (check one) ☒ Hispanic/Latino ☐ Not Hispanic/Latino	6. Race (check all that apply) ☐ Asian ☐ American Indian or Alaskan Native ☐ Black or African American ☐ White ☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM

1. Type of Report (check all that apply) ☒ Adverse Event ☐ Product Problem (e.g., defects/malfunctions) ☐ Product Use/ Medication Error ☐ Problem with Different Manufacturer of Same Medicine	2. Outcomes Attributed to Adverse Event (check all that apply) ☒ Death Date of death (dd-mmm-yyyy): (b) (6) ☐ Life-threatening ☐ Disability or Permanent Damage ☐ Hospitalization (initial or prolonged) ☐ Congenital Anomaly/Birth Defect ☐ Other Serious or Important Medical Events ☒ Required Intervention to Prevent Permanent Impairment/Damage
3. Date of Event (dd-mmm-yyyy) 10 - May - 2020	4. Date of this Report (dd-mmm-yyyy) 12 - May - 2020

5. Describe Event, Problem or Product Use/Medication Error
Received off-label Tocilizumab for treatment of lab-confirmed COVID-19 while on a high flow nasal canula (requiring 100% FIO2) on 4/14/2020.

(Continue on page 2)

6. Relevant Tests/Laboratory Data Ferritin = 817 CRP = 28.5	Date (dd-mmm-yyyy) (b) (6) (b) (6)

(Continue on page 2)

7. Other Relevant History, including Preexisting Medical Conditions (e.g., allergies, pregnancy, smoking and alcohol use, liver/kidney problems, etc.)
T2DM, hypertension, hyperlipidemia, obstructive sleep apnea

(Continue on page 2)

C. PRODUCT AVAILABILITY

1. Product Available for Evaluation? (Do not send product to FDA) ☐ Yes ☒ No ☐ Returned to Manufacturer on (dd-mmm-yyyy)	2. Do you have a picture of the product? (check yes if you are including a picture) ☐ Yes

D. SUSPECT PRODUCTS

1. Name, Strength, Manufacturer/Compounder (from product label) Does this report involve cosmetic, dietary supplement or food/medical food?	#1 ☐ Yes #2 ☐ Yes
#1 - Name and Strength Tocilizumab 400mg	#1 - NDC # or Unique ID 50242-137-01
#1 - Manufacturer/Compounder Genentech	#1 - Lot #
#2 - Name and Strength	#2 - NDC # or Unique ID
#2 - Manufacturer/Compounder	#2 - Lot #

2. Dose or Amount #1 400mg #2	Frequency once	Route IV
3. Treatment Dates/Therapy Dates (give best estimate of length of treatment (start/stop) or duration.) #1 Start 27 - Apr - 2020 #1 Stop 27 - Apr - 2020 Is therapy still on-going? ☐ Yes ☒ No #2 Start #2 Stop Is therapy still on-going? ☐ Yes ☐ No		4. Diagnosis for Use (indication) #1 COVID-19 #2
5. Product Type (check all that apply) #1 ☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar #2 ☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar	6. Expiration Date (dd-mmm-yyyy) #1 #2	
7. Event Abated After Use Stopped or Dose Reduced? #1 ☐ Yes ☐ No ☒ Doesn't apply #2 ☐ Yes ☐ No ☐ Doesn't apply	8. Event Reappeared After Reintroduction? #1 ☐ Yes ☐ No ☒ Doesn't apply #2 ☐ Yes ☐ No ☐ Doesn't apply	

E. SUSPECT MEDICAL DEVICE

1. Brand Name	2a. Common Device Name	2b. Proceeds
3. Manufacturer Name, City and State		
4. Model #	Lot #	5. Operator of Device ☐ Health Professional ☐ Patient/Consumer ☐ Other
Catalog #	Expiration Date (dd-mmm-yyyy)	
Serial #	Unique Identifier (UDI) #	
6a. If Implanted, Give Date (dd-mmm-yyyy)	6b. If Explanted, Give Date (dd-mmm-yyyy)	
7a. Is this a single-use device that was reprocessed and reused on a patient? ☐ Yes ☐ No	7b. If Yes to Item 7a, Enter Name and Address of Reprocessor	
8. Was this device serviced by a third party servicer? ☐ Yes ☐ No ☐ Unknown		

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

1. Product names and therapy dates (Exclude treatment of event)

(Continue on page 2)

G. REPORTER (See confidentiality section on back)

1. Name and Address Last Name: (b) (6) First Name: (b) (6) Address: (b) (6) City: (b) (6) State/Province/Region: (b) (6) ZIP/Postal Code: (b) (6) Country: USA Phone #: (b) (6) Email: (b) (6)			
2. Health Professional? ☒ Yes ☐ No	3. Occupation Pharmacist	4. Also Reported to: ☐ Manufacturer/Compounder ☒ User Facility ☐ Distributor/Importer	
5. If you do NOT want your identity disclosed to the manufacturer, please mark this box: ☐			

Reaser Form

Total Pages: 2

U.S. Department of Health and Human Services
Food and Drug Administration

MEDWATCH

FORM FDA 3500 (2/20) (continued)

The FDA Safety Information and
Adverse Event Reporting Program

(CONTINUATION PAGE)

For VOLUNTARY reporting of
adverse events, product problems
and product use/medication errors

Page 2 of 2

B.5. Describe Event or Problem (continued)

Risks and benefits discussed with patient and consent obtained.

Dose administered (b) (6)

Patient transferred to ICU (b) (6) secondary to intubation

(b) (6) - noted to have leukocytosis (WBC = 36.7) and CT chest and abdomen was ordered showing pneumonia of the colon. Empiric cefepime, vanco, and metronidazole were thus started

Patient expired on (b) (6)

[Back to Item B.5](#)

B.6. Relevant Tests/Laboratory Data (continued)

AST = 22

Date (dd-mmm-yyyy)

(b) (6)

Relevant Tests/Laboratory Data

Bilirubin, direct = 0.2

Date (dd-mmm-yyyy)

(b) (6)

ALT = 16

ANC = 7.7

Additional comments

[Back to Item B.6](#)

B.7. Other Relevant History (continued)

[Back to Item B.7](#)

F.1. Concomitant Medical Products and Therapy Dates (Exclude treatment of event) (continued)

All treatments given between (b) (6) -Current day

Simvastatin, amlodipine, aspirin, metoprolol succinate, Milk of magnesia, insulin glargine, ondansetron, hydroxychloroquine, morphine, furosemide, enoxaparin, propofol infusion, fentanyl, fentanyl infusion, norepinephrine infusion, vasopressin infusion, midazolam, regular insulin infusion, pantoprazole, heparin infusion, bumetanide, amlodarone drip, metoprolol tartrate, potassium phosphate, potassium chloride, magnesium sulfate, calcium chloride, vancomycin, cefepime, digoxin, calcium gluconate, sodium phosphate, lorazepam, epinephrine infusion, hydrocortisone, sodium polystyrene, methylprednisolone, ketamine infusion, metronidazole, sodium bicarbonate, phenylephrine infusion

[Back to Item F.1](#)

All dates displayed in the report are in EST(GMT-05:00) time zone

Basic Details			
Company Unit	CDER-CTU	Originating Account	FAERS
Source Medium	MWO (Drug)	Source Form Type	E2B XML 3500
Priority	High		
Override Auto Calculation Rule	No		
FDA Received Date	19-May-2020	CTU Received Date	19-May-2020
CTU Triage Date		CTU Data Entry Date	
Report Type	Spontaneous	Report Classification	Drug
Assign To	User		
User/Group			
Forward to Department	☒ CDER (CDER-OSE-RSS-CTU@fda.hhs.gov) (E2B)		
Case Priority	Direct		

Contact				
Case Reporter	First Name	Last Name	Email Address	Phone
☒	(b) (6)	(b) (6)	(b) (6)	(b) (6)

A. PATIENT INFORMATION	
Patient Identifier (In Confidence)	(b) (6)
Age	65 Year(s)
Date of Birth	
Gender	Male
Weight	116.3 kg
Ethnicity (Check single best answer)	
Race (Check all that apply)	☐ Asian ☐ American Indian or Alaskan Native ☐ Black or African American ☐ White ☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM	
Type of Report (check all that apply)	☒ Adverse Event ☐ Product Use/Medication Error ☐ Product Problem (e.g., defects/malfunctions) ☐ Problem with Different Manufacturer of Same Medicine
Serious	Yes
Outcome Attributed to Adverse Event (Check all that apply)	☒ Death ☒ Life Threatening ☐ Hospitalization (initial or prolonged) ☐ Other Serious or Important Medical Events ☐ Disability or Permanent Damage ☐ Congenital Anomaly/Birth Defects ☐ Required Intervention to Prevent Permanent Impairment/Damage

Date of Death	(b) (6)	
Date of Event	13-May-2020	
Date of this Report	19-May-2020	

Describe Event, Problem or Product Use Error

Describe Event, Problem, or Product Use Error: PEA Arrest (b) (6) suspect primarily respiratory/allergic, occurred 20-25 minutes after tocilizumab (Actemra) infusion

Relevant Test/Laboratory Data 1 of 1

Test Name		Test Date	
Test Result		Test Unit	
Low Test Range		High Test Range	
More Information Available?			

Additional Comments

Other Relevant History, Including Preexisting Medical Conditions

COVID-19

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)	No
Returned to Manufacturer on	
Do you have a picture of the product? (check yes if you are including a picture)	No

D. PRODUCT(S) 1 of 3

Suspect	Yes	
Does this report involve cosmetic, dietary supplement or food/medical food?		
Primary?	Yes	
Type	Drug/Biologic	
Product Name	tocilizumab	
Strength	20 mg/ml - milligrams per millilitres	If Other
Manufacturer/Compounder		
NDC# or Unique ID	50242-137-01	

Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar
Event Abated After Use Stopped or Dose Reduced?	No
Event Reappeared after Reintroduction ?	Doesn't Apply

Drug Therapy 1 of 1

Dose or Amount	800 mg milligram(s)	If Other	
Frequency	Other	If Other	once
Route	Intravenous (Not otherwise specified)	If Other	
Dosage Form			
Start	13-May-2020		
Stop	13-May-2020		
Therapy Duration		If Other	
Is therapy still on-going?	No		
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

COVID-19

D. PRODUCT(S) 2 of 3

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Ceftriaxone		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	

Frequency		If Other	
Route		If Other	
Dosage Form			
Start	11-May-2020		
Stop	12-May-2020		
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

D. PRODUCT(S) 3 of 3

Concomitant	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Enoxaparin		
Strength		If Other	
Manufacturer/Compounder			
NDC# or Unique ID			
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?			
Event Reappeared after Reintroduction ?			

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency		If Other	
Route		If Other	
Dosage Form			
Start	11-May-2020		
Stop	16-May-2020		
Therapy Duration		If Other	
Is therapy still on-going?			
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

E. SUSPECT MEDICAL DEVICE

Brand Name		
Common Device Name		
Procode		
Manufacturer Name		
City		
State		
Model #		
Lot #		
Catalog #		
Expiration Date		
Serial #		
Unique Identifier (UDI)#		
Operator of Device	☐ Health Professional ☐ Patient/Consumer ☐ Other	
Other		
If Implanted, Give Date		
If Explanted, Give Date		
Is this a single-use device that was reprocessed and reused on a patient?		
If Yes for the above field, Enter Name and Address of Reprocessor		
Was this device serviced by a third party?		

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

CONCOMITANT MEDICAL PRODUCT DESCRIPTION

G. REPORTER 1 of 1

Primary?	Yes	
Reporter is Patient?		
Title		
Last Name	(b) (6)	
Middle Name		
First Name	(b) (6)	

Address	(b) (6)	
City	(b) (6)	
State/Province/Region	(b) (6)	
Country	UNITED STATES	If Other
ZIP/Postal Code	(b) (6)	
Phone	(b) (6)	
Email	(b) (6)	
Fax		
Reporter Organization		
Department		
Reporter Speciality		
Health Professional?	Yes	
Occupation	Pharmacist	If Other
Also Reported to	☐ Manufacturer/Compounder ☐ User Facility ☐ Distributor/Importer	
If you do NOT want your identity disclosed to the manufacturer, please mark this box (Confidentiality Requested):	No	

All dates displayed in the report are in EST(GMT-05:00) time zone

Basic Details			
Company Unit	CDER-CTU	Originating Account	FAERS
Source Medium	MWO (Drug)	Source Form Type	E2B XML 3500
Priority	Urgent		
Override Auto Calculation Rule	No		
FDA Received Date	29-May-2020	CTU Received Date	29-May-2020
CTU Triage Date		CTU Data Entry Date	
Report Type	Spontaneous	Report Classification	Drug
Assign To	User		
User/Group			
Forward to Department	☒ CDER (CDER-OSE-RSS-CTU@fda.hhs.gov) (E2B)		
Case Priority	Direct		

Contact				
Case Reporter	First Name	Last Name	Email Address	Phone
☒	(b) (6)	(b) (6)	(b) (6)	(b) (6)

A. PATIENT INFORMATION	
Patient Identifier (In Confidence)	(b) (6)
Age	30 Year(s)
Date of Birth	
Gender	Female
Weight	104 kg
Ethnicity (Check single best answer)	Hispanic/Latino
Race (Check all that apply)	☐ Asian ☐ American Indian or Alaskan Native ☐ Black or African American ☐ White ☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM	
Type of Report (check all that apply)	☒ Adverse Event ☐ Product Use/Medication Error ☐ Product Problem (e.g., defects/malfunctions) ☐ Problem with Different Manufacturer of Same Medicine
Serious	Yes
Outcome Attributed to Adverse Event (Check all that apply)	☒ Death ☐ Life Threatening ☐ Hospitalization (initial or prolonged) ☐ Other Serious or Important Medical Events ☐ Disability or Permanent Damage ☐ Congenital Anomaly/Birth Defects ☐ Required Intervention to Prevent Permanent Impairment/Damage

Date of Death	(b) (6)	
Date of Event	29-May-2020	
Date of this Report	29-May-2020	

Describe Event, Problem or Product Use Error

Describe Event, Problem, or Product Use Error: Hydroxychloroquine Sulfate treatment under Emergency Use Authorization (EUA): Covid- 19 treatment	(b) (6)

Relevant Test/Laboratory Data 1 of 1

Test Name	COVID 19	Test Date	25-May-2020
Test Result	Positive	Test Unit	
Low Test Range		High Test Range	
More Information Available?			

Additional Comments

Other Relevant History, Including Preexisting Medical Conditions

Kidney failure

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)	Yes
Returned to Manufacturer on	
Do you have a picture of the product? (check yes if you are including a picture)	No

D. PRODUCT(S) 1 of 2

Suspect	Yes
Does this report involve cosmetic, dietary supplement or food/medical food?	
Primary?	Yes
Type	Drug/Biologic
Product Name	Hydroxychloroquine
Strength	200 mg milligram(s) If Other
Manufacturer/Compounder	Actavis
NDC# or Unique ID	00591-3041-01
Product Type(check all that apply)	☐ OTC

	☐ Compounded ☐ Generic ☐ Biosimilar	
Event Abated After Use Stopped or Dose Reduced?	No	
Event Reappeared after Reintroduction ?	Yes	

Drug Therapy 1 of 1

Dose or Amount	400 mg milligram(s)	If Other	
Frequency	Daily	If Other	
Route	Oral	If Other	
Dosage Form			
Start	19-Apr-2020		
Stop	23-Apr-2020		
Therapy Duration		If Other	
Is therapy still on-going?	No		
Lot Number	1385969A		
Expiration Date	31-Jul-2021		

Diagnosis for Use (indication) 1 of 1

Covid-19

D. PRODUCT(S) 2 of 2

Suspect	Yes
Does this report involve cosmetic, dietary supplement or food/medical food?	
Primary?	
Type	Drug/Biologic
Product Name	Actemra
Strength	400 mg milligram(s) If Other
Manufacturer/Compounder	Genetech
NDC# or Unique ID	50242-137-01
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar
Event Abated After Use Stopped or Dose Reduced?	No
Event Reappeared after Reintroduction ?	Yes

Drug Therapy 1 of 1

Dose or Amount	400 mg milligram(s)	If Other	
Frequency	Other	If Other	x1

Route	Intravenous (Not otherwise specified)	If Other	
Dosage Form			
Start	27-Apr-2020		
Stop	27-Apr-2020		
Therapy Duration		If Other	
Is therapy still on-going?	No		
Lot Number	B2097B01		
Expiration Date	30-May-2022		

Diagnosis for Use (indication) 1 of 1

Covid-19

E. SUSPECT MEDICAL DEVICE

Brand Name	
Common Device Name	
Procode	
Manufacturer Name	
City	
State	
Model #	
Lot #	
Catalog #	
Expiration Date	
Serial #	
Unique Identifier (UDI)#	
Operator of Device	☐ Health Professional ☐ Patient/Consumer ☐ Other
Other	
If Implanted, Give Date	
If Explanted, Give Date	
Is this a single-use device that was reprocessed and reused on a patient?	
If Yes for the above field, Enter Name and Address of Reprocessor	
Was this device serviced by a third party?	

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

CONCOMITANT MEDICAL PRODUCT DESCRIPTION

G. REPORTER 1 of 1

Primary?	Yes	
Reporter is Patient?		
Title		
Last Name	(b) (6)	
Middle Name		
First Name	(b) (6)	
Address	(b) (6)	
City	(b) (6)	
State/Province/Region	(b) (6)	
Country	UNITED STATES	If Other
ZIP/Postal Code	(b) (6)	
Phone	(b) (6)	
Email	(b) (6)	
Fax		
Reporter Organization		
Department		
Reporter Speciality		
Health Professional?	Yes	
Occupation	Pharmacist	If Other
Also Reported to	☐ Manufacturer/Compounder ☐ User Facility ☐ Distributor/Importer	
If you do NOT want your identity disclosed to the manufacturer, please mark this box (Confidentiality Requested):	Yes	

All dates displayed in the report are in EST(GMT-05:00) time zone

Basic Details			
Company Unit	CDER-CTU	Originating Account	FAERS
Source Medium	MWO (Drug)	Source Form Type	E2B XML 3500
Priority	High		
Override Auto Calculation Rule	No		
FDA Received Date	04-Jun-2020	CTU Received Date	04-Jun-2020
CTU Triage Date		CTU Data Entry Date	
Report Type	Spontaneous	Report Classification	Drug
Assign To	User		
User/Group			
Forward to Department	☒ CDER (CDER-OSE-RSS-CTU@fda.hhs.gov) (E2B)		
Case Priority	Direct		

Contact				
Case Reporter	First Name	Last Name	Email Address	Phone
☒	(b) (6)	(b) (6)	(b) (6)	

A. PATIENT INFORMATION	
Patient Identifier (In Confidence)	(b) (6)
Age	70 Year(s)
Date of Birth	
Gender	Female
Weight	108 kg
Ethnicity (Check single best answer)	Not Hispanic/Latino
Race (Check all that apply)	☐ Asian ☐ American Indian or Alaskan Native ☐ Black or African American ☒ White ☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM	
Type of Report (check all that apply)	☒ Adverse Event ☐ Product Use/Medication Error ☐ Product Problem (e.g., defects/malfunctions) ☐ Problem with Different Manufacturer of Same Medicine
Serious	Yes
Outcome Attributed to Adverse Event (Check all that apply)	☒ Death ☐ Life Threatening ☐ Hospitalization (initial or prolonged) ☐ Other Serious or Important Medical Events ☐ Disability or Permanent Damage ☐ Congenital Anomaly/Birth Defects ☐ Required Intervention to Prevent Permanent Impairment/Damage
Date of Death	(b) (6)

Date of Event	25-May-2020
Date of this Report	04-Jun-2020

Describe Event, Problem or Product Use Error	
Describe Event, Problem, or Product Use Error: Patient received tocilizumab 5/23/20 for COVID-19 and on 5/25 blood culture patient was positive for candida. This is in line with case reports describing candidemia with tocilizumab due to the immunosuppressive effects. patient also began to grow aspergillus and mold due to lowered immune system	

Relevant Test/Laboratory Data				1 of 1
Test Name		Test Date		
Test Result		Test Unit		
Low Test Range		High Test Range		
More Information Available?				

Additional Comments	

Other Relevant History, Including Preexisting Medical Conditions	
history of COPD, Asthma, hypertension, GERD and anxiety	

C. PRODUCT AVAILABILITY	
Product Available for Evaluation? (Do not send product to FDA)	
Returned to Manufacturer on	
Do you have a picture of the product? (check yes if you are including a picture)	No

D. PRODUCT(S)				1 of 1
Suspect	Yes			
Does this report involve cosmetic, dietary supplement or food/medical food?				
Primary?	Yes			
Type	Drug/Biologic			
Product Name	tocilizumab			
Strength	400 mg milligram(s)	If Other		
Manufacturer/Compounder				
NDC# or Unique ID				
Product Type(check all that apply)	☐ OTC ☐ Compounded			

	☒ Generic ☐ Biosimilar
Event Abated After Use Stopped or Dose Reduced?	Doesn't Apply
Event Reappeared after Reintroduction ?	Doesn't Apply

Drug Therapy 1 of 1

Dose or Amount		If Other	
Frequency	Other	If Other	once
Route	Intravenous (Not otherwise specified)	If Other	
Dosage Form			
Start	23-May-2020		
Stop	23-May-2020		
Therapy Duration		If Other	
Is therapy still on-going?	No		
Lot Number			
Expiration Date			

Diagnosis for Use (indication) 1 of 1

COVID-19

E. SUSPECT MEDICAL DEVICE

Brand Name	
Common Device Name	
Procode	
Manufacturer Name	
City	
State	
Model #	
Lot #	
Catalog #	
Expiration Date	
Serial #	
Unique Identifier (UDI)#	
Operator of Device	☐ Health Professional ☐ Patient/Consumer ☐ Other
Other	
If Implanted, Give Date	
If Explanted, Give Date	
Is this a single-use device that was reprocessed and reused on a patient?	

If Yes for the above field, Enter Name and Address of Reprocessor	
Was this device serviced by a third party?	

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

CONCOMITANT MEDICAL PRODUCT DESCRIPTION	

G. REPORTER 1 of 1

Primary?	Yes	
Reporter is Patient?		
Title		
Last Name	(b) (6)	
Middle Name		
First Name	(b) (6)	
Address		
City	(b) (6)	
State/Province/Region	(b) (6)	
Country	UNITED STATES	If Other
ZIP/Postal Code	(b) (6)	
Phone		
Email	(b) (6)	
Fax		
Reporter Organization		
Department		
Reporter Speciality		
Health Professional?	Yes	
Occupation	Pharmacist	If Other
Also Reported to	☐ Manufacturer/Compounder ☐ User Facility ☐ Distributor/Importer	
If you do NOT want your identity disclosed to the manufacturer, please mark this box (Confidentiality Requested):	No	

All dates displayed in the report are in EST(GMT-05:00) time zone

Basic Details			
Company Unit	CDER-CTU	Originating Account	FAERS
Source Medium	MWO (Drug)	Source Form Type	E2B XML 3500
Priority	High		
Override Auto Calculation Rule	No		
FDA Received Date	23-Jun-2020	CTU Received Date	23-Jun-2020
CTU Triage Date		CTU Data Entry Date	
Report Type	Spontaneous	Report Classification	Drug
Assign To	User		
User/Group			
Forward to Department	☒ CDER (CDER-OSE-RSS-CTU@fda.hhs.gov) (E2B)		
Case Priority	Direct		

Contact				
Case Reporter	First Name	Last Name	Email Address	Phone
☒	(b) (6)	(b) (6)	(b) (6)	(b) (6)

A. PATIENT INFORMATION	
Patient Identifier (In Confidence)	(b) (6)
Age	67 Year(s)
Date of Birth	
Gender	Female
Weight	81 kg
Ethnicity (Check single best answer)	Hispanic/Latino
Race (Check all that apply)	☐ Asian ☐ American Indian or Alaskan Native ☐ Black or African American ☐ White ☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM	
Type of Report (check all that apply)	☒ Adverse Event ☐ Product Use/Medication Error ☐ Product Problem (e.g., defects/malfunctions) ☐ Problem with Different Manufacturer of Same Medicine
Serious	Yes
Outcome Attributed to Adverse Event (Check all that apply)	☒ Death ☐ Life Threatening ☐ Hospitalization (initial or prolonged) ☐ Other Serious or Important Medical Events ☐ Disability or Permanent Damage ☐ Congenital Anomaly/Birth Defects ☐ Required Intervention to Prevent Permanent Impairment/Damage

Date of Death		
Date of Event	22-Jun-2020	
Date of this Report	23-Jun-2020	

Describe Event, Problem or Product Use Error

Describe Event, Problem, or Product Use Error: Covid-19, patient was on Actemra and Ivermectin

Relevant Test/Laboratory Data 1 of 1

Test Name	COVID 19	Test Date	20-May-2020
Test Result	Positive	Test Unit	
Low Test Range		High Test Range	
More Information Available?			

Additional Comments

Other Relevant History, Including Preexisting Medical Conditions

C. PRODUCT AVAILABILITY

Product Available for Evaluation? (Do not send product to FDA)	No
Returned to Manufacturer on	
Do you have a picture of the product? (check yes if you are including a picture)	No

D. PRODUCT(S) 1 of 2

Suspect	Yes
Does this report involve cosmetic, dietary supplement or food/medical food?	
Primary?	Yes
Type	Drug/Biologic
Product Name	Actemra
Strength	400 mg milligram(s) If Other
Manufacturer/Compounder	Genetech
NDC# or Unique ID	5024213701
Product Type(check all that apply)	☐ OTC

	☒ Compounded ☐ Generic ☐ Biosimilar
Event Abated After Use Stopped or Dose Reduced?	Yes
Event Reappeared after Reintroduction ?	Doesn't Apply

Drug Therapy 1 of 1

Dose or Amount	400 mg milligram(s)	If Other	
Frequency	Other	If Other	x1
Route	Intravenous (Not otherwise specified)	If Other	
Dosage Form			
Start	04-Jun-2020		
Stop	04-Jun-2020		
Therapy Duration		If Other	
Is therapy still on-going?	No		
Lot Number	B2097b02		
Expiration Date	31-May-2022		

Diagnosis for Use (indication) 1 of 1

Covid-19

D. PRODUCT(S) 2 of 2

Suspect	Yes		
Does this report involve cosmetic, dietary supplement or food/medical food?			
Primary?			
Type	Drug/Biologic		
Product Name	Ivermectin		
Strength	3 mg milligram(s)	If Other	
Manufacturer/Compounder	(b) (4)		
NDC# or Unique ID	4279980601		
Product Type(check all that apply)	☐ OTC ☐ Compounded ☐ Generic ☐ Biosimilar		
Event Abated After Use Stopped or Dose Reduced?	No		
Event Reappeared after Reintroduction ?	Doesn't Apply		

Drug Therapy 1 of 1

Dose or Amount	12 mg milligram(s)	If Other	
Frequency	Other	If Other	Q48h x2 doses

Route	Oral	If Other	
Dosage Form			
Start	22-May-2020		
Stop	24-May-2020		
Therapy Duration		If Other	
Is therapy still on-going?	No		
Lot Number	A1002156A		
Expiration Date	30-Sep-2021		

Diagnosis for Use (indication) 1 of 1

Covid-19

E. SUSPECT MEDICAL DEVICE

Brand Name	
Common Device Name	
Procode	
Manufacturer Name	
City	
State	
Model #	
Lot #	
Catalog #	
Expiration Date	
Serial #	
Unique Identifier (UDI)#	
Operator of Device	☐ Health Professional ☐ Patient/Consumer ☐ Other
Other	
If Implanted, Give Date	
If Explanted, Give Date	
Is this a single-use device that was reprocessed and reused on a patient?	
If Yes for the above field, Enter Name and Address of Reprocessor	
Was this device serviced by a third party?	

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

CONCOMITANT MEDICAL PRODUCT DESCRIPTION

G. REPORTER 1 of 1

Primary?	Yes		
Reporter is Patient?			
Title			
Last Name	(b) (6)		
Middle Name			
First Name	(b) (6)		
Address	(b) (6)		
City	(b) (6)		
State/Province/Region	(b) (6)		
Country	UNITED STATES	If Other	
ZIP/Postal Code	(b) (6)		
Phone	(b) (6)		
Email	(b) (6)		
Fax			
Reporter Organization			
Department			
Reporter Speciality			
Health Professional?	Yes		
Occupation	Pharmacist	If Other	
Also Reported to	☐ Manufacturer/Compounder ☐ User Facility ☐ Distributor/Importer		
If you do NOT want your identity disclosed to the manufacturer, please mark this box (Confidentiality Requested):	Yes		

All dates displayed in the report are in EST(GMT-05:00) time zone

Basic Details			
Company Unit	CDER-CTU	Originating Account	FAERS
Source Medium	MWO (Drug)	Source Form Type	E2B XML 3500
Priority	High		
Override Auto Calculation Rule	No		
FDA Received Date	26-Jun-2020	CTU Received Date	26-Jun-2020
CTU Triage Date		CTU Data Entry Date	
Report Type	Spontaneous	Report Classification	Drug
Assign To	User		
User/Group			
Forward to Department	☒ CDER (CDER-OSE-RSS-CTU@fda.hhs.gov) (E2B)		
Case Priority	Direct		

Contact				
Case Reporter	First Name	Last Name	Email Address	Phone
☒	(b) (6)	(b) (6)		

A. PATIENT INFORMATION	
Patient Identifier (In Confidence)	Unspecified
Age	
Date of Birth	(b) (6)
Gender	Male
Weight	65.6 kg
Ethnicity (Check single best answer)	Not Hispanic/Latino
Race (Check all that apply)	☒ Asian ☐ American Indian or Alaskan Native ☐ Black or African American ☐ White ☐ Native Hawaiian or Other Pacific Islander

B. ADVERSE EVENT, PRODUCT PROBLEM	
Type of Report (check all that apply)	☒ Adverse Event ☐ Product Use/Medication Error ☐ Product Problem (e.g., defects/malfunctions) ☐ Problem with Different Manufacturer of Same Medicine
Serious	Yes
Outcome Attributed to Adverse Event (Check all that apply)	☒ Death ☐ Life Threatening ☐ Hospitalization (initial or prolonged) ☐ Other Serious or Important Medical Events ☐ Disability or Permanent Damage ☐ Congenital Anomaly/Birth Defects ☐ Required Intervention to Prevent Permanent Impairment/Damage
Date of Death	(b) (6)

Date of Event	17-Apr-2020
Date of this Report	26-Jun-2020

Describe Event, Problem or Product Use Error

Describe Event, Problem, or Product Use Error: Tocilizumab 400mg IV one time dose for Covid-19 given on (b) (6)

Types of Reactions: Blood Dyscrasia, increase in liver enzymes, duodenal ulcer - continuous upper GI bleeding, decrease in platelet count and Hct/Hgb. Suspected DIC prior to Tocilizumab administration, but worsening platelet count post-administration. Elevated AST/ALT post-administration. Platelets count continues to drop. Action Taken: Protonix 80mg q12h IVPB given. Patient was transferred to higher level of care immediately for IR intervention where patient continued to experience GI bleeding noted with melena, decrease in Hct/Hgb. DIC was treated with cryoprecipitate. Several GI Consults were done. As per GI Consult, patient had upper and lower GI bleeding with thrombocytopenia and requires multiple blood transfusions. On (b) (6) Upper GI endoscopy and colonoscopy were performed which revealed 2 non bleeding duodenal ulcers as well as 2-3 cm bleeding duodenal ulcer with visible vessel s/p epinephrine and clipping. Rectal bleeding was treated with pRBC and platelet transfusion. Duodenal ulcers were addressed with epi injection and clip placement. A few IR embolizations of GI bleed (in setting of hemorrhagic shock) were performed. Exploratory laparotomy was performed along with over sewing of duodenal ulcer and retrograde duodenostomy tube placement. Conclusion: This is a level 6 ADR. As of (b) (6) patient weaned off vasopressors post-transfusion. He was hemodynamically stable with CBC mildly fluctuating, pending extubation. As of (b) (6) patient experienced an episode of melena, as per GI, more distal small bowel ulceration possibly ischemia from prior embolization was suspected. Patient was still admitted in high level of care hospital. On (b) (6) he was intubated for airways compromise needing pressors and RBCs for suspected septic shock and active bleed. After extended hospital stays (25 days), he developed VRE bacteremia and multiples bed ulcers and other complications. Unfortunately, his course did not improve and wife decided to remove patient from vent support on (b) (6) and he expired. Tocilizumab is known to cause gastrointestinal perforations. As per Manufacturer WARNINGS AND PRECAUTIONS: Gastrointestinal Perforations Events of gastrointestinal (GI) perforation have been reported in clinical trials, primarily as complications of diverticulitis in RA patients. Use ACTEMRA with caution in patients who may be at increased risk for GI perforation. Promptly evaluate patients presenting with new-onset abdominal symptoms for early identification of GI perforation.

Relevant Test/Laboratory Data 1 of 2

Test Name	HEMOGLOBIN	Test Date	(b) (6)
Test Result	6.0	Test Unit	GRAMS PER DECILITER
Low Test Range	14.0	High Test Range	18.0
More Information Available?			

Relevant Test/Laboratory Data 2 of 2

Test Name	HEMATOCRIT	Test Date	(b) (6)
Test Result	19.7	Test Unit	
Low Test Range	42%	High Test Range	52%
More Information Available?			

Additional Comments

Other Relevant History, Including Preexisting Medical Conditions

50 y.o male with PMH of ESRD, CAD, HFrEF (15%), DM2 (retinopathy, nephropathy), HTN, HLD, and depression. Covid (+) on (b) (6) with onset of symptoms since (b) (6) Patient was intubated on (b) (6) for acute hypoxic respiratory failure. Course: c/c DIC with UGIB (EGD with clipping of bleeding duodenal ulcer), transferred to higher level of care on (b) (6) for further interventions. S/P IR embolization, repeat EGD, ex-lap (re-intubation (b) (6) for ex-lap) with pyloromyotomy/pyloroplasty, retrograde duodenostomy and tube placement. Extubated on (b) (6) Further Course: c/b hemothorax vs emphysema (s/p chest tube), septic shock in setting of persistent VRE bacteremia +/- intrabdominal process and ischemic hepatitis with third intubation for airway compromise prompting return to MICU on (b) (6) The disease had progressed into multiple organs failure secondary to septic shock with little chance for recovery. Patient was not a candidate for further surgical interventions as per d/w Surgery.

C. PRODUCT AVAILABILITY	
Product Available for Evaluation? (Do not send product to FDA)	
Returned to Manufacturer on	
Do you have a picture of the product? (check yes if you are including a picture)	No

D. PRODUCT(S)		1 of 1
Suspect	Yes	
Does this report involve cosmetic, dietary supplement or food/medical food?		
Primary?	Yes	
Type	Drug/Biologic	
Product Name	TOCILIZUMAB	
Strength	400 mg milligram(s)	If Other
Manufacturer/Compounder	GENENTECH	
NDC# or Unique ID	50242013701	
Product Type(check all that apply)	☐ OTC ☒ Compounded ☐ Generic ☐ Biosimilar	
Event Abated After Use Stopped or Dose Reduced?	No	
Event Reappeared after Reintroduction ?	Doesn't Apply	

Drug Therapy		1 of 1
Dose or Amount	400 mg milligram(s)	If Other
Frequency	Other	If Other ONCE
Route	Intravenous (Not otherwise specified)	If Other
Dosage Form		
Start	17-Apr-2020	
Stop	17-Apr-2020	
Therapy Duration		If Other
Is therapy still on-going?	No	
Lot Number		
Expiration Date		

Diagnosis for Use (indication)		1 of 1
COVID-19		

E. SUSPECT MEDICAL DEVICE	
Brand Name	
Common Device Name	

Procode	
Manufacturer Name	
City	
State	
Model #	
Lot #	
Catalog #	
Expiration Date	
Serial #	
Unique Identifier (UDI)#	
Operator of Device	☐ Health Professional ☐ Patient/Consumer ☐ Other
Other	
If Implanted, Give Date	
If Explanted, Give Date	
Is this a single-use device that was reprocessed and reused on a patient?	
If Yes for the above field, Enter Name and Address of Reprocessor	
Was this device serviced by a third party?	

F. OTHER (CONCOMITANT) MEDICAL PRODUCTS

CONCOMITANT MEDICAL PRODUCT DESCRIPTION

G. REPORTER 1 of 1

Primary?	Yes	
Reporter is Patient?		
Title		
Last Name	(b) (6)	
Middle Name		
First Name	(b) (6)	
Address		
City		
State/Province/Region		
Country	UNITED STATES	If Other
ZIP/Postal Code		
Phone		
Email		

Fax			
Reporter Organization			
Department			
Reporter Speciality			
Health Professional?	Yes		
Occupation	Pharmacist	If Other	
Also Reported to	☐ Manufacturer/Compounder ☐ User Facility ☐ Distributor/Importer		
If you do NOT want your identity disclosed to the manufacturer, please mark this box (Confidentiality Requested):	Yes		