CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

125276Orig1s114

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

BLA # 125276	BLA Supplement # 114	If NDA, Efficacy Supplement Type: *(an action package is not required for SE8 or SE9 supplements)*
Proprietary Name: ACTEMRA® Established/Proper Name: tozilizumab Dosage Form: Injection		Applicant: Genentech, Inc. Agent for Applicant (if applicable):
RPM: Natasha Kormanik, MSN, RN, OCN		Division: Division of Hematology Products

NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

BLA Application Type: ☐ 351(k) ☐ 351(a)
Efficacy Supplement: ☐ 351(k) ☒ 351(a)

For ALL 505(b)(2) applications, two months prior to EVERY action:

- **Review the information in the 505(b)(2) Assessment and submit the draft[2] to CDER OND IO for clearance.**
- **Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)**

☐ No changes
☐ New patent/exclusivity *(notify CDER OND IO)*
Date of check:

Note: If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.

❖ Actions	
• Proposed action • User Fee Goal Date is 3/9/18	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics[3]	

[1] The **Application Information** Section is (only) a checklist. The **Contents of Action Package** Section (beginning on page 2) lists the documents to be included in the Action Package.
[2] For resubmissions, 505(b)(2) applications must be cleared before the action, but it is not necessary to resubmit the draft 505(b)(2) Assessment to CDER OND IO unless the Assessment has been substantively revised (e.g., new listed drug, patent certification revised).
[3] Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA.

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):
(confirm chemical classification at time of approval)

☐ Fast Track
☐ Rolling Review
☒ Orphan drug designation
☐ Breakthrough Therapy designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

(NOTE: Set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager;
Refer to the "RPM BT Checklist for Considerations after Designation Granted" for other required actions: CST SharePoint)

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☐ MedGuide
☐ Communication Plan
☐ ETASU
☐ MedGuide w/o REMS
☐ REMS not required

Comments:

❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information were issued	☐ None ☒ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☒ Other ASCO Burst
❖ Exclusivity	
• Is approval of this application blocked by any type of exclusivity (orphan, 5-year NCE, 3-year, pediatric exclusivity)? • If so, specify the type	☒ No ☐ Yes
❖ Patent Information (NDAs only)	
• Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	☐ Verified ☐ Not applicable because drug is an old antibiotic.

CONTENTS OF ACTION PACKAGE

Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included

Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Approval, 8/30/17
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☐ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling *(if it is division-proposed labeling, it should be in track-changes format)*	☐ Included
• Original applicant-proposed labeling	☒ Included
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	☐ Included
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s)*	N/A
❖ Labeling reviews *(indicate dates of reviews)*	RPM: ☒ None DMEPA: 8/9/17 DMPP/PLT (DRISK): 8/24/17 OPDP: 8/25/17 SEALD: ☒ None CSS: ☒ None Product Quality ☒ None Other: ☒ None
Administrative / Regulatory Documents	
❖ RPM Filing Review[4]/Memo of Filing Meeting *(indicate date of each review)* ❖ All NDA 505(b)(2) Actions: Date each action cleared by 505(b)(2) Clearance Committee	7/24/17 ☒ Not a (b)(2)
❖ NDAs/NDA supplements only: Exclusivity Summary *(signed by Division Director)*	☐ Completed (Do not include)
❖ Application Integrity Policy (AIP) Status and Related Documents http://www fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No

[4] Filing reviews for scientific disciplines are NOT required to be included in the action package.

• This application is on the AIP
  ○ If yes, Center Director's Exception for Review memo *(indicate date)*
  ○ If yes, OC clearance for approval *(indicate date of clearance communication)*
	☐ Yes ☒ No
	
	☐ Not an AP action

❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: orphan drug designation	
❖ Breakthrough Therapy Designation	☒ N/A
• Breakthrough Therapy Designation Letter(s) (granted, denied, an/or rescinded)	
• CDER Medical Policy Council Breakthrough Therapy Designation Determination Review Template(s) *(include only the completed template(s) and not the meeting minutes)*	
• CDER Medical Policy Council Brief – Evaluating a Breakthrough Therapy Designation for Rescission Template(s) *(include only the completed template(s) and not the meeting minutes)* *(completed CDER MPC templates can be found in DARRTS as clinical reviews or on the MPC SharePoint Site)*	
❖ Outgoing communications: letters, emails, and faxes considered important to include in the action package by the reviewing office/division (e.g., clinical SPA letters, RTF letter, Formal Dispute Resolution Request decisional letters, etc.) *(do not include OPDP letters regarding pre-launch promotional materials as these are non-disclosable; do not include Master File letters; do not include previous action letters, as these are located elsewhere in package)*	8/28/17; 8/25/17; 8/24/17; 8/23/17; 8/18/17; 8/15/17; 8/1/17 (2); 7/31/17; 7/7/17; 6/29/17; 6/7/17; 6/5/17
❖ Internal documents: memoranda, telecons, emails, and other documents considered important to include in the action package by the reviewing office/division (e.g., Regulatory Briefing minutes, Medical Policy Council meeting minutes)	
❖ Minutes of Meetings	
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☒ No mtg
• EOP2 meeting *(indicate date of mtg)*	☒ No mtg
• Mid-cycle Communication *(indicate date of mtg)*	☒ N/A
• Late-cycle Meeting *(indicate date of mtg)*	☒ N/A
• Other milestone meetings (e.g., EOP2a, CMC focused milestone meetings) *(indicate dates of mtgs)*	Guidance: 9/16/16 Pre-IND: 5/27/15
❖ Advisory Committee Meeting(s)	☒ No AC meeting
• Date(s) of Meeting(s)	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	No separate review. Refer to 8/29/17 Multidisciplinary Review (section 17).
Cross-Discipline Team Leader Review *(indicate date for each review)*	No separate review. Refer to 8/29/17 Multidisciplinary Review (section 1).
PMR/PMC Development Templates *(indicate total number)*	8/29/17; Refer to 8/29/17 Multidisciplinary Review

	(section 12). Total: 1 PMR
Clinical	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	No separate review. Refer to 8/29/17 Multidisciplinary Review (sections 2, 3, 4, & 7).
• Clinical review(s) *(indicate date for each review)*	Review Cosigned 8/22/17; Refer to 8/29/17 Multidisciplinary Review (sections 2, 3, 4, & 7)
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☒ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Refer to 8/29/17 Multidisciplinary Review (section 13.2).
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*[5]	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ N/A
❖ Risk Management • REMS Documents and REMS Supporting Document *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☒ None
❖ OSI Clinical Inspection Review Summary(ies) *(include copies of OSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ No separate review
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	No separate review. Refer to 8/29/17 Multidisciplinary Review (section 16).
Statistical Team Leader Review(s) *(indicate date for each review)*	No separate review. Refer to 8/29/17 Multidisciplinary Review (section 7).
Statistical Review(s) *(indicate date for each review)*	No separate review. Refer to 8/29/17 Multidisciplinary Review (section 7).

[5] For Part 3 combination products, all reviews from the reviewing Center(s) should be entered into the official archive (for further instructions, see "Section 508 Compliant Documents: Process for Regulatory Project Managers" located in the CST electronic repository).

Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	No separate review. Refer to 8/29/17 Multidisciplinary Review (section 15).
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	No separate review. Refer to 8/29/17 Multidisciplinary Review (section 6).
Clinical Pharmacology review(s) *(indicate date for each review)*	Review cosigned 8/22/2017; Refer to 8/29/17 Multidisciplinary Review (section 6).
❖ OSI Clinical Pharmacology Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☒ No separate review
• Supervisory Review(s) *(indicate date for each review)*	☒ No separate review
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Review Cosigned 8/22/17.
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ OSI Nonclinical Inspection Review Summary *(include copies of OSI letters)*	☒ None requested
Product Quality ☒ None	
❖ Product Quality Discipline Reviews[6]	
• Tertiary review (*indicate date for each review*)	☐ None
• Secondary review (e.g., Branch Chief) *(indicate date for each review)*	☐ None
• Integrated Quality Assessment (contains the Executive Summary and the primary reviews from each product quality review discipline) *(indicate date for each review)*	☐ None
❖ Reviews by other disciplines/divisions/Centers requested by product quality review team *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☐ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

[6] Do not include Master File (MF) reviews or communications to MF holders. However, these documents should be made available upon signatory request.

❖ Facilities Review/Inspection	
☐ Facilities inspections (indicate date of recommendation; within one week of taking an approval action, confirm that there is an acceptable recommendation before issuing approval letter) *(only original applications and efficacy supplements that require a manufacturing facility inspection(e.g., new strength, manufacturing process, or manufacturing site change)*	☐ Acceptable ☐ Withhold recommendation ☐ Not applicable

Day of Approval Activities	
❖ For all 505(b)(2) applications: • Check Orange Book for newly listed patents and/or exclusivity (including pediatric exclusivity)	☐ No changes ☐ New patent/exclusivity *(Notify CDER OND IO)*
• Finalize 505(b)(2) assessment	☐ Done
❖ For Breakthrough Therapy (BT) Designated drugs: • Notify the CDER BT Program Manager	☐ Done *(Send email to CDER OND IO)*
❖ For products that need to be added to the flush list (generally opioids): Flush List • Notify the Division of Online Communications, Office of Communications	☐ Done
❖ Send a courtesy copy of approval letter and all attachments to applicant by fax or secure email	☒ Done
❖ If an FDA communication will issue, notify Press Office of approval action after confirming that applicant received courtesy copy of approval letter	☒ Done
❖ Ensure that proprietary name, if any, and established name are listed in the *Application Product Names* section of DARRTS, and that the proprietary name is identified as the "preferred" name	☐ Done
❖ Ensure Pediatric Record is accurate	☐ Done
❖ Send approval email within one business day to CDER-APPROVALS	
❖ Take Action Package (if in paper) down to Document Room for scanning within **two business days**	

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/s/

NATASHA L KORMANIK
08/30/2017

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Monday, August 28, 2017 10:26 AM
To: bergan.john@gene.com; Megan Salt (salt.megan@gene.com)
Cc: Lee, Jennifer (CDER)
Subject: BLA 125276 Actemra Stats Information Request- due TODAY

Importance: High

Dear Mr. Bergan and Dr. Salt:

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for ACTEMRA® (tocilizumab).

We have the following information request:

The previous population PK model developed in patients with SJIA in Trials LRO320 and MRA326 was refined to re-estimate linear clearance (CL) and volume of distribution in central compartment (V_C) using PK data from patients with CRS in Novartis Trial ELIANA. All the other parameters including inter-individual variabilities (IIV) of CL and V_C, as well as residual errors, were fixed to the previous PK parameters given the limited sparse PK observations from a small sample size of patients with CRS. The goodness-of-fit plot (Figure 1) and visual predictive check plot (Figure 2) showed that the refined PK model could generally describe the data from patients with CRS well. CL was estimated to be 0.50 L/day (RSE = 10.8%) and V_C was estimated to be 1.8 L (RSE = 11.2%) in patients with CRS, which were higher than CL of 0.17 L/day and V_C of 0.94 L in patients with SJIA.

Figure 3 shows the median tendencies and the corresponding 2.5^{th} and 97.5^{th} percentiles of simulated PK time profiles based on refined PK model after four tocilizumab doses of 12 mg/kg (<30 kg weight) or 8 mg/kg (≥ 30 kg weight) via IV infusion over 1 hour every 24 hours, 12 hours or 8 hours in adult and pediatric patients 2 years of age and older with CRS. The simulated median (2.5^{th}, 97.5^{th} percentiles) of tocilizumab C_{max} was 259 µg/mL (131 µg/mL, 495 µg/mL) after four IV infusion doses administered every 24 hours, 295 µg/mL (144 µg/mL, 567 µg/mL) every 12 hours, and 312 µg/mL (151 µg/mL, 606 µg/mL) every 8 hours in 200 virtual patients with CRS. Overall, the simulated tocilizumab concentrations after four IV infusion doses, whether the doses were administered every 24 hours, 12 hours or 8 hours, were generally below the observed highest C_{max} of 649 µg/mL in five healthy subjects after a single dose of 28 mg/kg in Trial BP19461. Therefore, given the severity and life-threatening nature of CAR T cell-induced CRS and available treatment to manage potential tocilizumab induced neutropenia (e.g. G-CSF products), we recommend a total of four tocilizumab doses of 12 mg/kg (<30 kg weight) or 8 mg/kg (≥30 kg weight) with a dosing interval of at least 8 hours for adult and pediatric patients 2 years of age and older with CAR T cell-induced severe or life-threatening CRS.

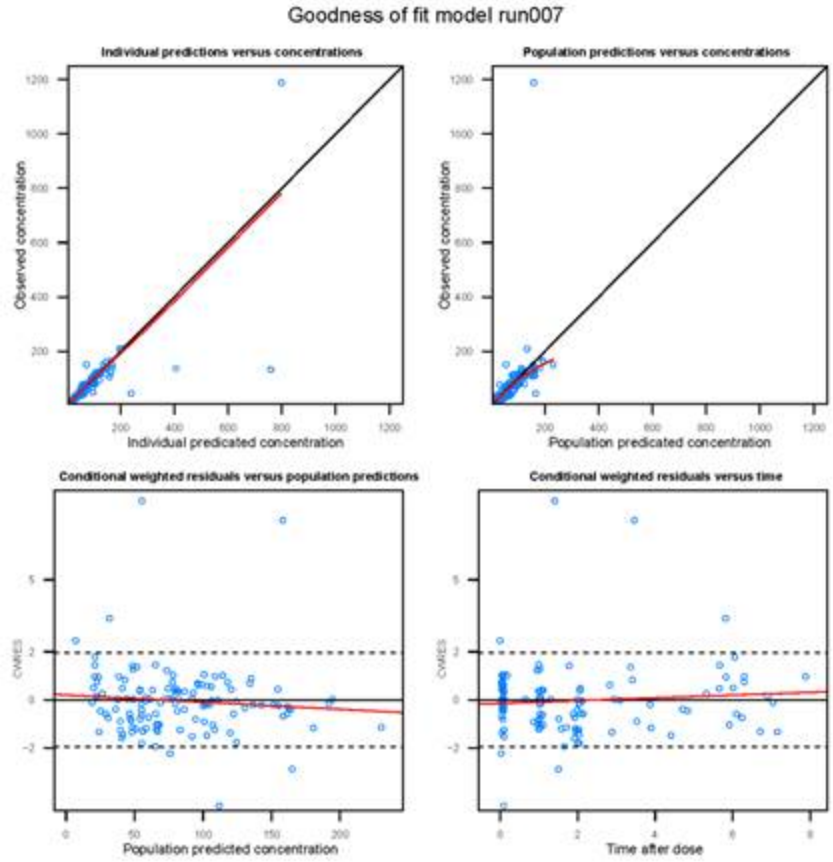


Figure 1: Goodness-of-fit Plots of the Refined PK Model.

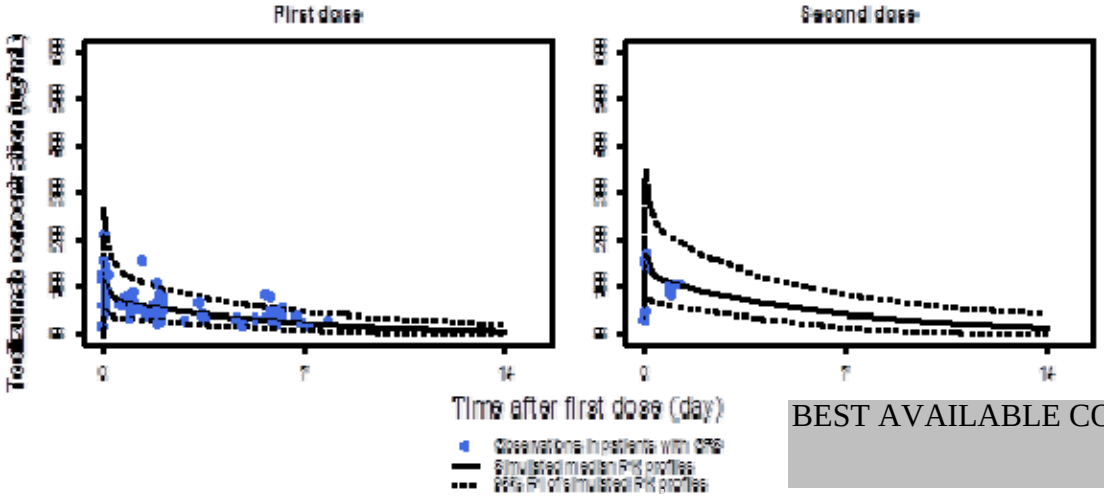
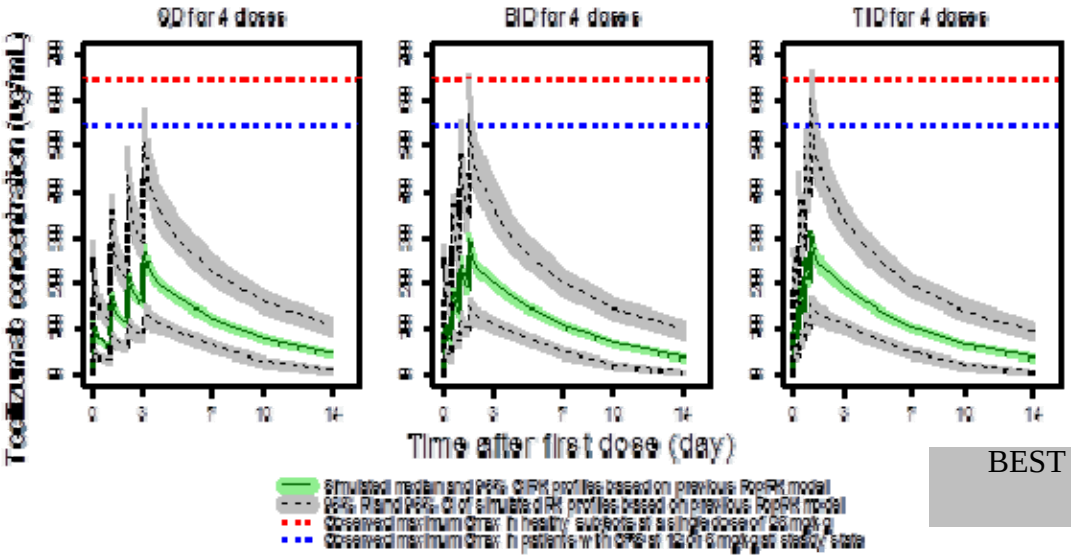


Figure 2: Visual Predictive Check Performed with the Refined PK Model for the Tocilizumab Serum Concentrations after First and Second Doses in Patients with CRS.



BEST AVAILABLE COPY

Figure 3: Simulated 2.5th, 50th and 97.5th Percentiles and Corresponding 95% Confidence Intervals of the Tocilizumab PK Profiles in Patients with CAR T cell-induced Severe or Life-threatening CRS after Four doses Every 24 Hours (Left Panel), 12 Hours (Middle Panel) or 8 Hours (Right Panel) in Patients with CRS.

Please confirm you are in agreement with the proposed dosing recommendation in the PI for CRS treatment using up to 4 doses of tocilizumab at least 8 hours apart.

We ask for the response by 5:00 PM (ET) Today- August 28, 2017. In addition to a courtesy copy by e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue
Building 22, Room 3245
Silver Spring, MD 20903
Office: 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
08/28/2017

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Friday, August 25, 2017 4:49 PM
To: bergan.john@gene.com; Megan Salt (salt.megan@gene.com)
Cc: Carioti, Theresa
Subject: BLA 125276 Actemra Label Negotiation #3/Final- due Monday by Noon
Attachments: BLA 125276 S-114 Label_Response2_Final_25Aug17_DHP_8-25-17.doc

Importance: High

Dear Mr. Bergan and Dr. Salt:

Please find attached the FDA revised version of the label for your review regarding BLA 125276/S-114/Actemra.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**
- Please address the comments directly to the document in tracked changes

Since this should be our last negotiation, unless you find further edits, please go ahead and insert the month and year throughout the label.

After you have made the changes, please e-mail the updated label by **12:00 PM (ET) on Monday- August 28,2017.** Please also submit a formal submission to your BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue
Building 22, Room 3245
Silver Spring, MD 20903
Office: 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
08/25/2017

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Thursday, August 24, 2017 10:33 AM
To: bergan.john@gene.com; Megan Salt (salt.megan@gene.com)
Subject: BLA 125276 S-114 Actemra Clinical Information Request- due today by 3:00 PM

Importance: High

Dear Mr. Bergan and Dr. Salt:

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for ACTEMRA® (tocilizumab).

We have the following clinical information request:

Provide a courtesy copy by e-mail of the clinical study report for BP19461 (just the report, no data files).

We ask for the response by 3:00 PM (ET)- today, August 24, 2017. In addition to a courtesy copy by e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue
Building 22, Room 3245
Silver Spring, MD 20903
Office: 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
08/24/2017

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Wednesday, August 23, 2017 5:38 PM
To: bergan.john@gene.com; Megan Salt (salt.megan@gene.com)
Subject: BLA 125276 Actemra Label Negotiation #2- due Friday by Noon
Attachments: BLA 125276 S-114 Label_Response1_FinalRedline_22Aug17_DHP 8-23-17.doc

Importance: High

Dear Mr. Bergan and Dr. Salt:

Please find attached the FDA revised version of the label for your review regarding BLA 125276/S-114/Actemra.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**
- Please address the comments directly to the document in tracked changes

After you have made the changes, please e-mail a revised label (in tracked changes word document) by **12:00 PM (ET) on Friday- August 25,2017.** Please also submit a formal submission to your BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue
Building 22, Room 3245
Silver Spring, MD 20903
Office: 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
08/23/2017

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Friday, August 18, 2017 3:23 PM
To: bergan.john@gene.com
Subject: BLA 125276 Actemra Label Negotiation #1- due Tuesday by 3:00 PM
Attachments: BLA 125276 S-114 Label_DHP 8-18-17.doc

Importance: High

Dear Mr. Bergan:

Please find attached the FDA revised version of the label for your review regarding BLA 125276/S-114/Actemra.

Please review the changes/comments and do the following to the same draft:

- Accept any changes that you agree with including all format/minor editorial changes
- Edit over the ones that you do not agree with **(do not reject any changes that the FDA proposed)**
- Please address the comments directly to the document in tracked changes

After you have made the changes, please e-mail a revised label (in tracked changes word document) by **3:00 PM (ET) on Tuesday- August 22,2017.** Please also submit a formal submission to your BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue
Building 22, Room 3245
Silver Spring, MD 20903
Office: 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
08/18/2017

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Tuesday, August 15, 2017 10:42 AM
To: bergan.john@gene.com
Subject: BLA 125276 S-114 Actemra PMR Negotiation #1
Attachments: PMR Actemra.doc

Importance: High

Dear Mr. Bergan:

As we continue our review of your Application, our normal policy is to consider labeling and post-marketing studies at this time, so that they can be completed in advance of any action date. We have determined that the following clinical trials are necessary as post-marketing requirements (PMRs) based on the data available to date. These brief descriptions of the necessary studies/trials are intended to describe the main objective and trial characteristics of interest. Please provide edits and comments in clarifying mutually acceptable descriptions of the key trial elements. We are available to discuss by tcon if needed. For new studies, submit the protocol for FDA review and concurrence prior to initiating. Note that the "Final Protocol Submission" date is the date by which you HAVE submitted a complete protocol that has already received full concurrence by FDA.

Upon mutual agreement, we ask you to submit both by email and officially a copy of the PMR study/trial to us with a statement that you agree to perform the trials as described and within the timelines that you specify for the trial. Note that milestone dates only need month and year. For milestone calculation purposes only, assume that an approval occurs on the PDUFA date.

Final PMR designation numbers will be assigned later.

Some things you can do to expedite this process:

1. For labeling and PMRs, reply to our drafts ASAP, and be sure to send the RPM a courtesy copy by email, of your edits in a WORD document that you officially submit. Use track changes to show YOUR edits. ACCEPT all of the track changes edits of ours with which you agree. You may provide annotation within the PI or, if extensive, in a separate document.

2. Assuming, and following a favorable action, you will then be submitting protocols intended to address the objectives of the PMRs agreed upon. We ask the following:

a. Send the RPM an email courtesy copy of the draft versions, in WORD, as well as to the EDR officially. Again, for iterations, accept track changes sent to you that you agree with, and only return to us YOUR edits in track changes.

b. It is critical that you advise, prominently, both with the email and to the EDR, that the protocol you are sending is to address a SPECIFIC POST MARKETING REQUIREMENT OR COMMITMENT (WITH THE PMR NUMBER). This helps the document room and us code the submission properly.

Kindly confirm receipt of this email and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP

10903 New Hampshire Avenue
Building 22, Room 3245
Silver Spring, MD 20903
Office: 240-402-4227
Natasha.Kormanik@fda.hhs.gov

BLA # Product Name:	BLA 125276/S-114/ Actemra® (tocilizumab)
PMR Description:	Further characterize the safety of tocilizumab in the treatment of patients with cytokine release syndrome. Submit the study report and data set (b) (4) .

PMR Schedule Milestones:	Draft Protocol Submission:	MM/DD/YYYY
	Final Protocol Submission:	MM/DD/YYYY
	Study or Trial Completion:	MM/DD/YYYY
	Final Report Submission:	MM/DD/YYYY

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/s/

NATASHA L KORMANIK
08/15/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125276/S-114

FILING COMMUNICATION –
NO FILING REVIEW ISSUES IDENTIFIED

Genentech, Inc.
Attention: John Bergan
Global Regulatory Leader
1 DNA Way
San Francisco, CA 94080

Dear Mr. Bergan:

Please refer to your supplemental Biologics License Application (sBLA) dated June 1, 2017, received June 1, 2017, submitted under section 351(a) of the Public Health Service Act for ACTEMRA® (tocilizumab).

We also refer to your amendments dated June 16 and July 6, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Priority**. Therefore, the user fee goal date is December 1, 2017.

However, we plan to act early on this application under an expedited review, provided that no significant application deficiencies or unexpected shifts in work priorities or team staffing prevent an early action.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 22, 2017. This date conforms to the 21st Century Review timeline for your application. If our review continues on an expedited timeline, we may communicate revised dates for labeling and postmarketing requirement/commitment requests.

At this time, we are notifying you that, we have not identified any potential review issues. Note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *PLLR Requirements for Prescribing Information* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), and Medication Guide. Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft

Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because the biological product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Natasha Kormanik, Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
08/01/2017

Tran, Quyen

From: Tran, Quyen
Sent: Tuesday, August 01, 2017 12:06 PM
To: 'bergan.john@gene.com'
Cc: Kormanik, Natasha
Subject: BLA 125276/S-114 Actemra - FDA Clinical Information Request - Due by August 3, 2017

Dear John,

Regarding your submission for BLA 125276/S-114 Actemra, we have identified the following clinical information request. Please respond via email by **COB August 3, 2017**, then followed with a formal submission to the BLA.

Clinical information request

In Module 2.6 Section 1.6, you refer to a study you are conducting in collaboration with Chugai Pharmaceuticals investigating the efficacy of tocilizumab for treatment of CRS in Japan. Please provide a copy of the protocol for this study.

Kindly confirm receipt of this email. Please let me know if you have any questions.

Thank you,
Quyen

Quyen Tran, PharmD
Regulatory Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

10903 New Hampshire Avenue
Silver Spring, MD 20993
301-796-2771|quyen.tran1@fda.hhs.gov

U.S. FOOD & DRUG ADMINISTRATION

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/s/

QUYEN B TRAN
08/01/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

BLA 125276/S-114

PRIORITY REVIEW DESIGNATION

Genentech, Inc.
Attention: John Bergan
Global Regulatory Leader
1 DNA Way
San Francisco, CA 94080

Dear Mr. Bergan:

Please refer to your supplemental Biologics License Application (sBLA) dated June 1, 2017, received June 1, 2017, submitted under section 351(a) of the Public Health Service Act for ACTEMRA® (tocilizumab).

We also refer to your amendments dated June 16 and July 6, 2017.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application is considered filed 60 days after the date we received your application in accordance with 21 CFR 601.2(a). The review classification for this application is **Priority**. Therefore, the user fee goal date is December 1, 2017.

We are reviewing your application according to the processes described in the *Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products*. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by August 22, 2017.

If you have any questions, call Natasha Kormanik, Regulatory Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Ann T. Farrell, MD
Director
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

ANN T FARRELL
07/31/2017

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Friday, July 07, 2017 10:20 AM
To: 'John Bergan'
Subject: RE: BLA 125276-S114 **Upcoming tisagenlecleucel 7-12-17 ODAC Request**

Good Morning John,

DHP has the following draft edits:

> Genentech/Roche (b) (4) has submitted a license application to update the Actemra/tocilizumab USPI with information for patients and physicians regarding the treatment of severe or life threatening cytokine release syndrome. As these Regulatory activities are out of scope of this ODAC we cannot comment further.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue
Building 22, Room 3245
Silver Spring, MD 20903
Office: 240-402-4227
Natasha.Kormanik@fda.hhs.gov

From: John Bergan [mailto:bergan.john@gene.com]
Sent: Thursday, July 06, 2017 2:29 PM
To: Kormanik, Natasha
Subject: BLA 125276-S114 **Upcoming tisagenlecleucel 7-12-17 ODAC Request**

Hi Natasha,

On Wednesday the Actemra CRS team had a teleconference with Novartis Regulatory regarding their upcoming ODAC for tisagenlecleucel next week. We agreed to provide Novartis with a response statement if a potential questions comes up from the committee about the Benefit/Risk of tisagenlecleucel and the safety concern of CRS and the use of tocilizumab used to treat severer CRS.

We wanted to check with your team if they are comfortable with the draft language below we are planning to provide Novartis. Can you please check with Dr. Farrell and Dr. Przepiorka and the Medical Leads working on the tisagenlecleucel ODAC if they are comfortable with the statement below. Can you let me know by EOB Friday or Monday morning if the statement is ok to provide.

Draft Statement:

Genentech/Roche [redacted] (b) (4) has submitted a license application to update the Actemra/tocilizumab USPI with information for patients and physicians regarding the treatment of severe or life threatening cytokine release syndrome. As these Regulatory activities are out of scope of this ODAC we cannot comment further.

Thanks,

John

John Bergan

Global Regulatory Leader ~ Hematology Franchise

Genentech Regulatory Affairs

650-243-7288

bergan.john@gene.com

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/s/

NATASHA L KORMANIK
07/07/2017

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Thursday, June 29, 2017 11:01 AM
To: bergan.john@gene.com; Megan Salt (salt.megan@gene.com)
Subject: BLA 125276 S-114 Actemra Labeling Information Request- due July 7, 2017

Importance: High

Dear John:

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for ACTEMRA® (tocilizumab).

We also refer to the efficacy supplement dated June 1, 2017. We have the following information request:

> An Electronic Content of Labeling (COL) in SPL format was not submitted under the sBLA. Please formally submit the COL under the BLA.

We ask for the response by 2:00 PM (ET) on July 7, 2017. Please also provide a courtesy copy by e-mail.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue
Building 22, Room 3245
Silver Spring, MD 20903
Office: 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
06/29/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

BLA 125276/S-114

ACKNOWLEDGMENT --
PRIOR APPROVAL SUPPLEMENT

Genentech, Inc.
Attention: John Bergan
Global Regulatory Leader
1 DNA Way
San Francisco, CA 94080

Dear Mr. Bergan:

We have received your Supplemental Biologics License Application (sBLA) submitted under section 351(a) of the Public Health Service Act for the following:

BLA NUMBER: 125276

SUPPLEMENT NUMBER: S-114

PRODUCT NAME: ACTEMRA® (tocilizumab)

DATE OF SUBMISSION: June 1, 2017

DATE OF RECEIPT: June 1, 2017

This supplemental application proposes the following change(s) ACTEMRA® (tocilizumab): update the US Prescribing Information (USPI) with a proposed new indication for ACTEMRA for the treatment of patients with severe of life-threatening (b) (4) cytokine release syndrome (CRS).

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on July 31, 2017, in accordance with 21 CFR 601.2(a).

FDAAA TITLE VIII RESPONSIBILITIES

You are also responsible for complying with the applicable provisions of sections 402(i) and (j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904).

Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 351 of the PHS Act, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at http://www.fda.gov/opacom/morechoices/fdaforms/default.html.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at: http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm. Additional information regarding Title VIII of FDAAA is available at: http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html. Additional information for registering your clinical trials is available at the Protocol Registration System website http://prsinfo.clinicaltrials.gov/.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains **BLA 125276/S-114** submitted on June 1, 2017, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

SUBMISSION REQUIREMENTS

Cite the application number listed above at the top of the first page of all submissions to this application. Send all submissions to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, call me at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Natasha Kormanik, MSN, RN, OCN®
Regulatory Health Project Manager
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

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/s/

NATASHA L KORMANIK
06/07/2017

Kormanik, Natasha

From: Kormanik, Natasha
Sent: Monday, June 05, 2017 1:27 PM
To: bergan.john@gene.com
Subject: BLA 125276 S-114 Actemra Clinical Information Request- due June 26, 2017

Importance: High

Dear Mr. Bergan:

Please refer to your Biologics License Application submitted under section 351 of the Public Health Service Act for ACTEMRA® (tocilizumab).

We have the following clinical information request:

> You have proposed (b) (4) severe or life-threatening cytokine release syndrome." (b) (4)

We ask for the response by 12:00 PM (ET) on Monday, June 26, 2017. In addition to a courtesy copy by e-mail, please also formally submit the response under the BLA.

Kindly confirm receipt of this e-mail and do not hesitate to contact me with any questions.

Kind Regards,
Natasha Kormanik, MSN, RN, OCN®
LCDR, U.S. Public Health Service
Regulatory Health Project Manager
Division of Hematology Products
FDA/CDER/OHOP
10903 New Hampshire Avenue
Building 22, Room 3245
Silver Spring, MD 20903
Office: 240-402-4227
Natasha.Kormanik@fda.hhs.gov

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/s/

NATASHA L KORMANIK
06/05/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 125952

MEETING MINUTES

Hoffmann-La Roche Inc.
c/o Genentech, Inc.
Attention: Shi-Ru Anderson
Regulatory Program Management
1 DNA Way, MS # 355F
South San Francisco, CA 94080-4990

Dear Ms. Anderson:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ACTEMRA® (tocilizumab).

We also refer to the meeting between representatives of your firm and the FDA on September 9, 2016. The purpose of the meeting was to discuss potential alternative registration pathways for the use of tocilizumab in the treatment of cytokine release syndrome, given the absence of a Roche/Genentech sponsored pivotal clinical trial program.

A copy of the official minutes of the meeting is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Natasha Kormanik, Regulatory Health Project Manager, at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Donna Przepiorka, MD, PhD
Acting Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	C
Meeting Category:	Guidance
Meeting Date and Time:	September 9, 2016 from 11:00 AM-12:00 PM (ET)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1417 Silver Spring, Maryland 20903
Application Number:	PIND 125952
Product Name:	ACTEMRA® (tocilizumab)
Indication:	Treatment of patients with severe or life-threatening Cytokine Release Syndrome (CRS)
Sponsor/Applicant Name:	Hoffmann-La Roche Inc.
Meeting Chair:	Donna Przepiorka, MD, PhD
Meeting Recorder:	Natasha Kormanik, MSN, RN, OCN®

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/ Division of Hematology Products
Ann Farrell, MD – Director
Albert Deisseroth, MD, PhD – Acting Associate Deputy Director
Donna Przepiorka, MD, PhD – Acting Clinical Team Leader
Aviva Krauss, MD – Clinical Reviewer
Yvette Kasamon, MD – Clinical Reviewer
Lori Ehrlich, MD, PhD – Clinical Reviewer
Nicholas Richardson, DO – Clinical Reviewer
Kelly Norsworthy, MD – Clinical Reviewer
Natasha Kormanik, MSN, RN, OCN® – Regulatory Health Project Manager

OHOP/ Division of Hematology, Oncology, Toxicology
Christopher Sheth, PhD – Supervisory Pharmacologist
Pedro Del Valle, PhD – Reviewer

Office of Clinical Pharmacology/ Division of Clinical Pharmacology V
Bahru Habtemariam, PharmD – Team Leader
Guoxiang Shen, PhD – Reviewer

Center for Biologics Evaluation and Research/ Office of Cellular, Tissue and Gene Therapies
Maura O'Leary, MD – Medical Officer

SPONSOR ATTENDEES

Shi-Ru Anderson, BS – Associate Program Director, Regulatory Program Management
Erhan Berber, MD – Senior Safety Science Leader, Safety Risk Management
Wayne Chu, MD – Senior Medical Director, Early Clinical Development
Wendy Douglass, PhD – Senior Clinical Development Scientist, Product Development
Evagoras Evagorou, PhD – Senior Global Regulatory Lead, Regulatory Program Management
Sara Gale, PhD, MPH – Research Scientist, Real World Data Science, Product Development (Epidemiology)
Navita Mallalieu, PhD – Director, Clinical Pharmacology
Lucy Rowell, MSc – Global Development Team Leader, Product Development
Stephen Wright, MD – Group Medical Director, Product Development
John Bergan, BS – Global Regulatory Lead, Regulatory Affairs
Bea Lavery, MSc – Senior Group Director, Regulatory Affairs
Michael Wenger, MD – Senior Group Medical Director, Product Development

1.0 BACKGROUND

On June 30, 2016, the Sponsor requested a type C meeting to discuss potential registration pathways for the use of tocilizumab in the treatment of cytokine release syndrome, given the absence of a Roche/Genentech sponsored pivotal clinical trial program.

On January 8, 2010, ACTEMRA® (tocilizumab) intravenous formulation was approved for the treatment of adult patients with moderately to severely active rheumatoid arthritis (RA) who had an inadequate response to one or more disease-modifying antirheumatic drugs, under Biologics License Application (BLA) 125276. On October 2013, a subcutaneous formulation was approved for the same indication, under BLA 125472. A pediatric intravenous formulation was later approved for the treatment of active systemic juvenile idiopathic arthritis (sJIA) and polyarticular JIA (pJIA) in patients 2 years of age and older (sBLA 125276/S-022 approved April 15, 2011 and sBLA 125276/S-064 approved April 29, 2013, respectively).

FDA sent Preliminary Comments to Hoffman-La Roche on September 1, 2016.

2.0 DISCUSSION

Question 1: *Does the Agency agree that there is a high unmet medical need for an effective treatment for severe or life-threatening CRS caused by cancer immunotherapies and other inciting agents?*

FDA Response to Question 1: Yes.

Discussion: No discussion.

Question 2: (b) (4)

(b) (4)

FDA Response to Question 2: (b) (4)

(b) (4) we recognize that there is a substantial unmet medical need, and we are willing to work with Genentech to determine the most efficient pathway to registration.

To this end, we recommend that you design a single-arm trial to quantitate the effect of tocilizumab for treatment of cytokine release syndrome to be conducted as a free-standing sponsored trial, a multicenter investigator-initiated trial, or a substudy of a clinical trial of a therapeutic agent with a high risk of serious or life-threatening cytokine release syndrome. Data from such a trial would need to be sufficient to inform a labeling revision for the proposed indication. We are especially interested in discussing the following critical design elements: criteria that describe the intended population (diagnosis and severity), treatment plan (tocilizumab dose and concomitant use of corticosteroids), the response endpoint used to assess efficacy (criteria and timing), and the expected response rate.

Discussion:

(b) (4) a prospective trial would be needed for a BLA supplement for treatment of cytokine release syndrome. The potential strategies for design of such a trial were discussed. FDA also clarified that the CBER CRS safety database was not designed to collect detailed data on treatment of CRS that would be sufficient to support licensure.

FDA confirmed that at the present time grades 3-4 CRS as defined by Lee et al 2014 would be suitable to use as the basis for eligibility. FDA also informed the Sponsor that an updated version of grading for CRS developed by consensus of the investigators following a RAC meeting was currently under discussion and might be available for use in the future. (b) (4)

(b) (4)

FDA recommended that the Sponsor use their retrospective study to determine the natural history of grades 3-4 CRS treated with supportive care alone and with tocilizumab in order to better assess the clinical benefit and time course of response to treatment with tocilizumab. FDA clarified that such data might be useful to formulate the criteria for the primary endpoint, timing for assessment of the primary endpoint, and limitations with regard to the magnitude of the treatment effect. FDA further emphasized that the sample size should be hypothesis-driven, and that a large study was not needed if the treatment effect was substantial.

Regarding the proposed dosing regimen, the Agency recommended that the Sponsor explore the relationship between change of biomarkers (such as IL-6 and other relevant cytokines) and tocilizumab exposure in the treatment of CRS, utilizing available data in the literature or those from the Sponsor's ongoing clinical trials with bispecific T-cell engaging antibodies. A population PK/PD model may be developed to characterize such relationship and then used to justify the proposed dosing regimen for the proposed clinical trial. FDA agreed in principle with up to two administrations of the proposed tocilizumab dose of 8 mg/kg but recommended that the Sponsor use the retrospective study data to confirm the utility of that dose. FDA also cautioned that high doses of dexamethasone might not be needed, and that the Sponsor should assess the available experience to determine whether lower doses or use of less potent corticosteroids would be more suitable.

The Sponsor expressed a desire to pursue (b) (4)

FDA agreed that patients with CRS from any of multiple etiologies could be included in the prospective trial, but whether stratification by inciting agent was warranted depended on the natural history that would be determined by the retrospective study. (b) (4)

The Sponsor discussed their development of several T-cell retargeting agents and asked whether they could use data from those studies if patients are treated with tocilizumab for CRS. FDA agreed in principle that such protocols could allow for treatment of CRS with tocilizumab, but the protocol needed to specify the criteria (i.e., Lee grades 3-4) when tocilizumab should be given and the dose and schedule to be used.

FDA indicated support for on-going discussions as the retrospective and prospective protocols are developed and recommended that the Sponsor request formal meetings with brief background material and specific questions for complicated or critical protocol design issues.

Question 3: (b) (4)

a) (b) (4)

b)

FDA Response to Question 3: Please refer to the response to Question 2.

Discussion: No discussion.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues identified.

5.0 ACTION ITEMS

No action items identified.

6.0 ATTACHMENTS AND HANDOUTS

Sponsor's responses to preliminary comments.

PIND 125952

Type C Meeting on 09 Sep 2016

Sponsor Questions as Follow-Up to Question 2 in FDA Preliminary Response
(Agency Letter Dated 01 Sep 2016, Ref ID 3980471)

Edit on 2016-09-08: Question 6 has been moved to become the first question.

[Formerly Question 6]

1. (b) (4)

[Former Questions 1 through 5 have been renumbered accordingly, with no other shifts]

2. (b) (4)


Lee-et-al-2014.pdf

3. Does the Agency agree that an appropriate clinical endpoint for tocilizumab in the treatment of severe or life-threatening CRS should include the following: (b) (4)

4. Does the Agency agree to the proposed TCZ dose regimen for CRS? Specifically
-- A single dose of TCZ (8 mg/kg IV) ± high dose IV corticosteroids
-- (b) (4)
-- (b) (4)

5. Given published literature indicating a high resolution rate of severe or life-threatening CRS with TCZ treatment, could the Agency comment on the sample size?

6. (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DONNA PRZEPIORKA
09/16/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 125952

MEETING MINUTES

Genentech, Inc.
Attention: John Bergan
Regulatory Project Management
1 DNA Way
South San Francisco, CA 94080-4990

Dear Mr. Bergan:

Please refer to your Pre-Investigational New Drug Application (PIND) file for ACTEMRA® (tocilizumab).

We also refer to the teleconference between representatives of your firm and the FDA on May 27, 2015. (b) (4)

(b) (4)

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Natasha Kormanik, Regulatory Project Manager at (240) 402-4227.

Sincerely,

{See appended electronic signature page}

Albert Deisseroth, MD, PhD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-IND

Meeting Date and Time: May 27, 2015 at 10:00 AM- 11:00 AM (EST)
Meeting Location: Teleconference

Application Number: 125952
Product Name: ACTEMRA® (tocilizumab)

Proposed Indication: (b) (4)

Sponsor/Applicant Name: Genentech, Inc.

Meeting Chair: Albert Deisseroth, MD, PhD
Meeting Recorder: Natasha Kormanik, MSN, RN, OCN®

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/ Division of Hematology Products
Ann Farrell, MD – Director
Albert Deisseroth, MD, PhD – Clinical Team Leader
Donna Przepiorka, MD, PhD – Medical Officer
Natasha Kormanik, MSN, RN, OCN® – Regulatory Health Project Manager

Office of Biostatistics/ Division of Biometrics V
Lei Nie, PhD – Biostatistics Team Leader
Kyung Yul Lee, PhD – Biostatistics Reviewer

(b) (4)

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