B.5. Describe event or problem

[continuation:] disease-related costs in patients with an indication for statin treatment according to the Joint European Guidelines.
Medical history included diabetes mellitus type II, peripheral occlusive artery disease, hypertension, an unspecified heart disease and a fatty liver caused by diabetes. Concomitant medication consisted of metformin and glibenclamide for diabetes, captopril for hypertension, nilvadipine for heart disease and clopidogrel for peripheral artery disease.
The patient started rosuvastatin 10 mg daily on 07-Jun-2002. After 17 weeks and 5 days on study medication, on 08-OCT-2002, he developed icterus with brown discolouration of urine. On the next day he was hospitalised and study drug withdrawn. Metformin, captopril, nilvadipine and clopidogrel were also withdrawn. Hepatopathy of unknown cause, most likely drug-induced was diagnosed. Sonography showed parenchymal liver damage but histology revealed normal liver tissue. Hepatitis B and C were excluded. No pathologic findings of other abdominal organs except for mild splenomegaly. The patient's condition improved and he was discharged on 21-Oct-02.
The investigator did not exclude a causal relationship to the study medication but stated that a proper evaluation must await the results of further investigation. He stated that a contributory role of concomitant medications cannot be ruled out. Serious criterion was hospitalisation
Further information was requested.

Summary of follow-up received on 22-Oct-02:
- Hepatopathy of unknown cause, most likely drug-induced
- rosuvastatin was stopped on 09-Oct-02
- patient's condition improved
- metformin, captopril, nilvadipine and clopidogrel were stopped too

Company Clinical Comment:
Jaundice and hepatocellular damage occurring in a subject with a history of fatty liver of diabetic etiology should probably not be considered related to study medication, especially when histology revealed normal liver tissue. However, given the temporal relationship between event and study medication, a contributory role of rosuvastatin cannot be ruled out completely. Co-medications captopril, nilvadipine and clopidogrel should also be considered as suspected drugs because liver disorders are labeled for these drugs.

B.6. Relevant tests/laboratory data, including dates

[continuation:] LAB 09-OCT-02: Hepatitis B and C was ruled out
SONOGRAPHY: parenchymal damage of liver
HISTOLOGY: normal liver tissue

Lab Test/Comment	Lab Value	Units	Date	Ref. to Normal	Low	High
BLOOD SEDIMENTATI	42/65	mm	10/08/2002			

MED WATCH	A.1. Patient Identifier	G.9. Mfr. report number	Page 3 of 4
		2002PK01036	

B.6. Relevant tests/laboratory data, including dates

[continuation:] ASAT	91	10/09/2002	INCREASED	< 37	
ASAT	17	10/15/2002	NORMAL	< 37	
ALAT	223	10/09/2002	INCREASED	< 65	
ALAT	80	10/15/2002	INCREASED	< 65	
GGT	942	10/09/2002	INCREASED	< 55	
GGT	657	10/15/2002	INCREASED	< 37	
AP	130	10/09/2002			
AP	150	10/15/2002			
TOTAL BILIRUBIN	2.1	10/09/2002	INCREASED	< 1	
TOTAL BILIRUBIN	0.7	10/15/2002	NORMAL	< 1	
WBC	11.5	10/09/2002	INCREASED		
WBC	7.6	10/15/2002		< 1	
HBS-AG	negative				
HBC-AK	negative				
HCV-AK	negative				

*

MED WATCH	A.1. Patient identifier	G.9. Mfr. report number	Page 4 of 4
	[redacted]	2002PK01036	

B.6. Relevant tests/laboratory data ,including dates

[continuation:]

C.10. Concomitant medical products and therapy dates (exclude treatment of event)

[continuation:] Name: PLAVIX Dates: NI to NI
Name: AZUGLUCON Dates: NI continuing

G.3. Report source (other:)

Source: [redacted]

APPEARS THIS WAY
ON ORIGINAL

2. MedWatch Report of a case of 73 year old patient with Jaundice and Transaminase elevation on 10mg of Rosuvastatin D3560L0001/2265/09060

U.S. Department of Health and Human Services

MEDWATCH

The FDA Safety Information and Adverse Event Reporting Program

AstraZeneca Pharmaceuticals

Page 1 of 7

Mfr report # 2002PK01330

FDA Use Only

A. Patient information

1. Patient identifier: [redacted] in confidence
2. Age at time of event: 73 yrs or Date of birth: [redacted]
3. Sex: ☐ female ☒ male
4. Weight: ____ lbs or 84 kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death ____
   - ☐ life-threatening
   - ☒ hospitalization - initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other: ____
3. Date of event: 12/02/2002
4. Date of this report: 05/07/2003
5. Describe event or problem

```
15-DAY IND ALERT

Clinical Event(s):
1 ICTERUS
2 CHOLECYSTITIS

A report has been received from study
investigator concerning a 73 year old male
patient who was enrolled in the ORBITAL study
D3560L00001, an open, randomised parallel
group study evaluating the effects of six
months rosuvastatin treatment plus additional
compliance initiatives compared to
rosuvastatin alone on long-term disease-
related costs in patients with an indication
for statin treatment according to the Joint
European Guidelines. *
```

6. Relevant tests/laboratory data, including dates

*

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

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Concomitant Disease(s): CHOLECYSTOLITHIASIS,
CORONARY ARTERY DISEASE
```

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 ROSUVASTATIN
   #2
2. Dose, frequency & route used
   #1 10 mg daily PO
   #2
3. Therapy dates (if unknown, give duration)
   #1 09/11/2002 to 12/03/2002
   #2
4. Diagnosis for use (indication)
   #1 HYPERCHOLESTEROLEMIA
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☒ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1 NI
   #2
7. Exp. date (if known)
   #1 NI
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☒ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # - for product problems only (if known)
   #1 NI #2
10. Concomitant medical products and therapy dates (exclude treatment of event)

```
Name: DELIX
Name: ASS "CT-ARZNEIMITTEL" Dates: 01/??/2002 to 12/02/
2002 *
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G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

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AstraZeneca Pharmaceuticals
A Business Unit of AstraZeneca LP,
1800 Concord Pike, P.O. Box 15437,
Wilmington, DE 19850-5437
```

2. Phone number: 302 886 2127
3. Report source (check all that apply)
   - ☒ foreign
   - ☒ study
   - ☐ literature
   - ☐ consumer
   - ☒ health professional
   - ☐ user facility
   - ☐ company representative
   - ☐ distributor
   - ☐ other: *

   DE
4. Date received by manufacturer: 22-APR-2003
5. (A)NDA # / IND # / PLA #
   pre-1938 ☐ yes
   OTC product ☐ yes
6. If IND, protocol #: D3560L00001
7. Type of report (check all that apply)
   - ☐ 5-day ☒ 15-day
   - ☐ 10-day ☐ periodic
   - ☐ initial ☒ follow-up # 1
8. Adverse event term(s): Jaundice NOS, Cholecystitis NOS
9. Mfr. report number: 2002PK01330

E. Initial reporter

1. Name & address — phone # NI

[redacted]

2. Health professional? ☒ yes ☐ no
3. Occupation: MEDICAL DOCTOR
4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA 3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages.

B.5. Describe event or problem

[continuation:] The patient started study medication on 11-Sep-2002. Concomitant drugs were ramipril and acetylsalicylic acid. Medical history included cholecystolithiasis. Other relevant medical history consisted of hepatitis B during second world war. On 02-Dec-2002, eleven weeks and six days after commencing study medication, he experienced icterus. Total bilirubin (7.12 mg/dl), AP (303 U/l), GGT (77 U/l), ASAT (699 U/l) and ALAT (914 U/l) were increased. WBC was normal. A performed CT on 03-Dec-2002 revealed suspected carcinoma of pancreatic head, cholecystitis and splenomegaly. In further clinical course pancreatic cancer and acute hepatitis A, B and C were excluded. Hepatitis serology showed negative HBsAg but positive IgM anti-HBc. ERCP showed no stenosis of biliary ducts. The physicians considered perhaps some gallbladder stones had passed but they could not exclude drug-induced reactions. Further details were unknown at time of the report. Study drug was withdrawn and lab values were improving.
The reporter considered that as long as pancreatic cancer had not been confirmed the events were possibly related to study medication. Serious criterion was hospitalisation.
CT scan on 09-Dec-2002 ruled out pancreatic tumor. Liver transaminases are decreasing. Patient is scheduled for a cholecystectomy on 27-Jan-2003. Cholecystectomy was not performed because it was not certain that a gallstone was present. Investigational method was not stated at the time of this report. Lab values, specifically GGT (20 U/L), ASAT (11 U/L), ALAT (12 U/L) and total bilirubin (0.86 mg/dl) returned to normal. No further investigation regarding hepatitis serology was carried out.

Company Clinical Comment
As with other HMG-CoA reductase inhibitors, increases in liver transaminases have been observed in a small number of subjects taking rosuvastatin. However, the elevation in transaminases observed in this subject does not appear to be related to study drug. The subject has a history of Hepatitis B during Second World War, but the presence of positive titers to IgM to anti-HB core and negative HB surface antigen suggests acute Hepatitis and not suggestive of previous infection. Therefore AstraZeneca disagrees with the investigators assessment of causality.

Summary of follow-up received on 10-Dec-02:
- Investigator considered event was not life-threatening
- lab values added

Summary of follow-up received on 16-Dec-02:
- pancreatic cancer and hepatitis A, B and C were excluded
- ERCP showed no stenosis of biliary ducts
- cholecystolithiasis added as concomitant disease added
- ramipril and acetylsalicylic acid added as concomitant drugs
- perhaps some gallbladder stones had passed

Summary of follow-up received on 17-Dec-02:
- lab values and patient's medical history added
- medical history included hepatitis B during second world war

Summary of follow-up received on 30-Jan-03: *

B.5. Describe event or problem

[continuation:] - hospital discharge letter,dated 20-Dec-02, received
- no evidence for a pancreatic tumor,
- diagnosis of mild intrahepatic cholestasis and a renal cyst left
- diagnosis of angiosclerosis of Aorta abdominalis
- patient is scheduled for a cholecystectomy on 27-Jan-03

Summary of follow-up information received on 22-Apr-2003:
- no evidence for gallstone, therefore cholecystectomy cancelled
- lab vaues for ASAT, ALAT, GGT, AP returned to normal
- no further investigation regarding hepatitis serology.
- narrative updated

B.6. Relevant tests/laboratory data, including dates

[continuation:] CT 04-DEC-02: CHOLECYSTITIS AND SUSPECTED CANCER HEAD OF PANCREAS. NO CONCREMENTS I GALLBLADDER, NORMAL BILE DUCTS, DUCTUS CHOLEDOCHUS DIFFICULT TO ASSESS. SPLENOMEGALY
ABDOMINAL SONOGRAPHY 09-DEC-02: NO CHOLECYSTOLITHIASIS
09-DEC-02: CT SCAN SHOWED NO EVIDENCE FOR PANCREATIC TUMOR; MILD INTRAHEPATIC CHOLESTASIS; SOFT TISSUE DENSE STRUCTURE IN THE AREA OF THE HEPATIC PORTAL, POSSIBLE REGIONAL SWELLING OF LYMPH NOI OR BILIARY DUCT; NO ENLARGEMENT OF ABDOMINAL LYMPH NODES; RENAL CYST LEFT; ANGIOSCLEROSIS OF AORTA ABDOMINALIS

Lab Test/Comment	Lab Value	Units	Date	Ref. to Normal	Low	High	
TOTAL BILIRUBIN	7.12	mg/dl	12/04/2002	INCREASED		< 1.1	
AP	303	U/l	12/04/2002	INCREASED		< 180	
GGT	77	U/l	12/04/2002	INCREASED		< 28	
GPT	914	U/l	12/04/2002	INCREASED		< 24	
GOT	699	U/l	12/04/2002	INCREASED		< 18	
WBC	5100	/ul	12/04/2002	NORMAL	4000	9400	*

MEDWATCH	A.1. Patient identifier	G.9. Mfr. report number	Page 4 of 7
		2002PK01330	

B.6. Relevant tests/laboratory data, including dates

[continuation:]

ERYTHROCYTES	4.56	Mio/ul	12/04/2002	NORMAL	4.5	6.3
HEMOGLOBIN	14.7	g/dl	12/04/2002	NORMAL	14	18
HEMATOCRIT	43	%	12/04/2002	NORMAL	38	52
PLATELETS	171000	/ul	12/04/2002	NORMAL	150000	440000
ASAT	195		12/06/2002			
ASAT	113		12/07/2002			
ASAT	59		12/10/2002			
ASAT	59		12/10/2002			
ASAT	58		12/12/2002			
ASAT	65		12/16/2002			
ALAT	577		12/06/2002			
ALAT	447		12/07/2002			
ALAT	185		12/10/2002			
ALAT	157		12/12/2002			

B.6. Relevant tests/laboratory data, including dates

[continuation:] ALAT	137	12/16/2002
GGT	62	12/06/2002
GGT	59	12/07/2002
GGT	53	12/10/2002
GGT	62	12/12/2002
AP	267	12/06/2002
AP	260	12/07/2002
AP	230	12/10/2002
AP	266	12/12/2002
AP	237	12/16/2002
TOTAL BILIRUBIN	11.0	12/06/2002
TOTAL BILIRUBIN	11.8	12/07/2002
TOTAL BILIRUBIN	7.6	12/10/2002
TOTAL BILIRUBIN	8.2	12/12/2002
TOTAL BILIRUBIN	6.0	12/16/2002

MEDWATCH	A.1. Patient identifier	G.8. Mfr. report number	Page 6 of 7
		2002PK01330	

B.6. Relevant tests/laboratory data, including dates

[continuation:]

HBSAG ABSENT	negative		12/03/2002			
ANTI-HEPBC IGM PRESENT	positive		12/03/2002			
HEP A IGG-ANTIBOD PRESENT	negative		12/03/2002			
CONJUGATED BILIRU	3.1	mg/dl	12/16/2002			
WBC	3.6	Tsd/ul	02/12/2003	DECREASED	4.0	9.4
ERYTHROCYTES	4.59	MIO/ul	02/12/2003	NORMAL	4.5	6.3
HAEMOGLOBIN	15.4	g/dl	02/12/2003	NORMAL	14	18
MCV	102	fl	02/12/2003	INCREASED	78	98
MCH	34	pg	02/12/2003	INCREASED	26	32
MCHC	33	g/dl	02/12/2003	NORMAL	32	36
THROMBOCYTES	157	Tsd/ul	02/12/2003	NORMAL	150	440
TOTAL BILIRUBIN	0.86	mg/dl	02/12/2003	NORMAL		1.1
AP	138	U/L	02/12/2003	NORMAL		180
GAMMA GT	20	U/L	02/12/2003	NORMAL		29
ASAT	11	U/L	02/12/2003	NORMAL		18

MEDWATCH	A.1. Patient Identifier	G.9. Mfr. report number	Page 7 of 7
	[redacted]	2002PK01330	

B.6. Relevant tests/laboratory data, including dates

[continuation:]

ALAT	12	U/L	02/12/2003	NORMAL	24

C.10. Concomitant medical products and therapy dates (exclude treatment of event)

[continuation:] Name: POTABA Dates: 09/??/2002 to 12/02/2002

G.3. Report source (other)

Source: [redacted]

AstraZeneca Pharmaceuticals
A Business Unit of AstraZeneca LP,
1800 Concord Pike, P.O. Box 15437,
Wilmington, DE 19850-5437

Mfr. Rep. #: 2002PK01330

Date: 07-MAY-2003

LISTING OF PRIOR SAFETY REPORTS SUBMITTED TO IND # [redacted]

ADVERSE EVENT: Cholecystitis NOS
(all preferred and included coded terms)

Manufacturer Report #	FDA Submission Date	Protocol Number	Country of Origin
2001UW06827	24-OCT-2001	4522IL/0034	
2001UW08219	26-OCT-2001	4522IL/0034	
2002PK01330	20-DEC-2002	D3560L00001	

ADVERSE EVENT: Jaundice NOS
(all preferred and included coded terms)

Manufacturer Report #	FDA Submission Date	Protocol Number	Country of Origin
2002PK01036	29-OCT-2002	D3560L00001	
2002PK01330	20-DEC-2002	D3560L00001	

3. MedWatch Report of a case of Rhabdomyolysis on 10mg of Rosuvastatin 2003SE02255

U.S. Department of Health and Human Services

MEDWATCH
The FDA Safety Information and Adverse Event Reporting Program

AstraZeneca Pharmaceuticals

Page 1 of 7

Mfr report # 2003SE02255

FDA Use Only

A. Patient information

1. Patient Identifier: in confidence
2. Age at time of event: 75 yrs (or Date of birth:)
3. Sex: ☒ female ☐ male
4. Weight: ____ lbs (or) 80 kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)
2. Outcomes attributed to adverse event (check all that apply)
   - ☐ death
   - ☒ life-threatening
   - ☒ hospitalization - initial or prolonged
   - ☐ disability
   - ☐ congenital anomaly
   - ☐ required intervention to prevent permanent impairment/damage
   - ☐ other:
3. Date of event: 04/20/2003
4. Date of this report: 05/30/2003
5. Describe event or problem

7-DAY IND ALERT

Clinical Event(s):
1 ACUTE RENAL FAILURE
2 COMA
3 SEPTIC SHOCK
4 URINARY INFECTION

A report has been received from an investigator regarding a 75-year-old female who was enrolled in study GISSI- HF with rosuvastatin versus placebo.

Medical history included diabetes mellitus type II (decompensated), cardiomyopathy, peripheral neuropathy with pains in the legs, chronic atrial fibrillation and congestive *

6. Relevant tests/laboratory data, including dates

*

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Concomitant Disease(s): CARDIOMYOPATHY, CHRONIC ATRIAL FIBRILLATION, CONGESTIVE HEART FAILURE, PERIPHERAL NEUROPATHY, TYPE II DECOMPANSATED DIABETES

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
   #1 ROSUVASTATIN
   #2
2. Dose, frequency & route used
   #1 10 mg QD
   #2
3. Therapy dates (if unknown, give duration)
   #1 11/26/2002 to 04/14/2003
   #2
4. Diagnosis for use (indication)
   #1 MI
   #2
5. Event abated after use stopped or dose reduced
   #1 ☐ yes ☐ no ☒ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
6. Lot # (if known)
   #1 NI
   #2
7. Exp. date (if known)
   #1 NI
   #2
8. Event reappeared after reintroduction
   #1 ☐ yes ☐ no ☒ doesn't apply
   #2 ☐ yes ☐ no ☐ doesn't apply
9. NDC # - for product problems only (if known)
   #1 NI #2
10. Concomitant medical products and therapy dates (exclude treatment of event)

Name: METFORAL Dates: 11/??/2002 to 04/21/2003
Name: TRIATEC Dates: 11/??/2002 to 04/21/2003
Name: LASIX Dates: 04/10/2003 to 04/21/2003 *

G. All manufacturers

1. Contact office - name/address (& mfr'ng site for devices)
   AstraZeneca Pharmaceuticals
   A Business Unit of AstraZeneca LP,
   1800 Concord Pike, P.O. Box 15437,
   Wilmington, DE 19850-5437
2. Phone number: 302 886 2127
3. Report source (check all that apply)
   ☒ foreign ☒ study ☐ literature ☐ consumer ☒ health professional ☐ user facility ☐ company representative ☐ distributor ☐ other: *
   IT
4. Date received by manufacturer: 16-MAY-2003
5. (A)NDA #: IND #: PLA #: pre-1938 ☐ yes OTC product ☐ yes
6. If IND, protocol #: G105
7. Type of report (check all that apply)
   ☐ 5-day ☐ 15-day ☒ 10-day ☐ periodic ☐ initial ☒ follow-up # 1
8. Adverse event term(s)
   Renal failure acute, Coma, Septic shock, Urinary tract infection NOS
9. Mfr. report number: 2003SE02255

E. Initial reporter

1. Name & address
   phone # NI
2. Health professional? ☒ yes ☐ no
3. Occupation: MEDICAL DOCTOR
4. Initial reporter also sent report to FDA ☐ yes ☐ no ☒ unk

FDA
3500A Facsimile

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.
* Item completed on continuation pages.

B.5. Describe event or problem

[continuation:] heart failure. Concomitant medication included ramipril, metformin hydrochloride, warfarin, furosemide, allopurinol and insulin human injection/isophane.

The patient was randomized to rosuvastatin on 26-Nov-2002. The study medication was stopped on 14-Apr-2003 because of clinical deterioration (worsening of heart failure). She was admitted to the GISSI-HF centre under the care of the investigator for congestive heart failure on 15-April-2003. The patient was asthenic with nausea and diarrhea since discharge on 18-April-2003. On 20-April-2003, she was taken to the Emergency Unit of another hospital and was transferred immediately to the Nephrology ward because of acute renal failure. Lab tests were performed and measured, WBC 25,000, Na 152, K 5.8: BUN 183: Creatinine 8.7: CK 10383 to 21632. A cerebral "computed axial tomography" showed no findings. The following day she went into a coma with hypotension, acidosis and anuria and was transferred to an intensive care unit. The patient underwent mechanical ventilation, hemodialysis and received treatment with Imipenem because of suspected septic shock. She improved and was awake in the afternoon on 22-Apr-2003. On 28-Apr-2003 she was transferred to the Nephrology ward with lab test measuring: BUN 26; Creatinine 3 and CK 424. On 12-May-2003, patient was treated with linezolid 600 mg BID and metronidazole 500 mg TID for urinary infection with Enterococco faecium. Fluconasolo and Cephalosporin were added to patient therapy with discovery of Pseudomonas and Candida tropicalis. The renal function continued to improve with serum creatinine 1.8 mg and CPK 226U/l on 16-May-2003 when she was transferred to the GISSI Heart Failure Center with the following diagnoses "Acute renal failure secondary to a very probable septic shock in a diabetic with chronic atrial fibrillation, urinary infection due to Enterococco Faecium, Pseudomonas Aeruginosa and Candida tropicalis, sacral Ulcer, trophyc ulcer in the legs".

After reviewing the discharge summary from 21-Apr-2003 to 16-May-2003, the investigator reported acute renal failure, coma, septic shock, urinary infection, Enterococco Faecium as serious adverse events and assessed all of them not to be causally related to rosuvastatin. Coma, septic shock and ranal failure were considered by the investigator to be life threatening. The investigator considered that the hemodynamic conditions of the septic shock might explain the rise in CK levels, which are back within normal ranges now.

Summary of follow-up information received by AstraZeneca 07-May-2003 and 08-May-2003: Lab values and further information on concomitant medications, the hospitalizations and the diagnosis of rhabdomyolysis.

Summary of follow-up information received by AstraZeneca 16-May-2003: The patient has been transferred from the nephrology ward to the internal medicine ward. Reason for acute renal failure was provided.

Summary of follow-up information received by AstraZeneca 19-May-2003: Hospitalization summary, additional laboratory results, the deletion of rhabdomyolysis as a serious adverse event and the attribution of raised CPK to Septic Shock, the addition of Coma as a serious adverse event and the change in causality assessment

Summary of follow-up information received by AstraZeneca 26-May-2003: Examinations done during the *

B.5. Describe event or problem

[continuation:] first hospitalization together with clarification of laboratory findings. Two additional serious adverse events of septic shock and urinary infection were added.

Summary of follow-up information received by AstraZeneca 28-May-2003: Summary of second hospitalization with additional laboratory findings.

Company Clinical Comment: Acute renal failure and coma occurred 6 and 7 days after stopping rosuvastatin. The investigator considered these events to be related to the septic shock and not rosuvastatin. The events of acute renal failure, coma, septic shock and urinary infection were all considered not causally related to rosuvastatin by the investigator.

B.6. Relevant tests/laboratory data, including dates

[continuation:] Cerebral assial tomography: negative. No signs or symptoms of mesenteric or cardiac ischemia.
16-May-2003: Negative blood culture.
15th to 18th April 2003: Thoraxicic x-ray, ECG and lab examinations.

Lab Test/Comment	Lab Value	Units	Date	Ref. to Normal	Low	High
CREATININE	0.8		11/??/2002			
K	3.79		11/??/2002			
GLUCOSE	208		11/??/2002			
BLOOD GLUCOSE	138	MG/DL	04/15/2003			
CREATININE	3.8	MG/DL	04/15/2003			
NA	152		04/21/2003			
K	5.8		04/21/2003			
BUN	183		04/21/2003			

MEDWATCH	A.1. Patient Identifier	G.8. Mfr. report number 2003SE02255	Page 4 of 7

B.6. Relevant tests/laboratory data, including dates

[continuation:] CREATININE 8.7 04/21/2003

CK	10383		04/21/2003
CK	21632		04/21/2003
BUN	26		04/28/2003
CREATININE	3		04/28/2003
CK	424		04/28/2003
[redacted]MPERATURE	37.5	CELCIUS	05/16/2003
WHITE CELLS	13600	/mmc	05/16/2003
HB	11.6	GR%	05/16/2003
PLATELETS	251000	/mmc	05/16/2003
N	100	MG%	05/16/2003
CREATININE	1.8	MG%	05/16/2003
AST	20	U/L	05/16/2003
ALT	7	U/L	05/16/2003
[redacted]A	140	mEq/L	05/16/2003

B.6. Relevant tests/laboratory data, including dates

[continuation:]

K	3.69	mEq/L	05/16/2003
CL	94	mEq/L	05/16/2003
CA	8.6	MG%	05/16/2003
INR	1.29		05/16/2003
PTT	33.9	SEC	05/16/2003
FIBRINOGENO	666	MG/DL	05/16/2003
CPK	226	U/L	05/16/2003
PH	7.55		05/16/2003
PCO2	97		05/16/2003
HCO3	38.4		05/16/2003
SATURATION O2	98	%	05/16/2003
HEMOGLOBIN	10.3		04/21/2003
WHITE CELLS	25000		04/21/2003
GLYCEMIA	140		04/21/2003
LDH	322		04/21/2003

B.6. Relevant tests/laboratory data, including dates

[continuation:]

LDH	535		04/21/2003
BILIRUBIN	0.6		04/21/2003
SGOT	172		04/21/2003
SGOT	316		04/21/2003
SGPT	58		04/21/2003
SGPT	90		04/21/2003
PH	7.31		04/21/2003
PACO2	24		04/21/2003
PAO2	73		04/21/2003
BE	13		04/21/2003
HCO3	11.7		04/21/2003
LACTATE	16		04/21/2003
PT	11	%	04/21/2003
PTT	49	SECONDS	04/21/2003

MEDWATCH	A.1. Patient identifier	G.3. MFR. report number 2003SE02255	Page 7 of 7

B.6. Relevant tests/laboratory data (including dates)

[continuation:]

C.10. Concomitant medical products and therapy dates (exclude treatment of event)

[continuation:] Name: ZYLORIC Dates: 04/15/2003 to 04/21/2003
Name: HUMULIN 30/70 Dates: 11/??/2002 to 04/21/2003
Name: WARFARIN Dates: ??/??/2001 to 04/21/2003

G.3. Report source (other:)

Source

4. MedWatch Report of a case of 46 year old patient with Renal Failure on 80mg of Rosuvastatin 0065/0044/0014

AstraZeneca Pharmaceuticals

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of 5

Mfr report # 2002UW01954

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event: 46 yrs or Date of birth:	3. Sex: ☒ female ☐ male	4. Weight: ____ lbs or 62.7 kgs
in confidence			

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 02/02/2002

4. Date of this report: 03/01/2002

5. Describe event or problem

15-DAY IND ALERT

Clinical Event(s):
1 ACUTE RENAL FAILURE

A report was received from a study investigator concerning a 46-year-old Hispanic female subject who was enrolled in A Six-week, Open label, Dose-comparison Study to Evaluate the Safety and Efficacy of Rosuvastatin versus Atorvastatin, Cerivastatin, Prsvastatin, and Simvastatin in Subjects with Hypercholesterolemia (ZD4522IL/0065).

The subject had a medical history of hypercholesterolemia, hypertension, *

6. Relevant tests/laboratory data, including dates

*

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Concomitant Disease(s): ABDOMINAL AORTIC STENOSIS, ACUTE BOWEL OBSTRUCTION, ANEMIA, CATARACTS, COUGH, DYSPNEA ON EXERTION, PERIPHERAL VASCULAR DISEASE, RARE *

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 ROSUVASTATIN
- #2 ZITHROMAX Z-PACK

2. Dose, frequency & route used
- #1 80 mg QD PO
- #2 500 mg QD PO

3. Therapy dates (if unknown, give duration)
- #1 12/26/2001 to 01/26/2002
- #2 01/23/2002 to 01/23/2002

4. Diagnosis for use (indication)
- #1 HYPERCHOLESTEROLEMIA
- #2 FEVER

5. Event abated after use stopped or dose reduced
- #1 ☐ yes ☐ no ☒ doesn't apply
- #2 ☐ yes ☐ no ☒ doesn't apply

6. Lot # (if known)
- #1 NI
- #2 NI

7. Exp. date (if known)
- #1 NI
- #2 NI

8. Event reappeared after reintroduction
- #1 ☐ yes ☐ no ☒ doesn't apply
- #2 ☐ yes ☐ no ☒ doesn't apply

9. NDC # - for product problems only (if known)
- #1 NI
- #2 NI

10. Concomitant medical products and therapy dates (exclude treatment of event)

Name: ASPIRIN "BAYER" Dates: 07/30/2001 continuing
Name: GUAIFENESIN Dates: 01/23/2002 to 01/27/2002

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)

AstraZeneca Pharmaceuticals
A Business Unit of AstraZeneca LP,
1800 Concord Pike, P.O. Box 15437,
Wilmington, DE 19850-5437

2. Phone number: 302 886 2127

3. Report source (check all that apply)
- ☐ foreign
- ☒ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 14-FEB-2002

5. (A)NDA # ____ IND # ____ PLA # ____ pre-1938 ☐ yes OTC product ☐ yes

6. If IND, protocol #: 4522IL/0065

7. Type of report (check all that apply)
- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☒ initial ☐ follow-up #____

8. Adverse event term(s)

RENAL FAILURE ACUTE

9. Mfr. report number: 2002UW01954

E. Initial reporter

1. Name, address & phone #

2. Health professional? ☒ yes ☐ no

3. Occupation: MEDICAL DOCTOR

4. Initial reporter also sent report to FDA? ☐ yes ☐ no ☒ unk

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages.

B.5. Describe event or problem

[continuation:] right-sided renal artery stenosis caused by external compressions relieved surgically (1979), claudication secondary to abdominal aortic stenosis for which Palmaz stenting was performed (1993), small-bowel obstruction secondary to volvulus (1992), chronic anemia, subclavian artery disease, rare headaches, peripheral vascular disease, trace mitral regurgitation, dyspnea on exertion, cough, anemia, and cataracts.

The subject was randomized to study drug on 26-Dec-2001. Her concomitant medications were Atacand 16 mg daily (from 05-Apr-1999 to 02-Feb-2002) and aspirin 81 mg daily. Her baseline creatinine was 0.7 mg/dL. On 11-Jan-2002 (Day 16) the subject had protocol scheduled laboratory tests that revealed a CK of 45 U/L, an ALT of 19 U/L, AST of 18 U/LL and a crestinine of 1.1 mg/dL. On 23-Jan-2002 (Day 28), the subject presented to her primary care physician complaining of coryza and "flu" symptoms. The physician prescribed guaifenesin and azithromycin on 23-Jan-2002, which the subject took until 25-Jan-2002 and 27-Jan-2002, respectively. On 26-Jan-2002 (Day 31) the subject discontinued ZD4522. Her trial participation terminated 28-Jan-2002 (Day 33). The subject was seen at the investigative site on 28-Jan-2002. At that time she complained of nausea, anorexia and fatigue. Laboratory testing on that date revealed a CK of 41 U/L, ALT of 15 U/L, AST of 23 U/L, and creatinine of 11.0 mg/dL. The subject was hospitalized on 02-Feb-2002 with acute renal failure. The investigator's initial impression was that the renal insufficiency was related, not to study drug, but to Atacand.

·e admitting physical examination revealed a tired well-developed well-nourished female with normal tal signs and no acute findings. The creatinine on admission was 13.7 mg/dL (local lab normal range 0.5-1.5 mg/dL). Urinalysis on admission (local lab) showed 30 mg/dL protein (normal = neg), small blood (normal = neg), many bacteria, 10-15 WBC/hpf (normal 0-3), 15/20 RBC/hpf (normal 0-5), 1-3 coarse granular and 5-8 hyaline casts/hpf. Urine culture showed mixed organisms. A duplex abdominal/renal scan performed on 04-Feb-2002 revealed no stenosis of either renal artery and a hypoechoic cortical matrix bilaterally with multiple small cystic masses in both kidneys. In the hospital, she responded rapidly to intravenous fluids and bicarbonate. Dialysis was not required. The subject was discharged from the hospital on 08-Feb-2002. Her creatinine at that time was 3.8 mg/dL (local lab).

After discussion with the nephrologist regarding the timing of the azithromycin administration, the investigator considered the event no longer related to Atacand but to azithromycin. The study drug could not be ruled out as a contributor to the event. On 13-Feb-2002, the patient had a creatinine of 2.2 mg/dl. The patient was scheduled for an outpatient visit to the nephrologist on 20-Feb-2002. At this visit a serum creatinine level would be obtained.

Follow up information received 14-Feb-2002 included updates to causality assessments, laboratory data, medical history, suspect drugs, and therapy dates.

Company Comment:
Acute renal failure is a labeled adverse event for azithromycin. Treatment with angiotensin receptor blockers (eg., candesartan, losartan) has also been associated with acute renal failure. Due to their temporal relationship, a possible role between rosuvastatin and the reported event cannot be tally excluded. *

MED WATCH	A.1. Patient identifier	G.8. Mfr. report number	Page 4 of 5
		2002UW01954	

B.5. Describe event or problem

[continuation:]

B.6. Relevant tests/laboratory data, including dates

[continuation:] 02-FEB-2002: URINALYSIS SHOWED 30 MG/DL PROTEIN (NORMAL = NEG), SMALL BLOOD (NORMAL = NEG), MANY BACTERIA, 10-15 WBC/HPF (NORMAL =0-3), 15/20 RBC/HPF (NORMAL =0-5), 1-3 COARSE GRANULAR AND 5-8 HYALINE CASTS/HPF. URINE CULTURE SHOWED MIXED ORGANISMS.
04-FEB-2002: DUPLEX ABDOMINAL/RENAL SCAN: REVEALED NO STENOSIS OF EITHER ARTERY AND A HYPOECHOIC CORTICAL MATRIX BILATERALLY WITH MULTIPLE SMALL CYSTIC MASSES IN BOTH KIDNEYS.

Lab Test/Comment	Lab Value	Units	Date	Ref. to Normal	Low	High
CREATININE BASELINE	0.7	MG/DL				
CK	45	U/L	01/11/2002			
ALT	19	U/L	01/11/2002			
AST	18	U/LL	01/11/2002			
CREATININE	1.1	MG/DL	01/11/2002			
CK	41	U/L	02/28/2002			
ALT	15	U/L	02/28/2002			
AST	23	U/L	02/28/2002			
CREATININE	11.0	MG/DL	02/28/2002			
CREAININE	13.7	MG/DL	02/02/2002		0.5	1.5
CREATININE	3.8	MG/DL	02/08/2002			

MED WATCH	A.1. Patient Identifier	G.8. Mfr. report number 2002UW01954	Page 5 of 5

B.6. Relevant tests/laboratory data, including dates

[continuation:]
CREATININE 2.2 MG/DL 02/13/2002

B.7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

[continuation:] HEADACHES, RENAL ARTERY STENOSIS, SUBCLAVIAN ARTERY DISEASE, TRACE MITRAL REGURGITATION
Race:HISPANIC

AstraZeneca Pharmaceuticals
A Business Unit of AstraZeneca LP,
1800 Concord Pike, P.O. Box 15437,
Wilmington, DE 19850-5437

Mfr. Rep. #: 2002UW01954

Date: 01-MAR-2002

LISTING OF PRIOR SAFETY REPORTS SUBMITTED TO IND #

ADVERSE EVENT: RENAL FAILURE ACUTE
(all preferred and included coded terms)

Manufacturer Report #	FDA Submission Date	Protocol Number	Country of Origin
2000UW03538	21-DEC-2001	4522IL/0025	
2001UW00740	22-MAY-2001	4522IL/0034	
2001UW15902	30-JAN-2002	4522IL/0065	

5. MedWatch Report of a case of 70 year old patient with Renal Failure on 80mg of Rosuvastatin 0065/0026/0049

AstraZeneca Pharmaceuticals

2001UW15902

MEDWATCH
E FDA MEDICAL PRODUCTS REPORTING PROGRAM

Page 1 of 5

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
in confidence	70 yrs or Date of birth:	☒ female ☐ male	169 lbs or kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☒ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 11/29/2001

4. Date of this report: 01/29/2002

5. Describe event or problem

7-DAY IND ALERT

Clinical Event(s):
1 RENAL FAILURE

A report was received from an investigator regarding a 70 year-old, female patient who entered a 6-week, Open label, Dose-comparison Study to Evaluate the Safety and Efficacy of Rosuvastatin versus Atorvastatin, Cerivastatin, Pravastatin, and Simvastatin in Patients with Hypercholesterolemia (ZD4522IL/0065). The patient began therapy with rosuvastatin 80 mg po daily on 14-Nov-2001 and subsequently experienced renal failure. The patient had a medical history of osteoporosis, hypertension, benign breast *

6. Relevant tests/laboratory data, including dates

*

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Concomitant Disease(s): BENIGN BREAST CYST, DEPRESSION, HYPERTENSION, INFLAMMATION, OSTEOPOROSIS, SUPPLEMENT

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
#1 ROSUVASTATIN
#2

2. Dose, frequency & route used
#1 80 mg QD PO
#2

3. Therapy dates (if unknown, give duration)
#1 11/14/2001 to 11/29/2001
#2

4. Diagnosis for use (indication)
#1 HYPERCHOLESTEROLEMIA
#2

5. Event abated after use stopped or dose reduced
#1 ☒ yes ☐ no ☐ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

6. Lot # (if known)
#1 NI
#2

7. Exp. date (if known)
#1 NI
#2

8. Event reappeared after reintroduction
#1 ☐ yes ☐ no ☒ doesn't apply
#2 ☐ yes ☐ no ☐ doesn't apply

9. NDC # - for product problems only (if known)
#1 NI
#2

10. Concomitant medical products and therapy dates (exclude treatment of event)

Name: DIOVAN *NOVARTIS* Dates: 01/01/2000 continuing
Name: VIOXX Dates: 01/01/2000 continuing
Name: NORVASC Dates: 03/03/2001 continuing *

G. All manufacturers

1. Contact office - name/address (& mfring site for devices)
AstraZeneca Pharmaceuticals
A Business Unit of AstraZeneca LP,
1800 Concord Pike, P.O. Box 15437,
Wilmington, DE 19850-5437

2. Phone number: 302 886 2127

3. Report source (check all that apply)
- ☐ foreign
- ☒ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

4. Date received by manufacturer: 24-JAN-2002

5. (A)NDA # / IND # / PLA #

6. If IND, protocol #: 4522IL/0065

pre-1938 ☐ yes

OTC product ☐ yes

7. Type of report (check all that apply)
- ☐ 5-day ☐ 15-day
- ☒ 10-day ☐ periodic
- ☐ initial ☒ follow-up # 2

8. Adverse event term(s)
RENAL FAILURE ACUTE

9. Mfr. report number: 2001UW15902

E. Initial reporter

1. Name, address & phone #

2. Health professional? ☒ yes ☐ no

3. Occupation: MEDICAL DOCTOR

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

* Item completed on continuation pages.

B.5. Describe event or problem

[continuation:] cyst, obesity, and depression. Concomitant medications included Diovan (valsartan), Vioxx (rofecoxib), Norvasc (amlodipine), selenium, and Paxil (paroxetine). At the scheduled visit prior to randomization to study drug (November 7, 2001), her creatinine was 1.0 mg/dl, ALT was 10 U/L, AST was 15 U/L, and ALP was 54 U/L. Her CPK at randomization was 51 U/L, ALT was 9 U/L, and AST was 13 U/L. On November 28, 2001 (Day 15), the CPK was 69 U/L, creatinine was 2.3 mg/dl, ALT was 8 U/L, AST was 13 U/L, and ALP was 75 U/L.

On November 29, 2001 (Day 16), the patient reported to the emergency room complaining of generalized achiness, right-sided abdominal pain, nausea, and vomiting. Gallstones were detected and the patient was treated (treatment unknown at this time) and sent home. Her creatinine was subsequently found to have been 3.0 mg/dl. On 29-Nov-2001, the investigator requested that the patient permanently stop study medication. On December 3, 2001 (Day 20), the patient returned to the hospital and was admitted with a diagnosis of renal failure of unknown etiology. The patient's creatinine was 8.0 mg/dl. The CPK was 137 U/L (ULN = 130 U/L) and the myoglobin was 195 ng/dl (ULN = 51 ng/dl). The treating physician reported that the liver function tests, lipase, amylase, and white blood counts were normal. Viral hepatitis was ruled out. The physician also reported that the patient had no fever and urinalysis was unremarkable. An abdominal ultrasound was positive for 3 gallstones. An abdominal CT scan and HIDA scan were negative. The patient was immediately scheduled for dialysis.

4-Dec-2001, the patient's creatinine was 9.4 mg/dl. On 6-Dec-2001, the physician reported that the etiology remained unknown and the patient was dialyzed on 4-Dec-2001 and 5-Dec-2001. On 6-Dec-2001, the patient was also scheduled to receive dialysis. On 6-Dec-2001, the physician reported that the creatinine was < 4.0 mg/dl, the CPK was 108 U/L, and myoglobin was 150 ng/dl. The patient was stable and not considered in critical condition, however, the abdominal pain persisted. As of December 10, 2001 the creatinine was 5.0 mg/dl and 4.8 mg/dl and the patient was receiving hemodialysis every other day. The abdominal symptoms had improved with the use of Reglan (metoclopramide). On December 10, 2001, a CT-guided renal biopsy revealed acute tubular necrosis of unknown etiology. On an unknown date, the patient was discharged from the hospital. At the time of this report, the patient was recovering. The patient had been receiving dialysis three times a week and was diagnosed with anemia. The patient was then decreased to two times a week for dialysis and was being treated with Epoetin and vitamin supplements for her anemia.

The investigator assessed the event to be severe in intensity, life threatening, and possibly related to rosuvastatin in view of the temporal sequence of the event and study drug administration.

Company comment: Concomitant angiotensin II antagonist (valsartan) and Cox 2 inhibitor (rofecoxib) therapy may have contributed to the event, as acute renal failure is listed for both of these drugs. Hopsital records are pending. It is difficult to assess the causal role of rosuvastatin until complete information is obtained. This is the first report of renal failure that is not associated with myopathy.

Follow-up received 20-Dec-2001 added kidney biospy results and additional creatinine value of 4.8 mg/dl. Ouctome updated to recovering from not yet recovered and on an unknown date, the patient was *

B.5. Describe event or problem

[continuation:] discharged from the hospital.

Follow-up received 10-Jan-2002, reporetd the patient had been receiving dialysis three times a week and remained weak. She was diagnosed with anemia.

Follow-up received 24-Jan-2002 reported the patient was reduced to dialysis two times a week. She was being treated with Epoetin and vitamin supplements for her anemia.

B.6. Relevant tests/laboratory data, including dates

[continuation:] LIVER FUNCTION TESTS, LIPASE, AMYLASE, AND WHITE BLOOD COUNTS WERE NORMAL AND VIRAL HEPATITIS WAS RULED OUT.
ABDOMINAL ULTRASOUND WAS POSITIVE FOR THREE GALLSTONES.
ABDOMINAL CT SCAN AND HIDASCAN WERE NEGATIVE.
10-DEC-2001: CT GUIDED RENAL BIOPSY SHOWED ACUTE TUBULAR NECROSIS OF UNKNOWN ETIOLOGY.

Lab Test/Comment	Lab Value	Units	Date	Ref. to Normal	Low	High
CREATININE	1.0	MG/DL	11/07/2001		0.7	1.4
LT	10	U/L	11/07/2001		5	25
AST	15	U/L	11/07/2001		8	22
ALP	54	U/L	11/07/2001		32	72
CPK	51	U/L	11/14/2001		0	120
ALT	9	U/L	11/14/2001		5	25
AST	13	U/L	11/14/2001		8	22
CPK	69	U/L	11/28/2001		0	120
CREATININE	2.3	MG/DL	11/28/2001		0.7	1.4

B.6. Relevant tests/laboratory data, including dates

[continuation:]

ALT	8	U/L	11/28/2001	5	25
AST	13	U/L	11/28/2001	8	22
ALP	75	U/L	11/28/2001	32	72
CREATININE	3.0	MG/DL	11/29/2001	0.7	1.4
CREATININE	8.0	MG/DL	12/03/2001	0.7	1.4
CPK	137	U/L	12/03/2001	10	130
MYOGLOBIN	195	NG/DL	12/03/2001	19	51
CREATININE	9.4	MG/DL	12/04/2001	0.7	1.4
CREATININE	<4.0	MG/DL	12/06/2001		
CPK	108	U/L	12/06/2001		
MYOGLOBIN	150	NG/DL	12/06/2001		
CREATININE	5.0	MG/DL	12/10/2001		
CREATININE	4.8	MG/DL	12/10/2001		

MEDWATCH	A.1. Patient Identifier	G.9. Mfr. report number	Page 5 of 5
		2001UW15902	

C.10. Concomitant medical products and therapy dates (exclude treatment of event)

[continuation:] Name: SELENIUM Dates: 01/01/1995 continuing
Name: PAXIL Dates: 03/03/2001 continuing

AstraZeneca Pharmaceuticals
A Business Unit of AstraZeneca LP,
1800 Concord Pike, P.O. Box 15437,
Wilmington, DE 19850-5437

Mfr. Rep. #: 2001UW15902

Date: 29-JAN-2002

LISTING OF PRIOR SAFETY REPORTS SUBMITTED TO IND #

ADVERSE EVENT: RENAL FAILURE ACUTE
(all preferred and included coded terms)

Manufacturer Report #	FDA Submission Date	Protocol Number	Country of Origin
2000UW03538	21-DEC-2001	4522IL/0025	
2001UW00740	22-MAY-2001	4522IL/0034	
2001UW15902	31-DEC-2001	4522IL/0065	

6. MedWatch Report of a case of 69 year old patient with Interstitial Nephritis on 80mg of Rosuvastatin 0034/0316/0025

MEDWATCH
THE FDA MEDICAL PRODUCTS REPORTING PROGRAM

AstraZeneca Pharmaceuticals

Page 1 of 13

Approved by FDA on 3/22/94

2001SE08724

FDA Use Only

A. Patient information

1. Patient identifier	2. Age at time of event:	3. Sex	4. Weight
in confidence	69 yrs or Date of birth:	☐ female ☒ male	NI lbs or NI kgs

B. Adverse event or product problem

1. ☒ Adverse event and/or ☐ Product problem (e.g., defects/malfunctions)

2. Outcomes attributed to adverse event (check all that apply)
- ☐ death
- ☐ life-threatening
- ☒ hospitalization - initial or prolonged
- ☐ disability
- ☐ congenital anomaly
- ☐ required intervention to prevent permanent impairment/damage
- ☐ other:

3. Date of event: 10/24/2001

4. Date of this report: 06/17/2002

5. Describe event or problem

15-DAY IND ALERT

Clinical Event(s):
1 INTERSTITIAL NEPHERITIS
A report has been received concerning a 69-year-old male who was enrolled in an open label, multicentre extension trial to assess the long-term safety and efficacy of ZD4522 (rosuvastatin) in subjects with hypercholesterolemia. After treatment with rosuvastatin 80 mg for 1 year and 6 months it was observed on routine study visit that he had developed proteinuria with active sediment associated with a rise in serum creatinine. A nephrologist recommended that the patient have a renal biopsy. Three weeks later the patient was hospitalised for the *

6. Relevant tests/laboratory data, including dates

*

7. Other relevant history, including preexisting medical conditions (e.g., allergies, race, pregnancy, smoking and alcohol use, hepatic/renal dysfunction, etc.)

Concomitant Disease(s): BACK ACHE, LEG ULCERS, STASIS LEG ULCERS

C. Suspect medication(s)

1. Name (give labeled strength & mfr/labeler, if known)
- #1 ROSUVASTATIN
- #2 ROSUVASTATIN

2. Dose, frequency & route used
- #1 80 mg daily PO
- #2 NI

3. Therapy dates (if unknown, give duration)
- #1 05/12/2000 to 11/30/2001
- #2 12/24/2001 to 04/15/2002

4. Diagnosis for use (indication)
- #1 HYPERCHOLESTEROLAEMIA
- #2 HYPERCHOLESTEROLAEMIA

5. Event abated after use stopped or dose reduced
- #1 ☐ yes ☐ no ☒ doesn't apply
- #2 ☐ yes ☐ no ☒ doesn't apply

6. Lot # (if known)
- #1 NI
- #2 NI

7. Exp. date (if known)
- #1 NI
- #2 NI

8. Event reappeared after reintroduction
- #1 ☐ yes ☐ no ☒ doesn't apply
- #2 ☐ yes ☐ no ☒ doesn't apply

9. NDC # - for product problems only (if known)
- #1 NI
- #2 NI

10. Concomitant medical products and therapy dates (exclude treatment of event)

Name: DISPRIN Dates: ??/??/1995 to NI
Name: FLAMAZINE
Name: BETADINE *AL PHARM KEATINGS DIV* *

G. All manufacturers

1. Contact office - name/address (& mfr/ng site for devices)

AstraZeneca Pharmaceuticals
A Business Unit of AstraZeneca LP,
1800 Concord Pike, P.O. Box 15437,
Wilmington, DE 19850-5437

2. Phone number: 302 886 2127

3. Report source (check all that apply)
- ☒ foreign
- ☒ study
- ☐ literature
- ☐ consumer
- ☒ health professional
- ☐ user facility
- ☐ company representative
- ☐ distributor
- ☐ other:

*

ZA

4. Date received by manufacturer: 05-JUN-2002

5. (A)NDA #
IND #
PLA #
pre-1938 ☐ yes
OTC product ☐ yes

6. If IND, protocol #: 4522IL/0034

7. Type of report (check all that apply)
- ☐ 5-day ☒ 15-day
- ☐ 10-day ☐ periodic
- ☐ initial ☒ follow-up # 4

8. Adverse event term(s)
NEPHERITIS INTERSTITIAL

9. Mfr. report number: 2001SE08724

E. Initial reporter

1. Name, address & phone #

[redacted]

2. Health professional? ☒ yes ☐ no

3. Occupation: MEDICAL DOCTOR

4. Initial reporter also sent report to FDA: ☐ yes ☐ no ☒ unk

FDA

Submission of a report does not constitute an admission that medical personnel, user facility, distributor, manufacturer or product caused or contributed to the event.

Item completed on continuation pages.

B.5. Describe event or problem

[continuation:] biopsy.
Follow-up information received 29-NOV-2001:
The patient was diagnosed with chronic interstitial nephritis, cause unknown. The medical history includes hypercholesterolaemia, stasis leg ulcers since '87, treated with flamazine, Betadine, topical steroids and intramuscular penicillin for over 10 years. The last Bicillin injection was in July 2001. Patient also has a history of backache and was hospitalized with inflammation of kidneys at age eight years. Patient recovered without known sequelae.
He has a history of heavy alcohol use but stopped totally in 1983. Concurrent medications are rosuvastatin 80 mg daily, 0.5 disprin daily for the past 18 months, intermittent intramuscular penicillin for chronic leg ulcers, and occasional paracetamol for pain. During the 6-week dietary lead- in period of the trial, prior to rosuvastatin exposure, there were two abnormal urinalyses; the first showed no protein but did show active sediment, the second showed 1+ protein and some bacteria, but no active sediment. Baseline serum creatinine in November 1999 was 84 mmol/l (1.1 mg/dl).
The subject was seen for a routine study visit in December 2000, at which time his serum creatinine had risen to 141 mmol/l (1.6 mg/dl). Urinanalysis was not performed. Creatinine was measured again at a study visit in October 2001, at which time the subject reported no symptoms but the serum creatinine was still elevated at 141 mmol/l and urinanalysis showed 3+protein with active sediment. LDL-C was 61 mg/dl from a baseline of 282 mg/dl. He was referred to a nephrologist who evaluated the subject in early November 2001. The subject remained asymptomatic and reported no edema. He had a ormal blood pressure and unremarkable physical exam. Local lab results were as follows: urinalysis revealed 1+ protein, 3+ blood, and numerous granular casts with moderate numbers of renal tubular cells. Complete blood count was unremarkable; ESR 31 mm/hour; Electrolytes, glucose, total protein, and albumin were normal; urea 10 mmol/l, creatinine 161 umol/l, glucose 3.9 mmol/l, total protein 80 g/l, albumin 44 g/l, total bilirubin 36 umol/l, conjugated bilirubin 10 umol/l. ALT 69 units/litre, alkaline phosphate 124 units/litre, creatinine kinase 238 units/litre. (Conventional units: urea 28 mg/dl, creatinine 1.8 mg/dl, glucose 70 mg/dl, total protein 8 gm/dl, albumin 4.4 gm/dl, total bilirubin 2.1 mg/dl, conjugated bilirubin 0.6 gm/dl). Baseline total bilirubin was elevated at 29 umol/l (1.7 mg/dl). HbsAg negative; Hepatitis C antibody negative; ANF negative. Serum protein electrophoresis revealed no paraproteins and a normal albumin.
Uncorrected creatinine clearance was 42 ml/min. Baseline creatinine clearance was 61 ml/min. Daily protein excretion was 1.6 g/day, urea 388 mmol/day, sodium 171 mmol/day, potassium 68 mmol/day. Repeat serum creatinine on 20-Nov-2001 was 140 mmol/l (1.6 mg/dl) and the urea 6.2 mmol/l (17mg/dl). Renal biopsy performed on 20-Nov-2001 revealed features of chronic tubulo-interstitial nephritis with moderate increase in fibrous tissue and occasional inflammatory cells in the interstitium. These features were suggestive of a chronic process, present for many months and resulting in gradual collagen deposition within the interstitium, rather than an acute process. The nephrologist was not sure of the cause of the chronic interstitial nephritis and felt that it was remotely possible that rosuvastatin therapy may be responsible. Rosuvastatin was stopped 2001-Nov-30. Rosuvastatin was restarted on December 24 2001 at which stage proteinuria disappeared. There was only slight trace of blood and no casts. Plasma creatinine was 113 mmol/l, urea 6.4 mmol and 24 hour protein 80 mg. Urine samples were collected on December 26 and 29 2001, January 2 and 5 2002. On all these samples showed no detectable blood, protein or casts. Urine sample from January 16 was cloudy and with innumerable casts of all varieties. Semi quantitative tests showed 1+ protein and 2+ blood. Nephrologic consult of January 18 reported patient used two tablets of paracetamol 4 days prior to and one tablet 10 *

B.5. Describe event or problem

[continuation:] days prior to hospital visit for mild headache. There were no associated symptoms suggesting urinary tract infection or features of any other systemic disorder. The patient had also taken his routine half a disprin. Clinical examination revealed no abnormalities. Urine microscopy confirmed the previous findings. 24 hour protein excretion was 600 mg, plasma creatinine 119 mmol/l and urea 6.9 mmol/l. The patient continued with rosuvastatin for another week. The patient had a paracetamol challenge test. Four days after the challenge with paracetamol, cast numbers appeared to have increased. Urinary blood and protein was the same. Patient was continued on rosuvastatin. The patient was seen again on April 10. Ten days prior to the consultation the patient had a brief period of diarrhoea but was otherwise entirely asymptomatic and clinically well. The patient had not taken any drugs other than his statin and disprin. Urinanalysis revealed the presence of large number of casts, 3+ blood and 2+ protein. Urea was 6.7mmol/l, creatinine 120 mmol/l and 24 hour urine protein 1 300 mg. Rosuvastatin was stopped April 15 2002.
Nephrologist's report:
The nephrologist saw the patient on 27-May-2002 at which time all symptoms had totally resolved. Laboratory tests confirmed the absence of significant proteinuria on the last two occasions.
20-May-2002: Protein/ creatinine ratio 13.1 (equivalent to 110 mg protein per 24 hours).
27-May-2002: Protein/ creatinine ratio 16.4 (equivalent to 159 mg protein per 24 hours).
Other chemistry: Sodium 137 mmol/l, potassium 3.9 mmol/l, potassium 3.9 mmol/l, urea 5.5 mmol/l, creatinine 108 mmol/l, AST 258, ALT 20, CPK 115, Hb 13.7, MCV 82, WCC 6.9, platelets 360, ESR 17. Creatinine clearance 57 ml/min (corrected).
The conclusion was that the patient has lost all his urine abnormalities for a period of six weeks whilst of rosuvastatin therapy. Therapy with another statin at an equivalent dose to rosuvastatin was considered acceptable with very careful urine examination for at least six weeks.
Follow-up information 2001-Dec-14: Stop-date for rosuvastatin (study drug) was received. Several blood test results received, added on the lab. page.
Follow up information received 31 Jan 2002: Reporter confirmed that a causal relationship is possible with the event and study drug.
Summary of follow-up information received on 30-Apr-2002: Progress report from Nephrologist.
8-MAY-2002: Corrected report: Information was added (to the "Summary of follow-up information" in the end of narrative) concerning the content in follow-up information received on 30-Apr-2002.
14-MAY-2002: Corrected report. Information about dechallenge and rechallenge, start and stop date for suspect drug. Correction made in narrative concerning LDL (lipids) values.
16-MAY-2002: Corrected report. More detailed information from the original "Progress report" received on 30-Apr-2002, regarding investigations by nephrologist has been added to the narrative. Company Clinical Comment was changed.
16-MAY-2002: Rechallenge dose and clarification of dates.
Summary of follow-up information received on 5-Jun-2002: Nephrologist's report, see section "nephrologist's report above.
Company Clinical Comment: Renal papillary necrosis may result from chronic acetaminophen use, particularly when dosage is greater than recommended and when combined with aspirin. Patient was on Dispirin according to a previous list of concomitant medications and in this update, patient was taking acetaminophen. Dosage and duration were not provided. The nephrologist stated that proteinuria observed by 16 January 2002 might have been due to paracetamol (acetaminophen). However, the nephrologist tried both paracetamol and rosuvastatin during the same period in the rechallenge, *

B.5. Describe event or problem

[continuation:] making causality assessment very difficult. Due to the temporal relationship, and quasi positive rechallenge information, a possible role between rosuvastatin and the reported event cannot be excluded.

B.6. Relevant tests/laboratory data, including dates

[continuation:]

Lab Test/Comment	Lab Value	Units	Date	Ref. to Normal	Low	High
HB	12.5	g/dl				
HAEMATOCRIT	0.37					
WCC	6 400					
PLATELETS	326					
ESR	31	MM/HOUR				
HBSAG	NEGATIVE					
HEPATITIS C ANTIB	NEGATIVE					
ANF	NEGATIVE					

B.6. Relevant tests/laboratory data, including dates

[continuation:]

SODIUM	142	MMOL/L					
POTASSIUM	4	MMOL/L					
UREA	10	MMOL/L					
CREATININE	161	UMOL/L					
GLUCOSE	3.9	MMOL/L					
TOTAL PROTEIN	80	G/L					
BUMIN	44	G/L					
TOTAL BILIRUBIN	36	UMOL/L					
CONJUGATED BILIRU	10	UMOL/L					
ALT	69	UNITS/L					
ALKALINE PHOSPHAT	124	UNITS/L					
CREATININE KINASE	238	UNITS/L					
WBC	5.4	K/cu mm	04/26/2000	NORMAL	4.8	10.8	
RBC	5.32	M/cu mm	04/26/2000	NORMAL	4.20	5.40	
HGB	14.8	gm/dL	04/26/2000	NORMAL	F 12.0	F 16.0	*

B.6. Relevant tests/laboratory data, including dates

[continuation:]

HCT	45.9	%	04/26/2000		36.0	46.0
MCH	27.8	pg	04/26/2000		27.0	31.0
MCHC	32.3 L	gm/dL	04/26/2000	DECREASED	33.0	33.7
RDW	13.6	%	04/26/2000	NORMAL	11.5	14.5
PLATELET COUNT	330	K/cu mm	04/26/2000	NORMAL	150	450
METAMYELOCYTES	0	%	04/26/2000	NORMAL	0	0
..AND NEUTROPHILES	0	%	04/26/2000	NORMAL	0	11
SEGMENTED NEUTROP	66	%	04/26/2000		36	66
LYMPHOCYTES	27	%	04/26/2000	NORMAL	24	44
ATYPICAL LYMPHOCY	0	%	04/26/2000	NORMAL	0	0
MONOCYTES	3	%	04/26/2000	NORMAL	0	11
EOSINOPHILES	3	%	04/26/2000	NORMAL	0	7
BASOPHILES	1	%	04/26/2000	NORMAL	0	3
SG (URINANALYSIS)	1.020		04/26/2000	NORMAL	1.002	1.035

MED WATCH	A.1. Patient Identifier	G.9. Mfr. report number	Page 7 of 13
		2001SE08724	

B.6. Relevant tests/laboratory data, including dates

[continuation:] PH (URINANALYSIS)	6.0		04/26/2000	NORMAL	5.0	8.0
COLOUR (URINANALYY	ELLOW		04/26/2000			
APPEARANCE (URINA	CLEAR		04/26/2000			
PROTEIN (URINANAL	NEG	mg/dL	04/26/2000			
GLUCOSE (URINANAN	EG	mg/dL	04/26/2000			
KETONES (URINANAN	EG	mg/dL	04/26/2000			
BILIRUBIN URINANAN	EG		04/26/2000			
BLOOD URINANALYSN	EG		04/26/2000			
URBC (URINANALYSIO	CC	HPF	04/26/2000	NONE	OCC/1-5	
UWBC (URINANALYSI	1-5	HPF	04/26/2000	NONE	OCC/1-5	
BACTERIA (URINANA	PRESENT H		04/26/2000	ABSENT		
HYALINE CASTS (UR?	???	LPF	04/26/2000	NONE		
FINELY GRANULAR C?	???	LPF	04/26/2000	NONE		
AMORPH CRYSTALS (N	ONE	LPF	04/26/2000	NONE		
CREATININE (SERUM	1.1	mg/dL	NORMAL	0.7	1.4	

MED WATCH	A.1. Patient identifier	G.3. Mfr. report number 2001SE08724	Page 8 of 13

B.6. Relevant tests/laboratory data ,including dates

[continuation:]

TOTAL BILIRUBIN (0.98		mg/dL	04/26/2000		0.10	1.10
SGPT (ALT)	20	mU/mL	04/26/2000	NORMAL	5	25
SGOT (AST)	20	mU/mL	04/26/2000	NORMAL	8	22
CPK	83	mU/mL	04/26/2000	NORMAL	0	120
FP GLUCOSE	94	mg/dL	04/26/2000	NORMAL	60	115
TOTAL CHOLESTEROL	355 H	mg/dL	04/26/2000	INCREASED	125	200
TRIGLYCERIDER (LI	110	mg/dL	04/26/2000	NORMAL	45	200
HDL (LIPIDS)	51	mg/dL	04/26/2000	NORMAL	35	60
LDL (LIPIDS)	282 H	mg/dL	04/26/2000	INCREASED	50	160
SGPT (ALT)	19	mU/mL	05/12/2000	NORMAL	5	25
SGOT (AST)	20	mU/mL	05/12/2000	NORMAL	8	22
CPK	82	mU/mL	05/12/2000	NORMAL	0	120
LDL	50	MG/DL	05/12/2000	NORMAL	50	160
SGPT (ALT)	22	mU/mL	06/08/2000	NORMAL	5	25
SGOT (AST)	23 H	mU/mL	06/08/2000	INCREASED	8	22

MED WATCH	A.1. Patient identifier	G.9. Mfr. report number 2001SE08724	

B.6. Relevant tests/laboratory data ,including dates

[continuation:]

CPK	86	mU/mL	06/08/2000	NORMAL	0	120
TOTAL CHOLESTEROL	144	mg/dL	06/08/2000	NORMAL	125	200
TRIGLYCERIDER (LI	73	mg/dL	06/08/2000	NORMAL	45	200
HDL (LIPIDS)	52	mg/dL	06/08/2000	NORMAL	35	60
LDL (LIPIDS)	77	mg/dL	06/08/2000	NORMAL	35	160
SGPT (ALT)	32 H	mU/mL	08/31/2000	INCREASED	5	25
SGOT (AST)	30 H	mU/mL	08/31/2000	INCREASED	8	22
CPK	107	mU/mL	08/31/2000	NORMAL	0	120
TOTAL CHOLESTEROL	150	MG/DL	08/31/2000	NORMAL	125	200
TRIGLYCERIDER	69	MG/DL	08/31/2000	NORMAL	45	200
HDL	57	MG/DL	08/31/2000	NORMAL	35	60
LDL	79	MG/DL	08/31/2000	NORMAL	50	160
SODIUM (SERUM)	144	MEQ/L	12/08/2000		133	145
POTASSIUM (SERUM)	3.7	MEQ/L	12/08/2000	NORMAL	3.5	5.0

B.6. Relevant tests/laboratory data, including dates

[continuation:] CREATININE (SERUM1.6 H MG/DL 12/08/2000 INCREASED 0.7 1.4

TOTAL PROTEIN	8.7 H	GM/DL	12/08/2000	INCREASED	6.0	8.0
CALCIUM	9.5	MG/DL	12/08/2000	NORMAL	8.5	10.5
PHOSPHORUS	2.6	MG/DL	12/08/2000	NORMAL	2.5	4.5
ALK PHOS >18	101 H	MU/ML	12/08/2000	INCREASED	32	72
GAMMA GT	40 H	MU/ML	12/08/2000	INCREASED	5	29
TOTAL BILIRUBIN	2.33 H	MG/DL	12/08/2000	INCREASED	0.10	1.10
SGPT (ALT)	59 H	MU/ML	12/08/2000	INCREASED	5	25
SGOT (AST)	41 H	MU/ML	12/08/2000	INCREASED	8	22
CPK	86	MU/ML	12/08/2000	NORMAL	0	120
ALBUMIN	4.9	GM/DL	12/08/2000	NORMAL	3.5	5.5
FP GLUCOSE	97	MG/DL	12/08/2000	NORMAL	60	115
SGPT (ALT)	68 H	MU/ML	02/15/2001	INCREASED	5	25
SGOT (AST)	51 H	MU/ML	02/15/2001	INCREASED	8	22
CPK	93	MU/ML	02/15/2001	NORMAL	0	120

B.6. Relevant tests/laboratory data ,including dates

[continuation:]

TOTAL CHOLESTEROL	133	MG/DL	02/15/2001	NORMAL	125	200
TRIGLYCERIDES	85	MG/DL	02/15/2001	NORMAL	45	200
HDL	46	MG/DL	02/15/2001	NORMAL	35	60
LDL	70	MG/DL	02/15/2001	NORMAL	50	160
SGPT (ALT)	33 H	MU/ML	05/09/2001	NORMAL	5	25
SGOT (AST)	27 H	MU/ML	05/09/2001	INCREASED	8	22
CPK	113	MU/ML	05/09/2001	NORMAL	0	120
TOTAL CHOLESTEROL	156	MG/DL	05/09/2001	NORMAL	125	200
TRIGLYCERIDES	79	MG/DL	05/09/2001	NORMAL	45	200
HDL	62 H	MG/DL	05/09/2001	INCREASED	35	60
LDL	78	MG/DL	05/09/2001	NORMAL	50	160
SGPT (ALT)	29 H	MU/ML	08/01/2001	INCREASED	5	25
SGOT (AST)	25 H	MU/ML	08/01/2001	INCREASED	8	22
CPK	109	MU/ML	08/01/2001	NORMAL	0	120
TOTAL CHOLESTEROL	148	MG/DL	08/01/2001	NORMAL	125	200 *

B.6. Relevant tests/laboratory data, including dates

[continuation:]

TRIGLYCERIDES	62	MG/DL	08/01/2001	NORMAL	45	200
HDL	62 H	MG/DL	08/01/2001	INCREASED	35	60
LDL	74	MG/DL	08/01/2001	NORMAL	50	160
24 HOUR URINE PRO	1300	MG				
SODIUM	137	MMOL/L	Unknown			
POTASSIUM	3.9	MMOL/L	Unknown			
UREA	5.5	MMOL/L	Unknown			
CREATININE	108	MMOL/L	Unknown			
AST	25					
ALT	20					
CPK	115					
HB	13.7					
MCV	82					
WCC	6.9					

*

MED WATCH	A.1. Patient Identifier	G.8. Mfr. report number	Page 13 of 13
	[redacted]	2001SE08724	

B.6. Relevant tests/laboratory data, including dates

[continuation:] PLATELETS 360

ESR 17

CREATININE CLEARE57 ML/MIN

PROTEIN/CREATININ13.1 05/20/2002
EQUIVALENT TO 159 MG PROTEIN PER 24 HOUR.

PROTEIN/CREATININ16.4 05/27/2002
EQUIVALENT TO 110 MG PROTEIN PER 24 HOUR

C.10. Concomitant medical products and therapy dates (exclude treatment of event)

[continuation:] Name: STEROIDS
Name: BICILLIN Dates: 07/??/2001 to NI

G.3. Report source (other)

Source [redacted]

AstraZeneca Pharmaceuticals
A Business Unit of AstraZeneca LP,
1800 Concord Pike, P.O. Box 15437,
Wilmington, DE 19850-5437

Mfr. Rep. #: 2001SE08724

Date: 17-JUN-2002

LISTING OF PRIOR SAFETY REPORTS SUBMITTED TO IND # [redacted]

ADVERSE EVENT: NEPHRITIS INTERSTITIAL
(all preferred and included coded terms)

Manufacturer Report #	FDA Submission Date	Protocol Number	Country of Origin
2001SE08724	21-MAY-2002	4522IL/0034	

9.2 Proteinuria, Hematuria and Increase in Serum Creatinine by Rosuvastatin Dose

URINE BLOOD INCREASES IN SUBJECTS WITH AN INCREASE IN URINE PROTEIN TO ++ OR GREATER FROM BASELINE [1] TO AVAILABLE URINALYSIS VISIT BY DOSE: ALL PHASE II/III CONTROLLED AND UNCONTROLLED CLINICAL TRIALS

DOSE AT URINALYSIS VISIT	NUMBER OF SUBJECTS WITH URINALYSIS RESULTS	INCREASE IN URINE PROTEIN TO ++ OR GREATER		INCREASE IN URINE BLOOD ASSOCIATED WITH INCREASE IN URINE PROTEIN TO ++ OR GREATER									
				INCREASE IN URINE BLOOD ASSOCIATED WITH INCREASE IN URINE PROTEIN TO ++ OR GREATER		CREATININE INCREASED > 30%		CREATININE INCREASED >20-30%		CREATININE INCREASED >10-20%		CREATININE INCREASED >0-10%	
	N	N	%	N	%	N	%	N	%	N	%	N	%
ZD4522 5 MG	852	15	1.8	5	0.6	1	0.1	0	0.0	1	0.1	2	0.2
ZD4522 10 MG	1258	20	1.6	3	0.2	0	0.0	0	0.0	0	0.0	0	0.0
ZD4522 20 MG	796	10	1.3	1	0.1	0	0.0	0	0.0	0	0.0	1	0.1
ZD4522 40 MG	997	34	3.4	14	1.4	2	0.2	5	0.5	2	0.2	1	0.1
ZD4522 80 MG	1129	149	13.2	96	8.5	29	2.6	18	1.6	14	1.2	13	1.2

[1] baseline is defined as the baseline from the controlled trial.

note*: denominators for percentages within a row are the number of subjects with urinalysis results within the dose.

note**: if baseline urine blood and/or urine protein values are unknown, these values are assumed to be 'none'.

NOTE*: 6 OUT OF 14 PATIENTS WITH PROTEINURIA AND HEMATURIA ON THE ROSUVASTATIN 40 MG DOSE HAD MISSING CREATININE DATA. DATA FROM THE NEXT AVAILABLE VISIT WAS USED FOR 5 OF THESE PATIENTS (NO FURTHER CREATININE DATA WAS AVAILABLE FOR ONE PATIENT). HOWEVER, AT THE NEXT AVAILABLE VISIT, ALL FIVE PATIENTS WERE ON THE 80 MG DOSE. THE CREATININE DATA FROM THESE 5 PATIENTS WAS AS FOLLOWS: CR > 30% - ONE PATIENT, CR >20-30% - ONE PATIENT, CR >0-10% - ONE PATIENT, CR < 0% 2 PATIENTS.

note*: 7 out of 96 patients with proteinuria and hematuria on the rosuvastatin 80 mg dose had missing creatinine data.

The sponsor in response to a FDA request generated this table.

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