

Appendix E

E. Selected Narratives for Patients with Serious Hepatic Adverse Events

Phase 3 trials

The Applicant's narratives for the 4 patients experiencing serious hepatic Adverse Events (AEs) in Phase 3 clinical trials of telithromycin are as follows:

Subject 0060/039 from Study 3006 (CAP, telithromycin): A 76-year-old female cigarette smoker with a history of hypercholesterolemia since 1992, hyperuricemia since 1997, s/p amygdalectomy (1928), was enrolled in Study 3006 and started on telithromycin 800 mg po qd on 11 Feb 1999 for treatment of community-acquired pneumonia. Sputum culture at pretherapy/entry yielded group A streptococci. During study she was also maintained on her other chronically used medications, pravachol (pravastatin sodium) 20 mg po qd for hyperlipedemia (since 1997) and allopurinol 200 mg po qd for hyperuricemia (since 1997). On 15 Feb 1999, she returned for Visit 2 and was noted to be clinically improved. Also noted during Visit 2 was asymptomatic elevation of her AST, ALT, and alkaline phosphatase. This led to discontinuation of telithromycin on 16 Feb 1999, and withdrawal from the study on 17 Feb 1999. Therapy was changed to Ceftin (cefuroxime axetil) 500 mg twice daily on 16 Feb 1999. Selected laboratory test results are presented in the following table.

Laboratory analyte	Day 1	Day 5	Day 7	Day 12
	11 Feb 99	15 Feb 99	17 Feb 99	22 Feb 99
AST/SGOT (NR 9-34 U/L)	37	295	66	24
ALT/SGPT (NR 6-32 U/L)	24	418	200	64
Alk phos (NR 35-115 U/L)	79	146	131	–
T. Bilirubin (NR 3-21 mmol/L)	17	22	10	–
Eosinophils (NR < 570 cells/10 ⁻⁶ L)	30	190	110	–
NR= normal range				

Both the investigator and the applicant assessed the "liver injury" (verbatim term) (coded as "liver damage") as possibly related to telithromycin. At the time of the elevated transaminases (15 Feb 1999) the patient reported mild diarrhea and associated abdominal pain. Her event resolved without sequelae.

Subject 0259/005 from Study 3008 (Tonsillopharyngitis, telithromycin): A 19-year-old white male with no significant past medical history experienced liver damage (verbatim term "drug-induced hepatic toxicity") characterized by increased AST (SGOT), ALT (SGPT), and lactate dehydrogenase (LDH) on 10 Apr 1999 after treatment with telithromycin for tonsillitis. The patient was diagnosed with tonsillopharyngitis (with a throat culture subsequently yielding group A β-hemolytic streptococci) and was enrolled in Study 3008. He began his course of telithromycin 800 mg po qd on 29 March 1999. He completed a 10-day course of telithromycin on 7 April 1999. On 10 April 1999, at the End of Therapy visit, subject 0259/005 was noted to have elevations in his transaminases

(AST = 273 U/L and ALT 124 U/L). The subject had no associated signs or symptoms, but stated that he had ingested an excessive amount of alcohol during the previous evening. By 18 April 1999, his AST, ALT and LDH had decreased to near baseline values and by 28 April 1999 had returned to baseline values. Relevant laboratory values for subject 0259/005 are presented in the following table.

Laboratory Analyte	29 Mar 99	1 Apr 99	10 Apr 99	18 Apr 99	28 Apr 99
	Pretherapy /entry	On-therapy	End of therapy	Test of cure	Late post-therapy visit
AST/SGOT (NR=11-36 U/L)	23	ND	273	29	19
ALT/SGPT (NR=6-43 U/L)	27	ND	124	44	28
Alk. Phos. (NR<250 U/L)	93	ND	79	79	79
T. Bilirubin NR= 3-21 μ mol/L	21	ND	14	22	15
SGGT(NR= 10-61 U/L)	31	ND	37	39	35
LDH (NR= 53-234 U/L)	192	ND	592	133	108
Eosinophils (NR < 570 cells/ 10^{-6} L)	180	ND	40	ND	ND
ND = not done, NR = normal range, TOC = posttherapy/test of cure, LPT = late posttherapy					

The investigator considered the observed transaminase elevation as possibly related to study medication but suspected the patient's reported excessive alcohol intake as the most probable cause of the patient's elevated AST, ALT, and LDH. The applicant noted that it is not known if the subject has early alcoholic liver disease or a history of chronic alcohol abuse.

Review of the patient's concomitant medications reveals that the patient took a dose of zinc-echinacea (amount of dose unknown) on 29 March 1999 and 17 April 1999 and a dose of Vitamin C (amount of dose unknown) on 28 March 1999 and 18 April 1999.

Subject 0425/011 from Study 3006 (CAP Clarithromycin): A 61-year-old white male with a history of CHF treated with digoxin, alcoholism (1970 through 5/1999), smoking (1952 until May 1999), melena (5/1999), and s/p amygdectomy (1942) was enrolled in study 3006 and received clarithromycin 500 mg po bid from 05 August 1999 to 14 August 1999 for treatment of CAP. On 17 August 1999 the patient was noted to have an "icteric syndrome" (verbatim term) (coded term jaundice) with choloria (T. Bilirubin 103 μ mol/L (NR 3-21 μ mol/L), alkaline phosphatase (658 U/L) [NR <121 U/L] and GGT (457 U/L) [NR 7-74 U/L]). The subject was withdrawn from the study on 17 Aug 1999 because he "no longer wished to continue". On 19 Aug 1999, a "disseminated neoplasm was found, with associated lung nodule, adrenal nodule, Douglas space nodule." increased The patient's case report forms note that his primary care physician and oncologist performed an abdominal ultrasound and a CT scan of the chest and abdomen.

These studies revealed the anatomic findings described above. The patient's physicians suspected a renal or hepatic source for the subject's apparent malignancy.

Laboratory Analyte	5 Aug 99	9 Aug 99	17 Aug 99
	Pretherapy	On-therapy	End of
	/entry		Therapy
AST/SGOT (NR<45 U/L)	21	14	41
ALT/SGPT (NR<48 U/L)	18	20	40
Alk. Phos. (NR<121 U/L)	89	136	658
T. Bilirubin (NR= 3-21 μ mol/L)	5	5	103
Eosinophils (NR < 560 cells/ 10^{-6} L)	320	0	830
NR = normal range			

The investigator assessed the icteric syndrome and disseminated neoplasm as not related to study medication, but rather attributed the event to "underlying/concomitant illness". The events had not resolved at the time of the report, but further follow-up within the study was not deemed necessary by the investigator. Further care of the patient for his suspected disseminated neoplasm was transferred to his primary care physician and oncologist.

Subject 502/1069 from Study 3000 (CAP telithromycin): A 53-year-old white male with a history of asthma (since 1975) and diabetes mellitus (since 1982) was enrolled in Study 3000 at center 502 in Tampere, Finland on 02 Feb 1999 with community-acquired pneumonia (CAP). He received telithromycin from 3 Feb 1999 through 12 Feb 1999, with a clinical outcome of cure. The investigator noted that the patient was feeling "quite well" after completing therapy for his CAP. Three days after the last dose (15 Feb 1999), he reported exposure to family members suffering from a gastroenteritis-like illness. Jaundice was not noted in the affected family members. Four days after his last dose of telithromycin (16 Feb 1999) he developed an acute illness with symptoms of fever, vomiting, and diarrhea. The vomiting and diarrhea resolved, but at visit 4 (22 Feb 1999) he still complained of fever (temperature 38.1°C tympanic; reportedly the patient had fevers to 39°C). At visit 4 he had an elevated ALT of 354 U/L (local laboratory). Of note is that the patient's ALT at baseline was elevated (81 IU/L [NR 0-49]) when tested at the local laboratory and when tested at the central laboratory (69 IU/L [NR 6-43 IU/L]). On 25 Feb 1999, three days after visit 4, his ALT was 1529 U/L (local laboratory). The subject was hospitalized with a diagnosis of hepatitis. Serologic testing for "Hepatitis A, B, and C was negative." EBV and CMV serologies were positive for IgG consistent with past infection. A percutaneous liver biopsy was performed on 02 March 1999. The pathologic material was reviewed at the Armed Forces Institute of Pathology (AFIP). The AFIP reading for this biopsy was: *Recent zone 3 ("centrilobular") necrosis with numerous tissue eosinophils, strongly suggestive of drug-induced liver disease.* The patient also had an abdominal ultrasound examination with findings consistent with fatty

liver. The subject was discharged from the hospital on 10 March 1999. The table below shows the patient's laboratory values for selected analytes.

Lab						Date												
	2/2	2/5	2/15	2/22	2/25	2/26	2/27	2/28	3/1	3/2	3/3	3/5	3/8	3/10	3/15	3/16	4/9	5/7
Local Laboratory																		
AST (NR<49 U/L)	38	-	-	-	-	170	-	-	-	-	-	-	-	-	-	-	-	-
ALT (NR<49 U/L)	81	-	-	354	1529	947	694	550	454	456	463	519	518	362	130	-	53	53
Alk Phos (NR 60-275 U/L)	-	-	-	-	169	164	194	260	242	259	-	-	261	251	-	-	169	28
T. Bilirubin (NR 2-20 mmol/L)	9	-	-	-	29	31	26	24	18	18	-	-	15	13	-	-	16	16
Central Laboratory																		
AST (NR 11-36 U/L)	36	29	35	167	-	-	-	-	-	-	-	-	193	-	-	-	-	-
ALT (NR 6-43 U/L)	69	69	69	280	-	-	-	-	-	-	-	-	463	-	-	-	-	-
Alk Phos (NR 31-110 U/L)	78	73	74	60	-	-	-	-	-	-	-	-	104	-	-	-	-	-
T. Bilirubin (NR 3-21 mmol/L)	7	6	9	10	-	-	-	-	-	-	-	-	10	-	-	-	-	-
Other Lab Values from the Local Laboratory																		
INR for PT (NR <1.20)	0.97	0.95	0.90	-	-	-	-	-	-	-	-	-	1.04	-	-	-	-	-
Absol. Eosinophils (cells/μL)†	774	-	-	960	1062	-	-	-	-	-	-	1729	2856	-	-	-	-	-
Hemoglobin (NR13.0-18.0 g/dL)	14.4	-	-	14.9	12.5	12.0	11.9	11.2	11.4	11.4	10.6	-	-	-	-	12.9	-	-
ESR (NR 0-20)	87	92	17	-	-	-	-	-	-	-	-	-	69	-	-	-	-	-
C-Reactive Protein (mg/L)	-	-	-	68	170	-	-	-	-	-	-	-	-	-	-	-	-	-
Other Lab Values from the Central Laboratory																		
Albumin (NR 33-49)	31	33	36	36	-	-	-	-	-	-	-	-	31	-	-	-	-	-
Total Protein (NR 61-84)	67	74	71	70	-	-	-	-	-	-	-	-	74	-	-	-	-	-
Absolute Eosinophils (NR 0.00-0.57 GI/L)	-	0.65	0.00	0.78	-	-	-	-	-	-	-	-	2.54	-	-	-	-	-
C-React. Prot. (NR 0-8mg/L)	120	77	5	66	-	-	-	-	-	-	-	-	8	-	-	-	-	-

NR = normal range
Lab values shown in Bold type are outside of the normal range

Central laboratory lab values are derived from the applicant's LAB_MEGA.xpt file for Study 3000. Normal ranges for central laboratory lab values are derived from laboratory reports and summaries whenever available.

*All dates are from the year 1999.

†Normal range for absolute eosinophils is typically considered as < 500 cells/uL

Normal ranges are provided whenever available

The patient's previous and concomitant medications as listed in the case report forms included:

- Fluticasone 2 puffs (1000 µg) inhaled bid for asthma which he had been taking since 1995
- Salbutamol inhaler used prn for asthma since 1979
- Atrovent 1 mL inhaled 5 x a day from 01 March 1999 to 10 March 1999
- Nasonex aerosol 200 µg nasal inhalation "x 1" started on January 1999
- Calcichew one 500 mg tablet "x1" started on 04 March 1999 for hypocalcemia
- Acetaminophen 500 mg tablets orally, frequency unknown started on 15 February 1999 to an unknown subsequent date in February 1999. The investigator notes in the previous and concomitant medication case report forms describe the acetaminophen use as "all together 6 tablets in one week". In the Serious adverse event CRF, the investigator notes "Pat. has also taken paracetamol 6 tbl's for treatment of fever (500mg/tabl.)"

The patient had not taken any herbal products of any kind.

Subject 1069 also had urinalyses performed on 02 February 1999, 05 February 1999, and 15 February 1999; all were negative for proteinuria, glycosuria, blood, and WBCs. There are no results for subsequent urinalyses (from the time period when subject 1069's transaminases were known to be elevated).

Additional diagnostic evaluations included serologic studies that were negative for HIV, *Toxoplasma*, "F-para-O", Tularemia (x2), *Legionella*, *Brucella*, *Mycoplasma*, *Coxiella burnetii*, *Fasciola hepatica*, and *Toxocara canis*. Serologic testing for EBV, CMV, and HSV was "low positive" with a negative IgM class antibody consistent with previous infection. He also had serologic testing for Ebola virus which returned with results of "low-positive", the significance of which is unclear. Stool examination for parasites was negative. The patient also had the following additional results from testing performed on 07 May 1999: CH50=68 U/mL; IgA=3.1g/L, IgG=12.7 g/L, (IgG1=4.53, IgG2=3.93, IgG4=3.34) [laboratory normal ranges not provided, typical normal ranges; CH50 (63-145 U/mL); IgA (0.5-3.5 g/L); IgG (5.0-12.0 g/L)].

Additional information from the patient's medical history revealed that prior determinations of ALT had shown "ALT was slightly increased up to 58 U/L in September 98 and to 51 U/L in October 98" [normal ranges not provided]. Prior to the episode of February 1999 described above, there was no known prior history of liver or autoimmune disease. The patient had no prior history of a liver biopsy or other diagnostic testing prior to the biopsy of 02 March 1999 and tests described above.

Additional history obtained from the patient related that he had previously been treated with macrolides: in August of 1998 he was treated with roxithromycin for 10 days. The patient was treated with azithromycin for "respiratory signs and sinusitis" on 13 October 1998 and 22 December 1998 (dosage and duration unknown). ALT was not measured during these courses of macrolide therapy.

The patient underwent a routine check-up on 12 November 1999 and was found to have an ALT=1331 U/L, T.Bili=25 umol/L (NR <20 umol/L). Eosinophilia was not present. Serologic tests for hepatitis A antibodies, HbsAg, HBc antibodies, and HCV antibodies, were negative. EBV and CMV serology results were consistent with old inactive infection. Antinuclear and anti-mitochondrial antibodies were negative. A serology for anti-smooth muscle antibodies yielded a titer of 1:1000. Serum immunoglobulin levels were IgG=18.1 g/L, IgA=5.48 g/L, IgM=2.07 g/L, IgE=471 kU/L [normal range not provided, typical normal ranges for IgA and IgG as noted, for IgM (0.3-2.3 g/L); IgE (0-380 kU/L)]. An ultrasound examination of the liver was reported as normal. The only medication that the patient reported taking was acetaminophen for headache. A percutaneous liver biopsy was performed on 27 December 1999. The liver biopsy material was reviewed at the Armed Forces Institute of Pathology. The AFIP reading on the liver biopsy was: *chronic hepatitis, probably autoimmune, with marked activity and extensive bridging fibrosis*. His ALT reportedly normalized rapidly and was 43 U/L on 03 February 2000.

On 19 July 2000, the patient reportedly had normal LFTs, a negative ANA, and negative serologic tests for anti-smooth muscle, anti-microsomal, and anti-thyroglobulin antibodies. At a subsequent follow-up visit on December 14, 2000, follow-up information notes that the patient's "LFTs normalized."

Study 3014 - Narratives for patients with HAESIs undergoing liver biopsy but not assessed as having a drug-related event

The Applicant's narratives for the two patients experiencing a hepatic adverse event of special interest (HAESIs) in Phase 3 clinical trials of telithromycin, and who underwent a liver biopsy but were not assessed as having a drug-related event are as follows:

Telithromycin

Patient #2250 001, a 51-year-old female with a history of surgery for uterine cancer, chronic right lower quadrant pain, elevated liver enzymes, and surgery for renal stones, was randomized to treatment with telithromycin 800 mg for 5 days for acute sinusitis. Concomitant medications included diovan HCT, estradiol, and Zyrtec. Baseline liver function tests were abnormal as noted below. Visit 2 labs (study day 15) continued to be abnormal as shown in the table below. Hepatitis A, B, and C serologies were negative. The patient underwent colonoscopy on study day 31 for abdominal pain, revealing two small hyperplastic polyps with focal adenomatous features in the ascending colon and Grade II hemorrhoidal disease. A CT scan of the abdomen was performed for persistent abdominal pain; on CT scanning the liver was diffusely hypodense, consistent with fatty infiltration. Laparoscopy with needle liver biopsy was performed on study day 40 and grossly revealed fatty infiltration of the liver, with no pathology available.

Analyte	Analyte value/flag			
	Normal range	Baseline	Day 16	Day 36*
ALT (U/L)	6 - 34	160 H	144 H	150 H
AST (U/L)	9 - 34	219 H	165 H	168 H

Alk phos (U/L)	35 – 123	142 H	164 H	155 H
Total bili (µmol/L)		10.0 ULN 20.8*	5.0 ULN 20.8*	10.26 ULN 18.7*
Direct bili (µmol/L)			2.0 ULN 6.9*	
* Reference values not provided. Value extrapolated from ratio of patient value to reference value.				

CEC Adjudication Summary: Not drug related (Adjudication Form Comments: Abnormalities in biochemical tests at baseline and remained rather stabilized elevated throughout. Had history of elevated enzymes.)

FDA assessment: Agreed with CEC assessment

Amoxicillin/clavulanate

Patient #0627 014, a 48 year-old male with a medical history of “other” cardiovascular disease was randomized to treatment with amoxicillin/clavulanate 875 mg BID for 7-10 days for CAP. Concomitant medications included Toprol XL, Zestoretic, Nasonex, and guaifenesin with dextromethorphan. He completed 10 days of treatment and was noted to have abnormal baseline transaminases, with ALT 216 U/L, AST 142 U/L, and normal ALK 96 U/L and Tbili 9 µmol/L. Subsequent hepatitis serology showed positive hepatitis C antibody. Transaminase levels continued to decrease over the period of observation, with late post-therapy (visit 3) values of ALT 130 U/L and AST 107 U/L. The patient was evaluated by a gastroenterologist and had a liver biopsy approximately two months after study entry that showed moderate chronic active hepatitis with bridging fibrosis.

CEC Adjudication Summary: Unrelated: Definite hepatitis C (Adjudication Form Comments: Abnormal baseline. ALT 216, AST 142. Hepatitis C positive. Aminotransferases gradually improved. Liver biopsy - chronic hepatitis.)

FDA assessment: Agreed with CEC assessment.