noted with >25 PMN, no epithelial cells and Gram-positive diplococci and cocci. The sputum culture grew 3+ *S. pneumoniae* resistant to erythromycin. There was no growth on the blood culture. At the on-therapy visit on 9/13/01, moderate chest pain and cough were noted. Mild chills, dyspnea, and sputum production (mucopurulent) were also present. The patient was afebrile and his respiratory rate was 20/min. Mild rales, rhonchi, and dullness to percussion were recorded on the PE. The patient was categorized as improved. He completed 7 days of telithromycin. An EOT visit occurred on 9/19/01. Mild chest pain, cough, dyspnea, and sputum production (mucoid) were present. The patient was afebrile and his respiratory rate was 18/min. Mild rales were noted on PE. The patient was unable to produce an adequate sputum sample for culture. The patient was considered improved. The patient withdrew from the study on 9/21/01 for personal reasons. However, an SAE form indicates that deterioration of his pneumonia started on — The form noted pyrexia, chest pain, and cough. The patient died on — with pneumonia as the cause of death. The CRF also listed "immunocompromised" as a cause of death, although no other information on an immunocompromised state is provided in the CRF.

(M.O. Comment: The patient should be categorized as a non-evaluable failure. It is clear that the patient completed telithromycin treatment, but had a recurrence of his infection within a week after treatment. Withdrawal from the study for personal reasons is a reason to consider the patient non-evaluable, though the patient completed the study procedures through the EOT visit. Unfortunately, there is limited information about the events surrounding the pneumonia recurrence and death.)

3012/4016/101

— is an 80 y/o female past-smoker, enrolled on 01/10/02. Her medical history includes asthma, COPD and hypertension. Baseline symptoms included moderate cough and dyspnea. Mild chills, chest pain, tachypnea, and sputum production (mucopurulent) were also noted. Her vital signs included an oral temperature of 37.4 °C, and a respiratory rate of 24/min. On PE, moderate rales and rhonchi were present. Mild dullness to percussion, wheezing, and egophony were also noted. CXR noted the presence of "COPD with diffuse bronchitis and bilateral basal bronchopneumonia". The infection was categorized as moderate. Sputum Gram stain was noted with 10-24 PMN, 10-24 epithelial cells, Gram-positive cocci, Gram-negative cocci, and Gram-negative bacilli. The sputum culture grew 1+ *H. parainfluenzae* (categorized as colonization) and "+ – " *S. pneumoniae* (categorized as responsible for infection) resistant to erythromycin and penicillin. The blood culture showed no growth. The patient had improved at the on-therapy visit on 1/14/02. Mild chest pain, cough and moderate sputum production (mucopurulent) were noted. Mild rales and rhonchi were the remaining signs on PE. Repeat sputum culture showed "+ –" *H. parainfluenzae* and alpha-hemolytic *Streptococci.* The patient completed 7 days of telithromycin. At the EOT visit on 1/17/02, the patient had mild cough and mild sputum production (mucoid). Mild rhonchi and wheezes were noted on PE. At the TOC visit on 1/29/02, mild cough and moderate sputum production (mucopurulent) were noted. Mild rhonchi and wheezes were present on PE. The CXR showed clearing of the bronchopneumonia. Sputum Gram stain at this

visit showed >25 PMN, <10 epithelial cells, and Gram-positive cocci. The sputum culture grew 1+ *H. influenzae* (categorized as colonization) and 3+ *S. pneumoniae* resistant to erythromycin and penicillin. An AE form indicates that bronchitis started on — The patient was started on ciprobay. The completion of study form indicated that the patient was asked to return after the sputum culture results were reported and was started on antibiotics. The investigator initially categorized the patient as cure with post-infectious stigmata, but later changed to failure (new antibiotic required in the following indirect situation associated with insufficient improvement: adverse event of bronchitis).

(M. O. Comment: The patient was treated for pneumonia and improved, but was started on antibiotics for persistent symptoms of infection at the TOC and sputum culture results. Improvement of radiographic findings of pneumonia was noted, and the patient was categorized as having bronchitis. This was the likely reason for the patient being listed as non-evaluable.)

Appendix D: Comparator Narratives – Drug Resistant S. pneumoniae

Amoxicillin Patient

Study 3001
3001/1004/011
This is a 55 y/o female with *S. pneumoniae* resistant to erythromycin but susceptible to penicillin (MIC = 0.03 μg/mL) and *Haemophilus influenzae* isolated from sputum. Her infection was considered mild. She met inclusion and exclusion criteria for pneumonia and was successfully treated with amoxicillin. She was considered evaluable and cured at the TOC visit.

Clarithromycin Patients

Study 3006
3006/0008/032
This is a 43 y/o male with *S. pneumoniae* resistant to PCN but susceptible to erythromycin (MIC = 0.06 μg/mL) isolated from sputum. He met inclusion and exclusion criteria for pneumonia and was successfully treated with clarithromycin. He was considered evaluable and cured at the TOC visit.

3006/0013/001
— is a 77 y/o male smoker enrolled on 5/14/98. His past history includes diabetes and treatment for neoplastic disease in the past. Baseline symptoms included severe cough moderate chills and sputum production (purulent). His vital signs included an oral temperature of 101.7 °F and a respiratory rate of 18/min. Moderate rhonchi, dullness to percussion and bronchial breath sounds were noted on PE. CXR showed a left lower lobe infiltrate and atelectasis of the right lower lobe. The infection was categorized as moderate. Sputum Gram stain included 10-24 PMN and <10 epithelial cells with Gram-positive diplococci and cocci and mixed flora. The sputum culture grew 3+ *S. pneumoniae* resistant to erythromycin (MIC = 1 μg/mL). At the on-therapy visit on 5/18/98, the patient was afebrile with moderate cough and mild sputum production. Moderate rhonchi and mild bronchial breath sounds were noted on exam. The patient was considered improved at this visit. The sputum culture grew normal flora. He completed 10 days of study drug on 5/23/98. The EOT visit occurred on 5/26/98. Mild cough and sputum production remained. All signs of infection had resolved on PE, and the patient was considered improved. At the TOC visit on 6/2/98, Mild cough was noted and mild bronchial breath sounds were noted on PE. CXR was considered improved with resolving infiltrate of the left lower lobe. The patient was categorized as cured (Improved or post-infectious stigmata). However, a late post-therapy visit was carried out in this patient on — because of recurrent symptoms. Moderate cough and mild chills were reported, though the patient was afebrile. Signs of infection were absent on PE. CXR showed the presence of a new infiltrate in the right lower lobe. There was no indication that other antimicrobial treatment was given.

(M. O. Comment: The patient met the criteria for cure at the TOC visit, although the recurrence of symptoms and new infiltrate of the opposite lung on CXR indicate failure of treatment.)

3006/0032/014

— is a 61 y/o male smoker enrolled on 04/19/99. Mild cough, chills and dyspnea were reported. Baseline symptoms also included moderate tachypnea and severe sputum production (purulent). His vital signs included an oral temperature of 99.9 °F and a respiratory rate of 24/min. Moderate rhonchi and mild rales, dullness, bronchial breath sounds and egophony were noted on PE. The CXR indicated findings of COPD with "accentuation of the bronchial markings in the posterior basal segments of both lower lobes". The infection was categorized as moderate. Sputum Gram stain included >25 PMN and Gram-positive diplococci without epithelial cells. *S. pneumoniae* resistant to penicillin and erythromycin (MIC = 2 µg/mL) was isolated by sputum culture. There was no growth on blood cultures. At the on-therapy visit on 4/21/99, moderate cough and mild dyspnea remained as symptoms. His respiratory rate was 16/min. Mild rhonchi and wheezes were present on PE. The patient was considered improved. The patient completed 10 days of clarithromycin on 4/29/99. The EOT/TOC visit occurred on 5/4/99. All baseline signs and symptoms of infection had resolved. CXR showed no acute disease. The patient was considered cured (return to pre-infection state). The patient did not return for a later follow-up visit.
(M. O. Comment: The patient missed the EOT visit and the information recorded in the TOC visit and EOT visit pages was the same. This patient was likely considered non-evaluable due to the timing of this TOC visit (6 days after stopping drug) and missing the EOT visit. However, given complete resolution on day 6 post-treatment, categorization as a non-evaluable cure was reasonable.)

3006/0037/014

— is a 41 y/o male smoker enrolled on 7/14/99. Baseline symptoms included severe cough, and mild dyspnea. Moderate chest pain, chills, and mucopurulent sputum production were also reported. His vital signs included an oral temperature of 99.2 °F and a respiratory rate of 18/min. Moderate rales and rhonchi were noted on PE. CXR showed an infiltrate of the right upper lobe. The infection was categorized as moderate. Sputum Gram stain showed >25 PMN and <10 epithelial cells with Gram-positive cocci and Gram-negative bacilli. The sputum culture showed 3+ S. pneumoniae resistant to erythromycin (MIC = 512 µg/mL). At the on-therapy visit on 7/16/99, mild cough and sputum production (mucopurulent) were noted. His respiratory rate was 20/min and baseline PE findings were absent. He was considered improved. The patient completed 10 days of clarithromycin on 7/23/99. At the EOT visit on 7/26/99, only mild cough remained. At the TOC visit on 7/30/99, mild cough was still present. All other signs and symptoms were resolved. CXR was reported with "90% improvement in previously noted right upper lobe pneumonia". The patient was considered cured (return to pre-infection state). Telephone contact on 8/13/99 indicated no recurrence.

Study 4003
4003/3212/003
This is a 51 y/o female enrolled on 4/18/2000. The patient met all inclusion and exclusion criteria. CXR showed right middle and lower lobe pneumonia. She was categorized as having a moderate infection. The patient's blood culture grew S. pneumoniae resistant to erythromycin (MIC = 512 µg/mL). Sputum culture results included *S. pneumoniae*, *Haemophilus parainfluenzae*, and *Moraxella catarrhalis*. The patient on-therapy visit occurred on 4/23/2000. She stopped study drug treatment on that day for worsening pneumonia and septic arthritis. She was started on gentamicin and ceftazidime. The patient profile indicates that a repeat blood culture was not done. However, ERSP were isolated from the joint fluid withdrawn from the left knee. ERSP were also isolated from repeat sputum cultures. The patient was considered an evaluable treatment failure.

4003/3307/001
This is a 62 y/o female enrolled on 7/10/2000. The patient met all inclusion and exclusion criteria. Baseline symptoms included moderate cough and sputum production (mucopurulent). Mild tachypnea and severe dyspnea were also noted. She was reportedly afebrile. Moderate rhonchi and wheezing were noted on PE. CXR showed bilateral lower lobe infiltrates. Sputum Gram stain showed >25 PMN and <10 epithelial cells with Gram-positive diplococci and other Gram-positive bacteria. *S. pneumoniae* resistant to erythromycin (MIC = 512 µg/mL) was isolated by sputum culture. Blood culture showed no growth. She completed 10 days of clarithromycin treatment. At the TOC visit on 7/31/2000, all baseline signs and symptoms had resolved. Repeat CXR at the TOC visit showed marked improvement with residual peribronchial infiltration. The patient was considered cured (return to pre-infection state).

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/s/

John Alexander
3/31/04 10:46:38 AM
MEDICAL OFFICER

Janice Soreth
3/31/04 04:15:27 PM
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Medical Officer's Review of NDA 21-144
Ophthalmology Consultation

NDA 21-144		**Submission date:**	7/24/02
Ophthalmology Consult		**Review date:**	1/15/03

Sponsor	Adventis Pharmaceuticals
Drug Product:	Ketek (telithromycin)
Pharmacologic Category:	ketolide anti-infective
Proposed Indication:	Community-acquired pneumonia (CAP), Acute exacerbation of chronic bronchitis (AECB) and Acute sinusitis (AS)

Background:

During development of Ketek, ocular adverse events, most notably blurred vision was reported in a higher portion of patient treated with Ketek than controls.

Reviewed: Electronic Submission
Clinical Studies with emphasis on Study 1059 and Study 1064
Proposed package insert labeling
Integrated Summary of Safety

Executive Summary

I. Recommendations

A. Recommendation on Approvability

From an ophthalmologic prospective, the current proposed labeling does not provide sufficient warnings of the potential to impair vision. There is no objection to the approval of this NDA provided that the labeling is revised to include sufficient warning concerning the potential to impair vision. Specific changes to the proposed labeling have been identified in this review.

B. Recommendation on Phase 4 Studies and Risk Management Steps

It is recommended that additional studies are conducted to evaluate the effect on vision using doses between 800mg and 2400mg (i.e., 800, 1200, 1600, 2000 and 2400mg). The purpose of these studies would be to better quantitate the timing of the blurred vision events and in particular the effects on accommodation.

II. Summary of Clinical Findings

A. Brief Overview of Clinical Program

Two clinical studies evaluating vision were performed with telithromycin. Each study demonstrated an effect of telithromycin on vision.

Protocol 1059 & 1064

Ocular adverse events from all studies were reviewed.

B. Efficacy

Not evaluated in this review.

C. Safety

Ocular events, predominately blurred vision has been identified as a safety issue with the use of telithromycin. The blurred vision appears to occur in approximately 1% of patients taking 800mg and approximately 50% of patients taking 2400mg. The principal cause of the blurred vision has not been identified, but appears to be related to the ability to accommodate/release accommodation and its related effects on ocular motility. Based on the evidence to date, the effects appear to be temporary lasting from 30 minutes to 20 hours after each dose. More women than men reported blurred vision, however, in the controlled trials evaluating vision, there were more women enrolled than men.

Vision Studies

Title: Mechanism of blurred vision induced by HMR 3647 at single supraclinical doses (2400 mg) versus therapeutic single dose (800 mg) in a younger and older population. -1059

Investigator:
Study Centre:

Dates of Study: March 2-July 25, 2001

Design

This single center study was as follows for both groups: placebo-controlled, randomized, single dose, double blind, 3-way crossover design.

Population

Group I : 15 young healthy subjects male and female 18-40 years old

Group II : 15 older subjects male and female 50- <65 years old (subjects with presbyopia) The female/male ratio in each group was to be approximately equivalent.

Summary of subjects demographics

Parameter		Group I* N=15	Group II** N=15
Sex			
	male	7	6
	female	8	9
Age (years)			
Mean		26.3	55.8
SD		5.4	4.8
Range		18.0 - 37.0	49.0 – 63.0
BMI (kg/m^2)			
Mean		22.7	25.5
SD		3.7	2.4
Range		18.1 – 32.3	21.6 – 30.0

* 18-40 years old; ** 50-<65 years old

Treatments

- 800 mg of HMR 3647 (2 x 400 mg HMR 3647 tablets and 4 matching placebo tablets)
- 2400 mg of HMR 3647 (6 x 400 mg HMR 3647 tablets)
- Placebo : 6 matching placebo tablets Route

Eye examination

At 0 (baseline) and 1, 2, 3, 4, 6, 8, 24 hours after administration:

- Far and near visual acuity (each eye separately) measured with an EDTRS chart (results in LogMAR)
- Accommodation [with measurement of near point in meter and amplitude of accommodation as the inverse of near point distance, given in Diopters)] by means of a Clark rule
- Pupil diameter in mm
- Refraction [sphere (D), cylinder (D), axis (degrees) and spherical equivalent (D)]

- Clinical Eye evaluation: visual symptoms and local signs (pain, discomfort, foreign body sensation, photophobia, blurred vision, stinging, burning, tearing) At screening and between 4 and 8 h after administration
- Visual field with Amsler's grid rated as Normal/Abnormal
- Color Vision (test [illegible], rated as Normal/Abnormal
- Slit lamp examination (lids, cornea, lens iris, fundus scored as Normal/Abnormal)
- Intraocular pressure (mm Hg)

Results - Study subjects and conduct

In group I, 15 subjects, 7 male and 8 female (mean age 26 ± 5) were enrolled. In group II, 15 subjects, 6 males and 9 females (mean age 56 ± 5) were enrolled. All subjects received the 3 treatments and completed the study.

Subjects with blurred vision during the study

Sub #	Age/sex	Dose (mg)	Time post dose	Duration	Intensity	Description/symptoms	Eye exam	Other AE
2	18/F	2400	4 h	2 h	mild	blurred vision / far vision	No change	None
6	21/F	2400	6 h	1 h	mild	blurred vision / instability of far vision in both eyes	No change	Nausea
9	25/F	2400	3 h	1 h	mild	blurred vision / difficulty focusing eyes, short latent period is needed to focus for the far vision	No change	Nausea
5011	25/M	2400	3 h	30 min	mild	Blurred vision / short latent period to focus for the near and far vision	No change	Nausea Diarrhea

Sponsor's Conclusions

No blurred vision occurred with telithromycin 800 mg in this study.

At three times the therapeutic dose (2400 mg) blurred vision was only observed in 4 young subjects. This was described as a difficulty to focus at far distance, which means that it took them a longer time than usual to focus (approximately 2 to 5 seconds) and the effect was present for between 30 minutes and 2 hours. Blurred vision was not associated with alteration of visual parameters such as visual acuity, refraction, accommodation, intraocular pressure, pupil diameter, color vision or visual field (Amsler's grid). None of the older subject (50 to less than 65 years old) experienced a blurred vision and all parameters were normal throughout the study. These data support the absence of risk in angle closure glaucoma and retinal toxicity. Blurred vision was thus a transient, short duration, reversible effect.

This effect occurred at respective peak plasma and tear concentration for the subjects concerned, however no definitive conclusions can be drawn regarding a relation with the concentration. Telithromycin at doses of 800 mg and 2400 mg was otherwise safe and well tolerated with the most frequently observed TEAE were nausea and diarrhea.

Reviewer Comments: *There were no consistent measurable changes in visual function.*

Title
Assessment of ophthalmological safety of telithromycin at supraclinical single dose (2400 mg) in healthy subjects. -1064

Investigators, study site

Study duration and dates
First subject in: 15 January 2002 Last subject out: 5 April 2002

Design
Single-center, double-blind, randomized, placebo controlled, 2-way crossover, single-dose study with a 7-day-washout period.

Population
24 subjects (male and female) ≥18 years with at least 35% of subjects ≥50 but <65 years old.

Doses: - 2400 mg telithromycin (6x400 mg tablets) as a single dose
- placebo: 6 matching placebo tablets as a single dose

Reviewer's Comments: *The study did not enroll at least 35% of the subjects in the 50-65 year old age group as planned. Six patients instead of at least 9 were enrolled. No explanation is provided.*

Eye examination
At screening:
- Uncorrected and corrected visual acuity, fixation disparity test, refraction, intraocular pressure, color vision, slit lamp test with pupil dilation including a fundus photograph

Before dosing (Baseline), 3 hours and 7 days after last drug intake:
- Corrected far and near visual acuity (each eye separately)
- Contrast sensitivity function (each eye separately)
- Refraction (Sphere, Cylinder, Axis, spherical equivalent)
- Continuous recording of accommodation and pupil size using a autorefractor
- Slit lamp test: Lids, iris, cornea, lens, anterior chamber angle and fundus observation
- Color Vision : Test
- Visual field (threshold automated testing using a analyzer)
- Tear film stability using a tearscope
- Intraocular pressure by non contact tonometry

At the end of the study a fundus photograph was taken for each subject.

Results - Study subjects and conduct

Twenty-four healthy subjects from 19 to 64 years of age were randomized and treated in both treatment periods. The demographic details of this population at baseline are given in the following table.

Baseline characteristics (randomized and treated population)

Variable	Statistic	18-49 years	≥50 years
Subjects randomized and treated	N (%)	18 (100.0)	6 (100.0)
Male	N (%)	9 (50.0)	2 (33.3)
Female	N (%)	9 (50.0)	4 (66.7)
Age (years)	Mean ± SD	32.2 ± 8.6	55.8 ± 5.0
Weight (kg)	Mean ± SD	72.6 ± 13.7	82.0 ± 15.8
Height (cm)	Mean ± SD	170.3 ± 8.6	176.0 ± 8.4

Subjects with blurred vision during the study

Subj. No.	Age/Sex	Period	Treatment	Time after dosing	Duration	Intensity[a]
1	55/M	I	TEL	1h10	2h50	Moderate
2	20/F	I	TEL	3h20	18h29	Moderate
5	21/M	II	TEL	1h18	4h27	Mild
6	19/M	I	TEL	5h	0h53	Mild
10	30/F	I	Placebo	3h	18h55	Mild
10	30/F	II	TEL	2h50	3h15	Moderate
13	34/M	II	TEL	3h06	1h14	Mild
15	40/F	I	TEL	3h07	2h43	Mild
17	54/F	I	TEL	3h05	2h25	Mild
18	22/M	I	TEL	1h25	20h20	Mild
21	47/F	I	TEL	2h	5h30	Moderate
23	27/F	II	TEL	2h55	3h55	Mild
24	41/F	II	TEL	2h35	2h40	Mild

[a] As reported by the ophthalmologist in the clinical eye evaluation

Eye examination

There was no modification of the visual acuity except in subject 2, where near visual acuity was impaired during the episode of blurred vision (0.90 vs 0.00 logMAR at day –1 and other measurements) and which was described by the investigator as a difficulty to maintain focus on the chart.

There was no modification of the contrast sensitivity function.

Amplitude of accommodation was normal except in 2 subjects:

- Subject 2 during the episode of blurred vision, where the accommodation decreased from 10/10 D to 6/4 D in the right and left eye, respectively. This observation correlates with a decrease in near acuity for this subject and with the subject's difficulty to maintain focus at near distance.
- Subject 18 during the episode of blurred vision, where the accommodation decreased from 9.25/9.0 D to 6.25/6.0 D with respect to the right and left eye, respectively, but there was no modification in near visual acuity. However, this decrease could be correlated with the slight increase in reaction time to accommodate from far to near distance (2.01sec vs 1.28 sec at baseline) using the — autorefractor.

Refraction parameters were not clinically changed, and variation was similar, between placebo and telithromycin

No changes in visual field were observed. The maximum change was –1.86 dB (subject 2) for mean deviation and –0.42 dB (subject 6) for pattern standard deviation, neither of which represents a clinically relevant variation. (A decrease of at least 5 dB would be clinically relevant [18]).

There was no change in color vision, where the maximum change was 4 (score of sum of errors).

The intraocular pressure was not modified in the subjects with blurred vision (changes between –1.3 and 2.3 mmHg for left eye and –0.7 and 1.4 mmHg for right eye).

No change was seen in the anterior chamber angle, with values ranging between 3 and 4 for all subjects.

The slit lamp examination was normal except for subject 5, who showed a corneal epithelium disorder possibly due to rubbing his eye; this observation was reported as a possibly related TEAE.

Tear film was normal except in 3 subjects (Nos. 2, 17, 21) whose tear film was unstable, with a breakup time below 20 seconds. All these observations were reported as TEAEs and coded as "dry eye".

The fundus photographs did not show any changes.

Continuous recording of accommodation: Individual data for reaction and response times from the continuous recording of accommodation using the — . autorefractor are available in, and a complete analysis is available in. If subjects had at least one time ≥60 sec at baseline (unable to accommodate), they were excluded from the analysis because the test was not appropriate. Intrasubject variability was calculated from the 2 baselines (day-1 of each period). A change of twice the intrasubject standard deviation, as compared with the baseline, was considered as significant.

For near to far accommodation, at baseline the mean ± SD reaction time was 0.58 ± 0.13 sec and the mean ± SD response time was 1.82 ± 0.55 sec. For far to near accommodation at baseline, the mean ± SD reaction time was 0.74 ± 0.21 sec and the mean ± SD response time was 2.5 ± 1.27 sec.

Near-to-far reaction and response times:

- The near-to-far reaction and response times were not modified in 4 subjects (Nos. 5, 6, 18, 23).
- The near-to-far reaction and response times were increased in 4 subjects (Nos. 1, 2, 10, 15). Subjects 2 and 15 had the largest increases, with an inability to adapt to far vision (>60 sec). The other two subjects were able to adapt to far vision.
- Four subjects were unable to perform the near-to-far testing (baseline times >60 sec) due to their age (Nos. 13, 17, 21, 24).

Far-to-near reaction and response times:

- The far-to-near reaction and response times were not modified in 5 subjects (Nos. 1, 2, 5, 6, 23).
- The far-to-near reaction times were increased in 2 subjects (10 and 18), but their response times were normal.
- Five subjects were unable to perform the far-to-near testing (baseline times >60 sec) due to their age (No. 13, 15, 17, 21, 24).

The accommodation range (refraction for far distance minus refraction for near distance at steady state), as measured on the — autorefractor, was reduced in subject 2, confirming the difficulty in adapting between near and far distance, and increased in 2 older subjects (Nos. 21 and 24), suggesting an improvement in accommodation.

Pupil diameter for far or near vision was not modified during the dynamic accommodation testing.

Accommodation reaction time (s) and response time (s)					
Near to far					
		Reaction time (s)		Response time (s)	
		Placebo	Telithromycin	Placebo	Telithromycin
Day/time	Statistics		(2400 mg)		(2400 mg)
Day -1	N	24	24	24	24
Mean (SD)		20.40 (28.61)	20.36 (28.63)	21.25 (28.00)	21.13 (28.08)
Median		0.76	0.64	2.28	2.00
Range		0.30 - 60.00	0.27 - 60.00	0.67 - 60.00	0.60 - 60.00
Day 1	N	23	24	23	24
Mean (SD)		**18.65** (27.96)	**30.36** (30.29)	**21.91** (28.45)	**30.91** (29.72)
Median		**0.64**	**31.43**	**2.18**	**31.71**
Range		0.31 - 60.00	0.18 - 60.00	0.58 - 60.00	0.91 - 60.00
Day 7	N	12	12	12	12
Mean (SD)		25.42 (30.53)	25.30 (30.63)	26.22 (29.83)	25.89 (30.11)
Median		1.18	0.70	3.57	1.84
Range		0.27 - 60.00	0.33 - 60.00	0.63 - 60.00	1.33 - 60.00
Far to near					
Day -1	N	24	24	24	24
Mean (SD)		20.51 (28.52)	22.95 (29.32)	21.61 (27.88)	24.06 (28.52)
Median		0.87	0.84	1.86	3.03
Range		0.45 - 60.00	0.43 - 60.00	0.95 - 60.00	0.69 - 60.00
Day 1	N	23	24	23	24
Mean (SD)		**21.38** (28.83)	**27.92** (30.14)	**25.04** (28.77)	**28.38** (29.71)
Median		**0.85**	**1.54**	**2.34**	**2.88**
Range		0.63 - 60.00	0.50 - 60.00	1.21 - 60.00	1.00 - 60.00
Day 7	N	12	12	12	12
Mean (SD)		30.39 (30.92)	25.39 (30.55)	30.75 (30.55)	25.84 (30.16)
Median		30.51	0.84	31.23	1.95
Range		0.57 - 60.00	0.53 - 60.00	1.24 - 60.00	1.04 - 60.00

Dynamic accommodation - Accommodation range (D)			
Day -1	N	24	24
Mean (SD)		1.21 (0.96)	1.39 (1.09)
Median		1.34	1.87
Range		0.00 - 2.59	-0.55 - 2.91
Day 1	N	23	24
Mean (SD)		1.43 (0.95)	1.32 (0.94)
Median		1.72	1.69
Range		-0.05 - 2.43	-0.42 - 2.52
Day 7	N	12	12
Mean (SD)		0.91 (1.12)	1.69 (0.89)
Median		0.16	2.01
Range		-0.10 - 2.38	0.01 - 2.72

Reviewer Comment: *There is an increase in the time necessary for accommodation and for the release of accommodation.*

Investigator Comments for Individual Subjects

Subject 1 54 YO Male
The subject complained of blurred vision more in left eye, with no significant change in contrast sensitivity function. At 9:40 am the subject reported left eye contrast poorer than right eye for distance. Distance and near corrected vision were normal. Accommodation was equal in each eye, with no red eye, no relative afferent pupil defect, and normal corneal reflexes. During the test session the subject showed an increase in both reaction time and response time but only in the condition near to far. There was no change in NITBUT but the accommodation range was increased.

Subject 2 20 YO Female
The subject complained of blurred near vision at assessment and during color vision. She had great difficulty in accommodating during the [redacted] test. The amplitude of accommodation was reduced whilst changing from test on the right eye to the left eye. The right eye was also found to be reduced upon re-testing to confirm the initial measure. There was an initial reduction from 11 D to 7 D with the right eye, and from 11 D to 4.5 D with the left eye. The right eye was then shown to have reduced further to 4.5 D. Near vision reduced in the right eye and left eye from 0.00 to 0.9. The subject showed an increase in both reaction time and response time for the near to far condition. The increase was so great because the subject was unable to perform the task. The amplitude of accommodation was reduced objectively as well as subjectively. The NITBUT time was also reduced. During near visual acuity testing, the subject found the test very difficult to carry out and found it very difficult to focus on a stimulus. Actually she lost ability to focus at near distance due to a failure in accommodation. Dizziness and nausea could have influenced the performance.

Subject 5 21 YO Male
The subject complained of slowness in focussing. There was no change in reaction time or response time, nor in amplitude of accommodation. There was no reduction in NITBUT, but the subject had a slight corneal disturbance in the right eye alone, possibly due to rubbing the eye.

Subject 6 19 YO Male
The blurred vision occurred 5 hours post dose, i.e. 2 hours post examination. The subject complained of "ghosting" (horizontal diplopia). Retest showed that there was a slight reduced contrast sensitivity function in the left eye (1.50). Patient reported monocular vision sharper than binocular. Amplitude of accommodation was 9D (right eye) and 8.50 D (left eye). Cover test showed approximately 6 prism diopters latent exophoria with good recovery. (See File note in the CRF). Pupillary responses were normal. There was no change at the time of testing (2 hours post drug) in any parameter.

Subject 10 30 YO Female
The subject complained of blurred vision, a delay in focussing at distance, a feeling of dizziness and lack of coordination. In period II, the near to far response time was increased. The high value (2.8 seconds) recorded at period I day –1, and the subsequent lower values at the next 2 measurements are considered to be the result of practice effects. There was also a reduction in objective accommodation range.

Subject 13 33 YO Male
The blurred vision concerned the distant vision and the subject rated this as mild. The subject was unable to carry out both near to far and far to near accommodation changes. Unfortunately this result is confounded by the fact that during period II day –1, he was also unable to carry out the test. No other changes were seen. Despite his young age (33), he had a low accommodation range (early presbyopia or lack of effort?). He refused a fundus photograph (absence of motivation).

Subject 15 40 YO Female
Near to far reaction time was increased and NITBUT was reduced. There were no other changes in any parameter. Unfortunately, on the last day of testing (PII day 7) the subject was unable to carry out the test entirely.

Subject 17 54 YO Female
Blurred vision at distance. This elderly subject was unable to carry out the [redacted] test due to inadequate ability to accommodate at any time during the study. At the time of blurred vision, NITBUT was reduced, but there were no other significant changes. On period II day 1 there was an abnormality on slit lamp examination consisting of minor superficial corneal disturbance, probably lens related (not clinically significant).

Subject 18 22 YO Male
The blurred vision was described as hard to focus. There was stinging and discomfort on [redacted] 2002, which only concerned the left eye and started at approximately 12:00. At the time of blurred vision there was an increase in near to far response time but no other changes on any parameter.

Subject 21 47 YO Female
Blurred vision at distance cannot focus. The subject was unable to carry out the [redacted] test due to inadequate accommodation range. NITBUT was reduced at the time of blurred vision but there was no change in any other parameter. Additionally, accommodation range increased.

Subject 23 27 YO Female
During the blurred vision, the subject was unable to focus. It took time to focus near to far or far to near and both eyes were affected. There were no changes in any parameter of any test.

Subject 24 41 YO Female
Difficulty in focussing; the subject's head and eyes did not appear to act together (subjective). Near things appeared to move (both eyes). There was no change in any parameter but the subject was unable to carry out the [redacted] test.

Reviewer's Comments: *Overall, there were a significant number of subjects with impairments in accommodation and release of accommodation. Not all patients were able to appropriately perform the examination. There were no significant effects on other parameters.*

There were no clinically significant changes in visual acuity, visual fields, contrast sensitivity, intraocular pressure or color vision.

Eye disorder treatment-emergent adverse events during the study								
System organ class/	Number (%) of subjects							
Preferred term	Possibly related TEAEs				All TEAEs			
	Placebo		Telithromycin		Placebo		Telithromycin	
Total subjects	24(100.0)		24(100.0)		24(100.0)		24(100.0)	
Eye disorders	2	(8.3)	14	(58.3)	5	(20.8)	14	(58.3)
Vision blurred	1	(4.2)	12	(50.0)	1	(4.2)	12	(50.0)
Dry eye	1	(4.2)	3	(12.5)	2	(8.3)	3	(12.5)
Ocular discomfort	0	(0.0)	2	(8.3)	0	(0.0)	2	(8.3)
Blepharospasm	0	(0.0)	1	(4.2)	0	(0.0)	1	(4.2)
Corneal epithelium disorder	0	(0.0)	1	(4.2)	0	(0.0)	1	(4.2)
Diplopia	0	(0.0)	1	(4.2)	0	(0.0)	1	(4.2)
Eye pain	0	(0.0)	1	(4.2)	1	(4.2)	1	(4.2)
Photophobia	0	(0.0)	1	(4.2)	0	(0.0)	1	(4.2)
Eye irritation	0	(0.0)	0	(0.0)	1	(4.2)	0	(0.0)

Sponsor's Conclusions

After single oral administration of 2400 mg telithromycin, plasma pharmacokinetic parameters were in the range of those obtained in previous studies at the same dose, with a mean C_{max} of 5.11 mg/L and a median t_{max} of 3h.

At the supraclinical dose of 2400 mg, telithromycin induced blurred vision in 50% of the subjects. This was described as a difficulty to focus at far distance. The effect occurred at the peak concentration (but without relationship to the plasma concentration) and had a short duration (median 2h50).

There was no evidence of retinal toxicity because there was no change in the visual field, color vision or fundus, or in the contrast sensitivity function, and there was no evidence of a risk for angle closure glaucoma because there was no change in intraocular pressure or anterior chamber angle.

In one case, blurred vision was associated with reduced near visual acuity resulting from difficulties to focus, and in 2 cases it was associated with a reduced amplitude of accommodation but not with any alteration of far visual acuity, refraction or tear film.

Difficulty in focusing at a far distance was consistently reported during the episodes of blurred vision; however there was no clear demonstration that near-to-far or far-to-near adaptation was impaired, as shown by the continuous recording of accommodation and pupil size.

Overall there were no significant differences between telithromycin and placebo in any of the visual parameters.

Reviewer's Comments: *The sponsor's conclusions are not supported by the study results, particularly the last two statements. There is a clear demonstration of difficulties in near to far and far to near adaptation.*

Visual Adverse Events reported in post-marketing

Blurred vision	84
Visual disturbance	42
Accommodation disorder	12
Diplopia	9
Reduced visual acuity	3
Photophobia	2
Myosis	2
Mydriasis	2
Strabismus	2
Uveitis	1
Blindness/visual loss	1
Photopsia	1
Increased lacrimation	1

Reviewer Comments: *These events were consistent with the findings in the controlled studies.*

Ocular Events from All Sources reported through October 1, 2002

MedDRA PT	Total
Vision blurred	109
Visual disturbance NOS	68
Accommodation disorder	17
Diplopia	13
Eyelid oedema	5
Visual acuity reduced	5
Photophobia	4
Asthenopia	2
Binocular eye movement disorder NOS	2
Miosis	2
Mydriasis	2
Strabismus	2
Visual field defect NOS	2
Abnormal sensation in eye	1
Blindness	1
Chromatopsia	1
Conjunctivitis	1
Erythema of eyelid	1
Eye irritation	1
Eye pain	1
Eye pruritus	1
Eye redness	1
Eyelid disorder NOS	1
Eyelid ptosis	1
Herpes zoster ophthalmic	1
Lacrimation increased	1
Periorbital oedema	1
Photopsia	1
Scotoma	1
Uveitis NOS	1
Vitreous floaters	1
Xanthopsia	1
Grand Total	252

* Includes adverse events reported in clinical trials prior to drug approval on 09-July-2001 (and prior to PSUR No. 1).

Reviewer Comments: *There were no additional, unexpected ocular findings.*

Summary of Clinical Findings

Efficacy

Not evaluated in this review.

Safety

Ocular events, predominately blurred vision has been identified as a safety issue with the use of telithromycin. The blurred vision appears to occur in approximately 1% of patients taking 800mg and approximately 50% of patients taking 2400mg. The principal cause of the blurred vision has not been identified, but appears to be related to the ability to accommodate/release accommodation and its related effects on ocular motility. Based on the evidence to date, the effects appear to be temporary lasting from 30 minutes to 20 hours after each dose. More women than men reported blurred vision, however, in the controlled trials evaluating vision, there were more women enrolled than men.

Regulatory Recommendations

Recommendation on Approvability

From an ophthalmologic prospective, the current proposed labeling does not provide sufficient warnings of the potential to impair vision. There is no objection to the approval of this NDA provided that the labeling is revised to include sufficient warning concerning the potential to impair vision. Specific changes to the proposed labeling have been identified in this review.

Recommendation on Phase 4 Studies and Risk Management Steps

It is recommended that additional studies are conducted to evaluate the effect on vision using doses between 800mg and 2400mg (i.e., 800, 1200, 1600, 2000 and 2400mg). The purpose of these studies would be to better quantitate the timing of the blurred vision events and in particular the effects on accommodation.

/S/

Wiley A. Chambers, MD
Supervisory Medical Officer, Ophthalmology

cc: NDA 21-144
HFD-520
HFD-550/Chambers

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/s/

Wiley Chambers
1/23/03 11:25:39 PM
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MEDICAL OFFICER

MEDICAL OFFICER REVIEW OF NDA 21-144 AMENDMENT; HEPATIC ADVERSE EVENTS OF SPECIAL INTEREST

Date of Submission:	July 24, 2002
Date Review Completed:	Draft: January 13, 2002 Final: February 28, 2003
Applicant:	Aventis Pharmaceuticals, Inc.
Drug Product Established Name:	Telithromycin
Materials Reviewed:	NDA 21-144 Amendment; Clinical/Statistical, Case Report Forms Original NDA 21-144 Medical Officer Hepatic Safety Review, August 22, 2001 Anti-Infective Drugs Advisory Committee Minutes, April 26, 2001 Approvable Letter, June 1, 2001
Medical Officer:	Janice Pohlman, M.D.

EXECUTIVE SUMMARY

This review summarizes the hepatic adverse events observed in Study 3014, a large randomized, open-label trial evaluating the safety of telithromycin versus amoxicillin/clavulanate in the treatment of outpatients with respiratory tract infections.

The original NDA for telithromycin for treatment of respiratory tract infections was submitted to the Agency on March 1, 2000. During the review of that application and in subsequent discussion by the Anti-Infective Drugs Advisory Committee on April 26, 2001, safety concerns, including potential for hepatotoxicity, were raised. Preclinical pharmacology and toxicology had identified the liver as the primary organ for toxicity in all three animal species tested. Phase I studies had shown elevated alanine aminotransferase and aspartate aminotransferase levels in elderly subjects treated with a single high dose (2000 mg) of telithromycin. Hepatic adverse events were observed in 2% (40 of 2045) of telithromycin-treated patients during Phase III testing, a rate similar to that for comparators. However, there were two serious hepatic adverse events plausibly associated with telithromycin administration. One case, involving a 56-year-old male receiving treatment for community-acquired pneumonia, was particularly concerning. Four days after completing a 10-day course of telithromycin, he developed a symptomatic gastrointestinal illness, accompanied by elevation of transaminases (ALT 7x ULN, AST 5x ULN, total bilirubin <1.6x ULN), with liver biopsy demonstrating centrilobular necrosis with eosinophilic infiltration consistent with drug-induced hepatitis. The transaminase elevations resolved; however, eight months later he was noted to have asymptomatic elevation of transaminases (ALT 1331 U/L), with a liver

biopsy showing chronic hepatitis with marked activity and extensive bridging necrosis. The second case involved an elderly female on concomitant pravastatin and allopurinol, treated for community-acquired pneumonia, who developed marked, asymptomatic transaminase elevations (ALT 13x ULN, AST 9x ULN) that resolved approximately one week after treatment was discontinued. These cases factored into the recommendation by the AIDAC and the Division's decision to require a larger safety study prior to drug approval.

Study 3014 was designed to examine adverse events of special interest, including hepatic events, in a large population (24,000, with 12,000 receiving telithromycin) of patients with acute community-acquired respiratory infections. The population was to be enriched for subjects at increased risk for hepatic events, including those with community-acquired pneumonia, age greater than 50 years, history of hepatic impairment, or concomitant medications, including CYP34A inhibitors. The study was powered to detect with 95% confidence adverse events occurring at rates of at least 1 in 4,000. Hepatic adverse events were identified by the investigator and included reports of hepatitis, jaundice, or worsening of pre-existing hepatic dysfunction and all cases of ALT $\geq$ 3x ULN. A hepatic clinical expert committee selected by the Sponsor and blinded to treatment assignment reviewed all hepatic adverse events for determination of the hepatic safety endpoint which was defined as possible drug-related clinically significant hepatic injury. This endpoint required the patient to have symptoms (such as fatigue, nausea, vomiting, or jaundice) and ALT $\geq$ 3x ULN occurring in temporal relationship to drug administration and resolving with cessation of treatment, in the absence of other significant hepatic pathology (such as acute or chronic viral hepatitis).

The rates of hepatic adverse events were similar between treatment groups, with the telithromycin treatment group (800 mg qD for 5-10 days) having 111 events in 12159 patients (0.91%) versus the amoxicillin/clavulanate treatment group (875 mg for 7-10 days) having 98 events in 11978 patients (0.82%). The majority of hepatic adverse events were asymptomatic in both treatment groups (82% in the telithromycin group and 80.6% in the amoxicillin/clavulanate group), although in those patients who were symptomatic, study drug had a possible relationship with the event in 14/18 (77.8%) of the telithromycin-treated patients compared to 10/18 (55.6%) of the amoxicillin/clavulanate-treated group. The most common symptoms were fatigue and nausea.

FDA medical review determined that there were six possible drug-related, clinically significant hepatic injury endpoints, with four occurring in the telithromycin-treatment group and two in the amoxicillin/clavulanate group (the Applicant's hepatic CEC concluded that there were three and two endpoints, respectively). All four of the events in the telithromycin treatment group were confounded by other factors such as alternative medical diagnoses or concomitant medications. One of the two events in the amoxicillin/clavulanate treatment group was consistent with the well-recognized cholestatic jaundice syndrome associated with amoxicillin/clavulanate. One telithromycin-treated patient, who did not meet the endpoint definition due to asymptomatic elevation of transaminases, was treated for possible autoimmune hepatitis

with prednisone by the investigator. There was a slight trend for higher elevations in ALT and AST in the telithromycin treatment group, although this finding did not reach statistical significance. There was also a slight trend noted for a higher rate of increases in transaminase levels at late post-therapy follow-up in the telithromycin-treated group (71 of 664 (10.7%) at the late post-therapy visit) compared to the amoxicillin/clavulanate-treated group (49 of 659 (7.4%) at the late post-therapy visit).

Study 3014 indicates that the incidence of hepatic adverse events associated with telithromycin treatment was similar to that of the comparator, amoxicillin/clavulanate. The majority of events were asymptomatic and characterized predominantly by elevated transaminase levels. These elevated levels appeared to resolve over time, although there was a slightly higher incidence of abnormal transaminase levels noted in the telithromycin treatment group. While there were four hepatic endpoints of possible drug-related clinically significant hepatic injury noted in the telithromycin treatment group, all of these cases were confounded by other factors and hepatic laboratory abnormalities in these cases resolved over the approximately six month follow-up period. Despite these findings, concern remains regarding the patient from previous Phase 3 studies who was diagnosed with drug-induced hepatitis and subsequent chronic autoimmune hepatitis.

Based on the reported efficacy of telithromycin in the treatment of community-acquired pneumonia and acute bacterial sinusitis and the hepatic adverse event data generated from Study 3014, it is reasonable to approve telithromycin treatment for these indications. Based on the relatively short duration of treatment and single courses of telithromycin therapy observed in the study population, it is also reasonable to defer approval of telithromycin for treatment of acute exacerbation of chronic bronchitis, until such time as the risk-benefit ratio can be re-examined with post-marketing data on hepatotoxicity.

The Adverse Reactions section of the label should contain information regarding the hepatic adverse event information obtained from Phase 3 studies and Study 3014. This should include information on the most common hepatic adverse event noted, asymptomatic elevation of transaminase levels. It should also note that with cessation of the drug, resolution of these elevations generally occurs. Although the exact relationship between the case of probable telithromycin-related hepatitis and subsequent diagnosis of chronic autoimmune hepatitis in the patient from prior Phase 3 trials is not known, it should be included in the labeling to assist with post-marketing detection of future hepatic events.

Regulatory Background

NDA 21-144 was submitted to the Agency by Aventis Pharmaceuticals, Inc. on March 1, 2000. The efficacy and safety of telithromycin were the focus of an Anti-Infective Drugs Advisory Committee meeting on April 26, 2001, at which time the Committee voted against the approval of telithromycin for treatment of community-acquired pneumonia (CAP), acute bacterial sinusitis (ABS), and acute exacerbation of chronic bronchitis (AECB). This decision was based primarily on safety concerns related to telithromycin. In particular, the potential for telithromycin to cause hepatotoxicity and serious liver injury was a major factor in the recommendation to obtain additional safety information about this drug.

As noted in the hepatic safety review of the original NDA 21-144 submission by Dr. Edward Cox, the presence of the following factors raised significant concern about the hepatotoxic potential of telithromycin:

- Hepatotoxicity in the three animal species tested in preclinical studies.
- The Phase I studies where there was a clustering of hepatic adverse events in elderly patients receiving single 2000 mg doses.
- An excess of low level AST, ALT, and/or total bilirubin elevations in telithromycin-treated patients in comparative Phase III trials.
- A few patients, only in the telithromycin-treated group, with concomitant low level transaminase and total bilirubin elevations.
- Two serious hepatic events plausibly attributed to telithromycin, with one of the events involving marked hepatitis with a liver biopsy showing centrilobular necrosis and eosinophilic infiltration strongly suggestive of drug-induced liver disease. A subsequent biopsy nine months later showed chronic hepatitis, probably autoimmune.

The FDA presentation for telithromycin before the AIDAC on April 26, 2001 included discussion of the above noted case of possible drug-related hepatitis in a subject treated with telithromycin. This patient had presented with clinically symptomatic hepatitis, eosinophilia, and undergone liver biopsy after a course of telithromycin, with the pathology felt to be consistent with drug-induced hepatitis on review at the Armed Forces Institute of Pathology. After a quiescent period in which the patient was clinically well, he presented with asymptomatic elevations of transaminase levels and on a second liver biopsy was found to have pathologic findings consistent with autoimmune hepatitis (biopsy interpretation also confirmed by AFIP).

An Approvable Letter was issued by the Agency on June 1, 2001 and included the following recommendation regarding safety:

"It would be helpful to conduct a Phase III study of CAP/AECB/ABS to assess further adverse events associated with telithromycin, particularly in patients at increased risk for potential drug-related toxicity. Such a study should be randomized, with at least 35% of the recruited study population consisting of patients 50 years of age and older. Exclusion

criteria regarding concomitant medications should be minimized. Recruitment of patients with renal and/or hepatic impairment is encouraged. This study should include the monitoring and analysis of all adverse events, with particular attention to hepatic, visual, cardiovascular, and vasculitic adverse events."

The Applicant conducted Study 3014 primarily to address these concerns and to better characterize the hepatic risk profile of telithromycin in a usual care setting.

Study 3014 Background

Study 3014 was designed as a multi-center, randomized open-label trial, primarily to compare the safety of telithromycin 800 mg qD versus amoxicillin/clavulanate 875 mg BID in the treatment of respiratory tract infections, including CAP, ABS, and AECB, in a usual practice setting. Telithromycin treatment duration was five days for ABS and seven to ten days for CAP and AECB, while amoxicillin/clavulanate was administered for seven to ten days for all indications. The target population was 24,000 adult patients (12,000 per treatment group) with at least 35% of subjects ≥50 years of age, and 40% with CAP or AECB for safety risk enrichment. A study population of 12,000 telithromycin-treated patients would give a high probability of detection of an adverse event expected to occur at a rate of 1 per 4000 treated patients. For a complete overview of the objectives and general design of Study 3014, see Dr. George Rochester's review.

MO Comment: The comparator, amoxicillin/clavulanate, is a recognized cause of cholestatic jaundice, with most cases having a favorable prognosis. Retrospective cohort studies have suggested that the true rate of amoxicillin/clavulanate-associated cholestatic jaundice in some patient populations (particularly the elderly or those receiving prolonged therapy) may be greater than 10 cases per 100,000 prescriptions[1]. This recognized hepatotoxicity of amoxicillin/clavulanate and generally favorable prognosis must be weighed when attempting to compare and define the extent and nature of telithromycin's risk for hepatotoxicity.

In Study 3014, liver function tests, including alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALK), and total bilirubin (Tbili) were to be collected on all subjects at baseline (Day 1) and Visit 2 (Day 17-22). There was adequate laboratory data (baseline and Visit 2) available to assess hepatic safety in 12159/12277 randomized subjects (99.0%) in the telithromycin group and 11978/12147 randomized subjects (98.6%) in the amoxicillin/clavulanate group.

[1] Rodriguez LA *et al.* Risk of acute liver injury associated with the combination of amoxicillin and clavulanic acid. Arch Int Med 1996; 156:1327-1332.

Hepatic Adverse Events of Special Interest

Hepatic adverse events of special interest (HAESI) were identified by the investigator and included reports of hepatitis, jaundice, or worsening of pre-existing hepatic function, along with all cases of ALT ≥3 x upper limit of normal (ULN). These events were determined by the results of clinical laboratory testing, as well as questioning subjects about the occurrence of adverse events and physical assessment. HAESI were to be documented on the "Adverse Event" page of the CRF and forwarded to the sponsor's representative (CRO). The occurrence of a HAESI was to prompt a follow-up investigation, including a diagnostic work-up (physical exam, vital signs, and clinical laboratory reports), as outlined in the "Adverse event of interest" form (see Appendix A) provided to the investigator. Repeat liver function tests and additional laboratory data, as recommended in general medical practice, were to be performed by the investigator to assist in evaluation of hepatic events, such as hepatitis A, B, and C serology, white blood cell count with differential, and prothrombin time. Other diagnostic studies, if performed by the investigator, such as autoimmune serologic studies or diagnostic studies (such as ultrasound, CT scan, or liver biopsy), were to be reported to the medical monitor and Hepatic Clinical Expert Committee (CEC).

MO Comment: Although the Division had requested that the Sponsor submit a management algorithm for review prior to the study, this was not done. The Sponsor's algorithm for this study consisted of an "adverse event of interest" form (see Appendix A) to be completed by the investigator, as well as a hepatic laboratory kit including blood collection tubes for repeat hepatic function testing (transaminases, alkaline phosphatase, total and direct bilirubin), hepatitis serologies (hepatitis A IgM antibody, hepatitis B surface antigen, and hepatitis C antibody), complete blood count and differential, and prothrombin time. Additionally, a later submission from the Sponsor (response to FDA briefing package) indicated that a tube was also included for autoimmune serologies (anti-nuclear, anti-DNA, anti-mitochondrial, and anti-smooth muscle antibody testing). The investigators were instructed to conduct "follow-up laboratory investigations as recommended in general medical practice" to assist in assessment of the etiology of HAESIs. The details of diagnostic evaluation, beyond verification of abnormal liver function studies, were left to the investigator's discretion. Thus, related information was not obtained in a consistent manner with regard to extent or timing of work-up, making it difficult in some instances to determine the relation between study drug administration and occurrence of a HAESI.

The inconsistent results from use of the management algorithm given for investigators to follow in evaluation of HAESI are illustrated by analysis of follow-up laboratory testing as specified on the CRF. Actual numbers of follow-up laboratory tests conducted are shown in Tables 1 and 2.

TABLE 1

CRF-Documented Laboratory Tests Performed During Follow-Up of HAESIs			
	N = 209	Telithromycin N = 111	Amoxicillin/Clavulanate N = 98
LFT's	125 (60%)	65 (59%)	60 (61%)
Hepatitis serologies	110 (53%)	55 (50%)	55 (56%)
CBC with differential	105 (50%)	51 (46%)	54 (55%)
Prothrombin time	95 (46%)	48 (43%)	47 (48%)
Autoimmune serologies	27 (13%)	12 (11%)	15 (15%)
Ultrasound and/or CT scan	18 (9%)	7 (6%)	11 (11%)
Liver biopsy	2 (1%)	0	2 (2%)*

* Liver biopsy done in one subject prior to study enrollment. No confirmation (of biopsy) for second subject reported as having biopsy done. In fact, review of CRFs and narratives showed that there were actually three liver biopsies performed subsequent to enrollment in the study, with two in the telithromycin group and one in the amoxicillin/clavulanate group.

TABLE 2

Electronic Database-Documented Laboratory Tests Performed During Follow-Up of HAESIs			
	N = 209	Telithromycin N = 111	Amoxicillin/Clavulanate N = 98
LFT's	205 (98%)#	107 (96%)#	98 (100%)#
Hepatitis serologies	172 (82%)	89 (80%)	83 (85%)
CBC with differential	155 (74%)	81 (73%)	74 (76%)
Prothrombin time	112 (54%)	59 (53%)	53 (54%)
Autoimmune serologies	77 (37%)	38 (34%)	39 (40%)
Ultrasound and/or CT scan	*	*	*
Liver biopsy	*	*	*

These numbers are based on patients that had at least two hepatic profiles present in the database and may overestimate the actual number of tests performed as part of the hepatic kit.
* These tests were not included in the laboratory database. Information regarding whether these tests may have been done were included in attachments to the CRF or in narrative summaries contained in the Sponsor's study report

Table 1 shows the follow-up laboratory tests that were indicated by checked boxes on the CRF, Section B, 1-4. It is unclear whether this box was to be checked by the investigator or the Sponsor (CRO). Table 1 shows that this group of tests (LFT's, hepatitis serologies, CBC with differential, and prothrombin time), had similar rates of completion (46-60%), likely indicating that some investigators attempted to follow a standard algorithm for work-up of a HAESI. Table 2 gives a more precise idea of the degree and nature of the follow-up laboratory testing actually done, with performance rates ranging from 54% for prothrombin times to 98% for follow-up LFT's, indicating that investigators selecting blood collection tubes from the hepatic kit (versus CRF) chose a more limited work-up for HAESI. Autoimmune serologies were more infrequent in both CRF and electronic database records, likely reflecting the more optional nature of testing suggested by the CRF, with instruction to the investigator to forward results of such testing if performed. Compliance with repeat hepatic profile testing was high for both telithromycin and amoxicillin/clavulanate treated groups;

completion of other laboratory tests indicated by blood collection tubes in the hepatic kit sent to the investigator at the time of HAESI was more variable. It appears that additional follow-up laboratory tests were more commonly obtained in the comparator-treated group, introducing a potential reporting bias.

The HAESI were to be referred to the CEC for ongoing evaluation. The CEC charter called for this information to be forwarded to the CEC every two weeks. The panel, blinded to treatment assignment, reviewed medical history, concomitant medications, and symptoms provided by the investigator on the case report form (CRF), along with laboratory data and additional pertinent medical records for determination of the relationship of event occurrence to administration of study drug, as well as possible drug-related significant hepatic injury events. The CEC charter called for monthly meetings to adjudicate cases as to meeting the definition of safety endpoints. The CEC charter stated that "CEC members may request additional evaluations before making a final decision." The definition of possible drug-related significant hepatic injury includes a proviso that while not required for definition, findings of liver biopsy (when performed as medically indicated) will be requested for review.

MO Comment: According to the study report for 3014, investigator reports of HAESI were sent to the CEC at the end of the study. This effectively prevented the CEC from requesting additional diagnostic evaluations, including liver biopsy, which they were explicitly authorized to do under the CEC charter. As noted in the previous discussion about the management algorithm for HAESI, follow-up laboratory testing by the investigator, using the hepatic kit provided by the Sponsor, was not consistently done. The CEC adjudication forms for some patients noted the lack of specific information, such as hepatitis serology or autoimmune testing, and the aggregate evaluation at the end of the study did not allow for these tests to be completed in a timely manner.

The definition of possible drug-related significant hepatic injury used by the CEC required that all of the following conditions be met:

- Symptomatic liver damage (manifestations including nausea/vomiting, right upper quadrant pain, rash/pruritis, significant or unusual fatigue impacting daily activities, fever, dark urine, and jaundice).
- Associated ALT values of at least 3 x ULN occurring during observation in the absence of other causes, such as viral hepatitis, excessive alcohol or acetominophen ingestion, acute cholelithiasis, decompensated heart failure, malignant neoplasm, or other well-defined pathological processes.
- Temporal relationship, requiring new onset of symptoms on or later than Day 5 of treatment and a decrease in ALT $\geq$50% occurring within 30 days of drug cessation.

MO Comment: By excluding cases with other underlying hepatic pathology, this definition effectively converts the endpoint to one of definite, rather than possible, causality (see Appendix B).

The distribution of subjects with HAESIs was balanced between treatment groups. There were 111 events in 12159 telithromycin-treated patients (0.91%) versus 98 events in 11978 amoxicillin/clavulanate-treated patients (0.82%). Of those events reported to the CEC, 72.7% (80/111) of the telithromycin group events and 64.2% (63/98) of the amoxicillin/clavulanate group events were considered to be possibly related to study medication as determined by the FDA medical reviewer. The numerators for these rates include two telithromycin cases and one amoxicillin/clavulanate case considered indeterminate due to inadequate baseline or missing Visit 2 labs. Assessment of the relation between study drug and occurrence of a HAESI made by the FDA medical reviewer differed from that of the CEC for 27 subjects, with 13 telithromycin and 15 amoxicillin/clavulanate subjects reclassified by the FDA reviewer as having had possible drug-related events. The majority of differences between FDA reviewer and the CEC (16, of whom eight received telithromycin and eight received amoxicillin/clavulanate) were in subjects with hepatitis C who had transaminase increases from baseline levels that were felt by the CEC to be consistent with hepatitis C, although the FDA medical reviewer felt that drug effect could not be discounted in these cases. Additionally, there were eight patients with abnormal baseline transaminases (two in the telithromycin treatment group and six in the amoxicillin/clavulanate group) who had further increases in transaminase values with no known alternative hepatic pathology that were considered to be possibly related to study drug administration by the FDA medical reviewer.

MO Comment: The protocol does not specify precise categorical definitions of causality (that is, definite, probable, possible, unrelated), however, investigators were required to indicate their assessment of causality (either possibly related or not related) on the CRF. This assessment was to be done by answering the question; "Is there a reasonable possibility that the event is associated with the study medication (no or yes)?" The FDA medical reviewer used this to assign drug-related causality as possible or unrelated.

The majority of HAESIs in both treatment groups were asymptomatic, with 82% (91/111) of subjects in the telithromycin group and 80.6% (79/98) in the amoxicillin/clavulanate group free from symptoms. In the 36 subjects with a clinically symptomatic HAESI, study drug had a possible relationship in 14/18 (77.8%) of the telithromycin treatment group and in 10/18 (55.6%) amoxicillin/clavulanate treatment group as determined by the FDA medical reviewer. The symptoms noted most commonly were fatigue and nausea.

HAESIs adjudicated as possibly drug-related

There were five CEC-adjudicated cases of possible significant drug-related hepatic injury, with three occurring in the telithromycin-treated group and two in the amoxicillin/clavulanate group. Brief narratives of these events follow:

Telithromycin

- Patient #1567 009, a 58-year-old female, was randomized to telithromycin 800 mg for 7-10 days for AECB and took the medication for 10 days. Baseline and Visit 2 (Day 17) hepatic laboratory studies were within the normal range and are shown in the table below. On Day 21, the patient developed gross hematuria, along with fever and back pain, and was evaluated in the emergency room on Day 26 (a discrepancy was noted between investigator note in CRF indicating ER visit on Day 23 and ER letter and laboratory evaluation indicating visit on Day 26), with CBC notable for WBC 14.6 K/μL (ULN 11) with left shift (24 bands), urinalysis notable for positive leukocyte esterase, 1+ protein, 3+ blood, 2+ bilirubin, occasional RBCs, 10-20 WBCs/HPF, and many bacteria, although urine culture collected at the same time (difference of one minute on lab records) was $<10^5$ colonies/mL. The patient was treated with a 10 day course of ciprofloxacin 500 mg BID. Liver function tests on Day 26 showed mild elevation of transaminases with an elevated total bilirubin. Values for these laboratories and follow-up studies on Day 58 are shown in Table 3. Hepatitis serologies were negative for hepatitis A IgM antibody, hepatitis B surface antigen, hepatitis B IgM core antibody, and hepatitis C antibody.

TABLE 3

	Analyte value/flag				
Analyte (units)	Normal Range	Baseline	Day 17	Day 26	Day 59
ALT (U/L) -C	6 - 34	14	16		22
ALT (U/L) - L	8 - 35			66 H	
AST (U/L) - C	9 - 34	19	21		19
AST (U/L) - L	8 - 37			86 H	
Alk Phos (U/L) - C	35 - 123	91	90		89
Alk Phos (U/L) - L	30 - 120			196 H	
Total Bili (μmol/L) – C	ULN 20.9*	3.0	9.0	78.2#	9.0
Total Bili (mg/dL) - L	0.1 – 1.0			4.6 H	
Direct Bili (μmol/L) – C	ULN 7.0*			21.0#	3.0
Direct Bili (mg/dL) - L	0.0 – 0.3			3.0 H	

C = central laboratory value, L= local laboratory value
* Reference values not provided in Applicant-supplied narrative. Value extrapolated from ratio of patient value to reference value.
# Local laboratory measurement, converted from mg/dL using conversion factor of 1 mg/dL = 17 μmol/L

CEC adjudication summary: This is a medically complicated case. This patient had a symptomatic illness, with high bilirubin, but little elevation of

transaminase. This occurred in the setting of a febrile illness, apparently a urinary tract infection. The illness, whatever its cause, resolved. There is a compatible temporal relationship to study drug. We believe this illness is possibly related to study drug, although renal infection cannot be ruled out.

FDA Medical Reviewer Assessment: Agreed with the CEC, including the possibility that intercurrent illness (possible pyelonephritis) was also contributory.

- Patient #2004 002, a 72-year-old male with type II diabetes mellitus, hypertension, chronic left lower extremity lymphedema, congestive heart failure, coronary artery disease, chronic pleural effusion, and chronic anticoagulation, was randomized to treatment with telithromycin 800 mg for 7-10 days for CAP. Concomitant medications included Aceon, Coumadin, glyburide, Lasix, and spironazide. He completed 10 days of therapy and on visit 2 (Study Day 22) was noted to have liver function test abnormalities including transaminases, alkaline phosphatase, and total bilirubin as shown in the table below. These tests were repeated on Day 28, along with EBV titers, ANA, anti-DNA, hepatitis A, B, and C serologies, CBC with differential, and prothrombin time (PT). Lab tests were significant for a PT of 15.3 sec, a relative lymphocytosis with 54.9% lymphocytes on differential, and liver function tests as shown in the table below. Hepatitis serologies, ANA, and anti-DNA were negative. CT scan of the abdomen showed bilateral pleural effusions with segmental atelectasis at the right lung base, mild eventration of the right dome of the diaphragm, and a gallbladder with increased wall thickness and increased density, suggesting filling with stones and/or a significant amount of sludge. An ultrasound of the gallbladder demonstrated a contracted gallbladder with increased wall thickness with some sludge and very small low-density calculi, with the largest being 5 mm. On Day 30, the patient was admitted to the hospital with jaundice, treated with Levaquin, and on Day 35 underwent a laproscopic cholecystectomy with gallbladder pathology consistent with cholelithiasis and cholecystitis and a simultaneous liver biopsy showing cholestasis. He was treated with Unasyn post-operatively. One week post-operatively (Day 45), laboratory tests showed an absolute eosinophilia with 658 eosinophils/μL (ULN 200) and liver function studies as shown in Table 4. The final diagnosis for this hepatic abnormality by the investigator was choledocholithiasis.

TABLE 4

	Analyte value/flag					
Analyte	Normal range	Baseline	Day 23	Day 29	Day 45	Day 178
ALT (U/L)	6 – 35	17	270 H	158 H	36 H	25
AST (U/L)	11 – 36	19	162 H	100 H	50 H	25
Alk phos (U/L)	35 – 156	148	461 H	617 H	210 H	127
Total bili (µmol/L)	ULN 21.0*	17.0	104 H	79 H	23.94 H	9.0
Direct bili (µmol/L)	ULN 7.0*			46 H		

* Reference values not provided in Applicant-supplied narrative. Value extrapolated from ratio of patient value to reference value.

CEC adjudication summary: This was a very difficult case to interpret because of the gallbladder disease and was extensively discussed by the group. It was clearly a serious clinical event. Laboratory values were normal at baseline. There was a subsequent increase in ALT to 158, with drop to 50. Bilirubin rose to 104. Uncontrolled heart failure was also reported. This subject had an intercurrent laporascopic cholecystectomy. Liver biopsy showed cholestasis. An effect of drug cannot be discounted (possibly related to study drug), but may also be related to the concurrent gallbladder disease, as the possibility of passage of small calculi cannot be excluded.

FDA Medical Reviewer Assessment: Agreed with the CEC assessment. The liver biopsy was evaluated for the FDA by Dr. David Kleiner from NCI with histologic diagnosis showing mild combined cholestatic and hepatocellular injury consistent with possible etiologies of drug/toxic injury, or early, acute large duct obstruction. The biopsy also showed evidence of sinusoidal and periportal fibrosis attributed to history of diabetes mellitus.

- Patient #3440 001, a 75-year-old female with a history of coronary artery disease, angina/myocardial infarction, cholecystectomy, gastroesophageal reflux, hyperlipidemia, hypertension, and hypothyroidism, was randomized to telithromycin 800 mg for 5 days for acute sinusitis. Concomitant medications included Synthroid, Zestril, hydrochlorothiazide, Betapace, pravastatin, Nexium, vitamins D and E, calcium, and acetominophen. On Day 17, the patient had complaints of severe abdominal (epigastric) pain associated with fatigue, nausea, fever, and jaundice. The patient was hospitalized on Day 18 with elevated temperature (T 101°F), jaundice, and right upper quadrant and epigastric tenderness. Laboratory studies showed transaminase and ALK elevations shown in Table5, normal amylase, and mildly elevated lipase 314 U/L (normal range: 114-286). The patient was kept npo and pravastatin was withheld. Transaminase and ALK levels had decreased over the next 24 hours as shown in Table 5. Serologic testing for acute hepatitis A and B was negative, as was hepatitis C testing. Anti-DNA, ANA, ASMA, and AMA were negative as well. An abdominal CT scan was notable for prior cholecystectomy and no dilatation of the common bile duct. The patient continued to improve and was discharged from the hospital on Day 21 with a diagnosis of hepatitis with possible etiologies being

drug-related hepatitis (study drug versus pravastatin) and passed gallstone. By Day 29, laboratory studies were almost completely normal as shown in Table 5.

TABLE 5

	Analyte value/flag					
Analyte	Normal range	Baseline	Day 18	Day 19	Day 29	Day 64
ALT (U/L)	6 – 32	9	969 H	629 H	33 H	18
AST (U/L)	9 - 34	16	1357 H	333 H	18	17
Alk phos (U/L)	35 – 164	74	285 H	282 H	103	71
Total bili (µmol/L)		7 ULN 21.2*	30.78 H ULN 17.1*	18.81 H ULN 17.1*	5.0 ULN 20.8*	7.0 ULN 21.2*
Direct bili (µmol/L)					2.0 ULN 6.9*	
* Reference values not provided in Applicant-supplied narrative. Value extrapolated from ratio of patient value to reference value.						

CEC Adjudication Summary: This case represented a clinically overt significant hepatic injury with compatible temporal relationship. This case is felt to be a clinically serious problem. This patient had increases in ALT to 969, AST to 1357 and bilirubin to 1.8 mg/dl, associated with fatigue, nausea, jaundice and severe epigastric pain. A relation to drug use is possible or probable, but passage of a stone cannot be excluded.

FDA Medical Reviewer Assessment: Agreed with the CEC assessment.

Amoxicillin/clavulanate

- Patient #0604 004, a 43-year-old male, was randomized to receive amoxicillin/clavulanate 875/125 mg BID for 7-10 days for acute sinusitis and took medication for 10 days. At the time of study Visit 2 (Day 18), the patient was experiencing rash or pruritis (one check-box marked for these two events on hepatic AE CRF) and was noted to have isolated elevation of transaminases, with normal ALK and Tbili levels as shown in Table 6. The patient had completed therapy and withdrew from the study on Day 28 because he did not wish to continue; no further laboratory studies were obtained.

TABLE 6

	Analyte value/flag		
Analyte	Normal range	Baseline	Day 18
ALT (U/L)	6 – 43	50 H	154 H
AST (U/L)	11 – 36	35	68 H
Alk phos (U/L)	31 - 129	67	66
Total bili (µmol/L)		7.0 ULN 21.2*	9.0 ULN 20.9*
* Reference values not provided in Applicant-supplied narrative. Value extrapolated from ratio of patient value to reference value.			

CEC Adjudication Summary: This case represents clinically overt symptomatic hepatic injury with compatible temporal relationship to study drug. Baseline ALT was elevated at 50. ALT increased to 154 with normal bilirubin. The subject developed diarrhea, rash and pruritus, but refused any follow-up. The increase in transaminases were felt to be possibly related to study drug, but abnormal baseline and scant follow-up limit assessment.

FDA Medical Reviewer Assessment: Agreed with that of the CEC that this event was possibly related to amoxicillin/clavulanate administration; however, despite this event meeting the criteria established for clinically significant hepatic injury, it is more likely that the rash or pruritis were indicative of a hypersensitivity reaction rather than a clinically symptomatic hepatic event (hepatitis).

- Patient #2326 004, a 64-year-old female, was randomized to treatment with amoxicillin/clavulanate 875 mg BID for 7-10 days for AECB. However, the patient was continued on amoxicillin/clavulanate for the primary infection beyond the 10-day treatment period for an additional 14 days of therapy. Visit 2 occurred on Day 17, at which time all hepatic laboratory analyses were normal. On Day 28, the patient experienced nausea, pruritis, dark urine, and jaundice associated with abnormal hepatic laboratory tests, with the following values as shownin Table 7. These lab abnormalities were accompanied by a relative eosinophilia, with 6.4% eosinophils noted on differential. Amoxicillin/clavulanate was discontinued and the patient was treated with tapering doses of prednisone for hypersensitivity reaction and cholestasis (the reason given by the investigator was modified to cholestasis alone after medical monitor inquiry to investigator). On Day 33 (five days after discontinuing amoxicillin/clavulanate and starting prednisone), hepatic laboratory abnormalities had begun to resolve as shown in Table 7. By Day 69, hepatic laboratory values had decreased to normal values.

TABLE 7

	Analyte value/flag					
Analyte	Normal range	Baseline	Day 17	Day 28	Day 33	Day 69
ALT (U/L)	6 - 34	19	21	571 H	384 H	24
AST (U/L)	9 - 34	18	22	348 H	162 H	25
Alk phos (U/L)	35 – 123	38	38	182 H	143 H	46
Total bili (µmol/L)		10.0 ULN 20.8*	10.0 ULN 20.8*	86. 7# H 5.1 mg/dL	44.0 ULN 21.0*	9.0 ULN 20.9*
Direct bili (µmol/L)					21.0 ULN 7.0*	3.0 ULN 7.0*

* Reference values not provided in Applicant-supplied narrative. Value extrapolated from ratio of patient value to reference value.
# Local laboratory measurement, converted from mg/dL using conversion factor of 1 mg/dL = 17 µmol/L

CEC Adjudication Summary: This was a case of great interest. The subject was symptomatic. Baseline ALT, AST and bilirubin were normal. There was a rise in ALT to 571 and bilirubin to 5.1 mg/dL, with subsequent fall to normal for both. The subject was treated with prednisone. Eosinophils were as high as 6.4%. This event has a probable association to study drug.

FDA Medical Reviewer Assessment: Concur with CEC assessment. Cholestatic hepatitis has been associated with administration of amoxicillin/clavulanate, particularly after prolonged courses of therapy.

There were four additional cases of possible significant drug-related hepatic injury as indicated by clinical symptoms and laboratory evidence, with three cases occurring in the telithromycin group and one case in the amoxicillin/clavulanate group. However, these events were not considered to be drug-related by the CEC because of alternative explanations based on existing hepatic pathology. The FDA medical reviewer disagrees with the CEC exclusion of patient #0363 015 from the possible drug-related significant hepatic injury category. The rationale for this is presented with the patient case narrative below.

Telithromycin

Patient #0363 015, a 68-year-old female, was treated for AECB for five days (randomized to a 7-10 day regimen) with telithromycin. Concomitant medications included Accupril, Premarin, multivitamins (along with calcium and vitamin E supplements), and ibuprofen (daily dose not specified). At study Visit 2 (Day 19) the patient was noted to have fever (T 101.0°F), cough, and nausea, was started on therapy with Levaquin and Flumadine for the primary infection (AECB) versus possible influenza, and had post-therapy hepatic laboratory studies performed. Significant elevations were noted at this visit in transaminase levels, with an increased ALT of 150 U/L (baseline 27 U/L) and an AST of 91 U/L (baseline 28 U/L). ALK and Tbili remained within normal limits. As follow-up to these abnormal transaminases, additional

laboratory studies were obtained on Day 28 (following treatment with levofloxacin and Flumadine) and showed a further increase in transaminase levels, with an ALT of 402 U/L and an AST of 147 U/L. Additional laboratory at this time showed a relative and absolute eosinophilia, with a differential showing 24% eosinophils (normal: 0.0-6.8), and an absolute eosinophil count of 2.85 GG/L (normal range: 0.0-0.57). Laboratories drawn 32 days later (Day 60) showed resolution of the leukocytosis and eosinophilia, and improvement in transaminase levels, although these did not return to normal baseline, with an ALT of 97 U/L and an AST of 52 U/L.

CEC Adjudication Summary: Probable drug-related HAESI. Hepatic adjudication form comments: normal baseline, ALT rose to 402 and fell to 97. Bilirubin normal. Had fatigue and fever. Hepatitis serologies normal.

FDA medical reviewer assessment: Agreed with the CEC summary above, however, did not agree with exclusion from the possible drug-related clinically significant hepatic injury endpoint. The initial transaminase elevations at Study Day 19 were possibly related to telithromycin, although further elevation and eosinophilia noted at Day 28 could also have been caused by the administration of additional medications (Levaquin). However, this case was excluded by the CEC as a possible drug-related clinically significant hepatic injury although the rationale for this is not clear. The clinical symptomatology noted, including fever and nausea, might have been attributed by the CEC to an upper respiratory problem rather than hepatic symptomatology.

The FDA medical reviewer agreed with the CEC's exclusion of three cases of possible significant drug-related hepatic injury from endpoint categorization based on the alternative hepatic pathology present. These three cases are discussed below.

Telithromycin

Patient #0862 006, a 49-year-old female, was randomized to treatment with telithromycin 800 mg qD for 7-10 days for treatment of AECB and completed 10 days of treatment. The patient had a history of COPD, asthma, alcohol abuse, and hepatic impairment due to hepatitis C. The patient's baseline LFT's were abnormal as shown in Table 8 and the patient was asymptomatic. Further increase was noted in transaminase levels on Visit 2 hepatic laboratory studies done five days after completion of therapy. The patient was asymptomatic and refused laboratory follow-up. The investigator felt that the abnormal hepatic laboratories were secondary to hepatitis C and history of alcohol abuse.

TABLE 8

	Analyte value/flag		
Analyte	Normal range	Baseline	Day 16
ALT (U/L)	6 – 34	254 H	378 H
AST (U/L)	9 – 34	139 H	235 H
Alk phos (U/L)	31 – 106	91	87
Total bili (µmol/L)		7.0 ULN 21.2*	10.0 ULN 20.8*

* Reference values not provided in Applicant-supplied narrative. Value extrapolated from ratio of patient value to reference value.

CEC Adjudication Summary: Baseline abnormal (ALT 254; AST 139). Has hepatitis C. Alcohol abuse 7 years. Abnormalities increased but then she refused follow-up. Cannot assess based on available data. Temporal relationship not compelling to incriminate drug.

FDA Medical Reviewer Assessment: In this case, the patient had a marked abnormality in transaminase levels at baseline with a reported history of alcohol abuse by the investigator, as well as hepatitis C. Since the patient had abnormal baseline hepatic labs and two alternative explanations for hepatic pathology, this case is excluded from the CEC definition for a safety endpoint event.

Patient #3146 003, a 34-year-old female, was treated with 10 days of telithromycin, 800 mg qD, for AECB. Concomitant medications included Xanax, Lortab, and Adipex-P. Baseline hepatic laboratory studies were normal, as shown in the table below. On Day 18, the patient was reported to be asymptomatic, but was diagnosed with acute hepatitis B and also treated with Levaquin (reason unknown). The patient was hospitalized for further tests on Day 22. Laboratory tests for this period are shown in Table 9. While hospitalized, the patient had a CT scan of the abdomen that was reported as unremarkable except for the presence of multiple faintly calcified gallstones without evidence of acute complication. By seven weeks after the start of study medication, the hepatic abnormalities had resolved as shown in Table 9.

TABLE 9

	Analyte value/flag				
Analyte	Normal range	Baseline	Day 18	Day 25	Day 47
ALT (U/L)	6 – 34	18	2345 H	642 H	32[#]
AST (U/L)	9 – 34	23	1056 H	84 H	21[#]
Alk phos (U/L)	31 – 106	88	146 H	122 H	82[#]
Total bili (µmol/L)		10.0 ULN 20.8*	38.0 H ULN 21.0*	14.0 ULN 21.0*	6.84[#]
Direct bili (µmol/L)			12.0 H ULN 7.0*	7.0 ULN 7.0*	

[#] Local lab results
* Reference values not provided in Applicant-supplied narrative. Value extrapolated from ratio of patient value to reference value.

CEC Adjudication Summary: Normal baseline. Developed acute hepatitis B (hepatitis B core IgM and HbsAg both positive). Hospitalized. ALT rose to 2345 and AST 1056. Unrelated.

FDA Medical Reviewer Assessment: Agreed with the CEC's exclusion from the safety endpoint classification based on alternative hepatic pathology (acute hepatitis B) present.

Amoxicillin/clavulanate

Patient #0353 020, a 60-year-old female, with a medical history of hypertension, hyperlipidemia, and previous hepatic impairment (evidenced by elevated transaminase levels) was randomized to treatment with amoxicillin/clavulanate for treatment of AECB. Baseline hepatic testing was significant for elevated transaminases as shown in Table 10. The patient reported daily use of alcohol (2-3 glasses of wine per day) and rare use of acetominophen. Concomitant medications included Ziac, Diovan, and Xanax. The patient completed 10 days of treatment and at Visit 2 (Day 22) noted fatigue with hepatic testing revealing further mild elevation in transaminases as shown in Table 10. Hepatitis serologies and autoimmune tests were negative. The patient had an ultrasound performed on Day 33 that showed significant fatty infiltration of the liver, but was otherwise unremarkable. Hepatic testing showed some resolution of the elevation of transaminases toward the patient's previously abnormal baseline.

TABLE 10

	Analyte value/flag				
Analyte	Normal range	Baseline	Day 22	Day 23	Day 38
ALT (U/L)	6 – 34	94 H	116 H	106 H	73 H
AST (U/L)	9 – 34	50 H	54 H	51 H	32
Alk phos (U/L)	35-123	66	67	65	59
Total bili (μmol/L)		10.0 ULN 20.8*	12.0 ULN 21.1*	10.0 ULN 20.8*	10.0 ULN 20.8*
Direct bili (μmol/L)				2.0 ULN 6.9*	
* Reference values not provided in Applicant-supplied narrative. Value extrapolated from ratio of patient value to reference value.					

CEC Adjudication Summary: Abnormal baseline (ALT 94). No changes in aminotransferases over course. Ultrasound fatty liver. Unrelated.

FDA medical reviewer assessment: Agreed with the CEC.

Other HAESIs of Note

One subject in the telithromycin treatment group (Patient #0187 026), who did not meet the criteria for the CEC-adjudicated possible drug-related clinically significant hepatic injury endpoint, was diagnosed with possible autoimmune hepatitis by the investigator and treated with prednisone and will be discussed in narrative fashion below. One subject in the amoxicillin/clavulanate treatment group with cholestatic hepatitis, previously discussed in the positively adjudicated hepatic endpoint cases (Patient #2326 004), was also treated with prednisone, for a hypersensitivity-related event.

Patient #0187 026, a 60-year-old female with a history of asthma and recurrent cystitis was randomized to treatment with telithromycin for 7-10 days for AECB. Concomitant medications included Premarin, microzide Toprol XL, Allegra, Ativan, and Bactrim DS. The patient took 10 days of drug and was seen in follow-up at Visit 2 (Day 17), at which time hepatic laboratory values were similar to her normal baseline levels as shown in

Table 11. On Day 25, the patient was noted to have asymptomatic elevation of hepatic transaminases. Because of these elevations, the patient had a repeat ALT level drawn four days later which measured 245 U/L. Follow-up studies on Day 36 included a repeat hepatic profile, CBC with differential, hepatitis A, B, and C serologies, and autoimmune serologies, including ANA, AMA, and ASMA. Hepatic laboratory studies are shown below. CBC and differential results showed an absolute lymphocytosis of 3.67 GG/L, absolute eosinophilia of 0.75 GG/L, with 8.7% eosinophils. ANA was positive at 1:160 with a homogeneous pattern, with a negative anti-DNA, negative AMA, and positive ASMA. Hepatitis A IgM antibody, hepatitis B surface antigen, and hepatitis C antibody serologies were negative. On Day 33, an abdominal ultrasound was unremarkable, with no evidence of cholelithiasis, biliary duct dilatation, or focal liver lesions. Although the patient was asymptomatic, she was treated by the investigator for possible autoimmune hepatitis with prednisone at that time prior to an upcoming vacation out of her local area. Long-term (6 month) follow-up for this patient through her primary care physician indicates that she has been clinically well and has had no recurrence of abnormal hepatic laboratory tests.

TABLE 11

	Analyte value/flag					
Analyte	Normal range	Baseline	Day 17	Day 25	Day 36	Day 71
ALT (U/L)	6 – 34	21	30	113 H	347 H	30
AST (U/L)	9 - 34	22	21	85 H	183 H	21
Alk phos (U/L)	35 – 123	97	105	101	120	105
Total bili (µmol/L)		5.0 ULN 20.8*	8.5# 0.5 mg/dL	5.0 ULN 20.8*	7.0 ULN 21.2*	10.26 ULN 22.3*
Direct bili (µmol/L)						

* Reference values not provided in Applicant-supplied narrative. Value extrapolated from ratio of patient value to reference value.
# Local laboratory measurement, converted from mg/dL using conversion factor of 1 mg/dL = 17 µmol/L

CEC Adjudication Summary: Possibly related to drug (Adjudication form comments: Normal baseline. ALT rose to 347 and AST to183. Last data ALT 281 and AST 138. Hepatitis serologies negative. ANA and SMA positive. Eosinophilia developed.)

FDA Assessment: Agreed with CEC assessment. This patient was excluded from the hepatic safety endpoint determination of possible significant drug-related hepatic injury because there were no clinical symptoms associated.

HAESIs with Liver Biopsy Data

Three subjects (two in the telithromycin group and one in the amoxicillin/clavulanate group) had liver biopsies performed, presumably due to abnormalities in hepatic laboratory values noted during the course of this study. However, the timing of these biopsies, which were generally performed more than 30 days into the study, greatly

limited the amount of information they could provide in evaluating the relationship between study drug administration and occurrence of a HAESI. This was especially true given the presence of potentially confounding conditions such as cholecystitis or chronic hepatitis C infection. Narratives for these patients follow.

Telithromycin

- Patient #2004 002, was previously described with the CEC possible drug-related clinically significant hepatic events. Liver biopsy done on Day 35, at the time of laproscopic cholecystectomy, was reported by the Applicant to show cholestasis.

MO Comment: Evaluation of this biopsy for the FDA was done by Dr. David Kleiner, Chief of the Post-Mortem Pathology Section at NCI, and was found to have evidence of mild combined cholestatic and hepatocellular injury as noted earlier.

- 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 in Table 12. Visit 2 labs (Day 15) continued to be abnormal as shown in Table 12. Hepatitis A, B, and C serologies were negative. The patient underwent colonoscopy on 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 Day 40 and grossly revealed fatty infiltration of the liver, with no pathology available.

TABLE 12

	Analyte value/flag			
Analyte	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 in Applicant-supplied narrative. 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.

SERIOUS HAESI

The following patients were noted by the investigator to have serious adverse events (SAEs) that included abnormal liver function tests.

Telithromycin

Patient #0643 038, a 39-year-old female, was randomized to telithromycin 800 mg qD for 7-10 days for the treatment of AECB. The patient received two days of study medication but was discontinued due to progression of infection and failure of the drug. The patient was hospitalized for suspected sepsis and hypotension due to the primary infection. Antimicrobial therapy was initiated with clindamycin and ceftriaxone, as well as prednisone and acyclovir. Baseline liver function studies were normal as shown in Table 13. However, repeat liver function studies drawn on Day 22 (Visit 2 labs: twenty days after study drug was discontinued). These levels remained elevated at Visit 3 (Day 31), but had normalized by approximately 7 weeks post-therapy. This was a serious adverse event due to underlying illness and failure of study medication and required ICU admission due to possible airway compromise and a precaution against asphyxia.

TABLE 13

	Analyte value/flag				
Analyte	Normal range	Baseline	Day 22	Day 31	Day 52
ALT (U/L)	6 – 34	13	113 H	112 H	28
AST (U/L)	9 – 34	18	53 H	50 H	18
Alk phos (U/L)	31 – 106	50	54	54	43
Total bili (µmol/L)		7.0	10.0	7.0	
Direct bili (µmol/L)				2.0	
# Local lab results					

CEC Adjudication Summary: Normal baseline. ALT went up to 113 and AST to 53 followed by increases to ALT 153 and AST 82 with subsequent return to baseline. Hepatitis serologies negative. Probably related to drug.

FDA medical reviewer assessment: While the case represented a HAESI, the SAE reported by the investigator was for progression of the primary infection requiring hospitalization and not elevated LFT's. This patient was not considered by the CEC to meet the possible drug-related clinically significant hepatic injury endpoint most likely due to lack of associated clinical symptoms.

Patient #1310 039, a 53-year-old female, with medical history significant for chronic GERD and history of cervical cancer with hysterectomy, was randomized to telithromycin 800 mg qD for five days for treatment of acute sinusitis. Concomitant medications included Paxil, Ambien, Vioxx, Pletal, Theragran, and an antihistamine/decongestant. Baseline transaminase levels were mildly elevated as shown in Table 14. At study Visit 2 (Day 20), the patient was noted to have further elevation of ALT and also alkaline phosphatase, although she was asymptomatic. Repeat laboratories two days later demonstrated elevated values that were stable. Testing two weeks later continued to show elevation of transaminase levels, although there was a decrease from >10 x ULN to 5 x ULN. The hepatitis C serology was positive. A GI consult was done on Day 40 for chronic heartburn and indigestion along with nausea, vomiting, and upper abdominal pain, which were felt to be consistent with GERD and active alcohol ingestion (3-6 beers/day). On Day 51, upper endoscopy revealed hiatal hernia with moderate esophagitis and colonoscopy with colonic polyps. Transaminase levels had decreased to ALT 80 and AST 39. The investigator assessed the diagnosis of hepatitis C as a SAE because it was medically important.

TABLE 14

	Analyte value/flag				
Analyte	Normal range	Baseline	Day 20	Day 22	Day 35
ALT (U/L)	6 – 34	44 H	516 H	521 H	257 H
AST (U/L)	9 – 34	40 H		360 H	146 H
Alk phos (U/L)	35 - 123	92	138 H	140 H	108
Total bili (µmol/L)		5.0	15.0	9.0	10.0
Hepatitis C Antibody				Reactive	
# Local lab results					

CEC Adjudication Summary: Baseline ALT elevated to 44 and AST to 40. ALT rose to 521 then fell to 257. Hepatitis C positive. Possibly related: must consider role of hepatitis C.

FDA Medical Reviewer Assessment: Although the investigator cited the diagnosis of hepatitis C as a SAE due to its medical importance, this AE cannot be attributed to study medication. Study medication may have contributed to the level of transaminsae elevation seen, however.

Patient #1512 007, a 67-year-old female with medical history significant for cardiovascular disease and hypertension, was randomized to treatment with telithromycin 800 mg for 7-10 days for treatment of AECB. Concomitant medications included atenolol, Premarin, Zoloft, herbal medications (garlic), vitamin E, calcium supplements, and Zantac OTC. The patient completed 10 days of treatment with one missed dose. Liver function tests drawn at baseline were normal as shown in Table 15. At follow-up Visit 2 (Day 22), the patient complained of fatigue and polyuria, with laboratory studies significant for mildly elevated transaminases (shown in Table 15) and elevation of glucose (timing of blood sample in relation to last meal not noted). The patient was diagnosed with new onset non-insulin-dependent diabetes mellitus, which was noted as a serious adverse event by the investigator (medically important). On Day 32, the patient returned for follow-up of diabetes complaining of nausea and fatigue, with liver function studies done at this visit showing marked elevation in transaminase levels with an absolute eosinophilia. By Day 53, the transaminase levels had decreased, however ALT remained elevated from normal baseline levels.

TABLE 15

	Analyte value/flag					
Analyte	Normal range	Baseline	Day 22	Day 23	Day 32	Day 53
ALT (U/L)	6 - 34	10	75 H[#]	60 H	401 H	92 H[#]
AST (U/L)	15 - 37	15	69 H[#]	68 H	318 H	49 H[#]
Alk phos (U/L)	50 - 136	54		56	92	85[#]
Total bili (μmol/L)		3.0		5.0	5.0	8.6[#]
Direct bili (μmol/L)					2.0	
Glucose (mg/dL)	70 – 110		256 H[#]	92		
Eosinoophils abs (GG/L)	0.0 – 0.75				0.83 H	
[#] Local lab results						

CEC Adjudication Summary: Possible drug-induced liver injury. No alternative found.

FDA Medical Reviewer Assessment: Agree with the CEC assessment, however, the major elevation in transaminases occured quite late in relation to study drug administration (22 days after completion of therapy or study Day 32, with the ALT level at Visit 2 only 2.2x ULN which did not qualify as a HAESI). Although clinically symptomatic, with nausea and fatigue associated with the rise in transaminase levels, this patient was not considered to meet the criteria for possible drug-related clinically significant hepatic injury by the CEC.

Patient #3440 001
This patient was presented previously as an Other HAESI of Note with the presumptive diagnosis of autoimmune hepatitis by the investigator.

CEC Adjudication Summary: Possibly related to drug (Adjudication form comments: Normal baseline. ALT rose to 347 and AST to183. Last data ALT 281 and AST 138. Hepatitis serologies negative. ANA and SMA positive. Eosinophilia developed.)

FDA Assessment: Agreed with CEC assessment. Without a tissue diagnosis from a liver biopsy it is impossible to determine if this was indeed drug-induced hepatic injury or whether the patient had an underlying autoimmune disorder present that was detected at this time, although baseline LFT's did not indicate prior liver pathology. This patient was not considered by the CEC to meet the criteria for possible drug-related clinically significant hepatic injury, most likely due to the fact that she was asymptomatic.

Amoxicillin/clavulanate

Patient #0592 009, a 62-year-old female, was randomized to treatment with amoxicillin/clavulanate for ten days for acute bacterial sinusitis. The patient had elevated transaminase levels at baseline as shown in Table 16. The patient completed ten days of treatment. At Visit 2 (Day 20), the patient was noted to have marked elevations in transaminases and also elevated alkaline phosphatase as shown below, but was asymptomatic. Abdominal ultrasound was unremarkable. The patient continued to be asymptomatic and at Visit 3 (Day 35) showed resolution of transaminase levels to baseline with some resolution of alkaline phosphatase levels. The investigator assessed the elevation of LFT's to be serious as it was medically important.

TABLE 16

	Analyte value/flag					
Analyte	Normal range	Baseline	Day 20	Day 22	Day 29	Day 34
ALT (U/L)	6 - 34	89 H	535 H	413H	129 H	77 H
AST (U/L)	9 - 34	73 H	232 H	148 H	55 H	45 H
Alk phos (U/L)	35 - 123	85	267 H	342 H	257 H	158 H
Total bili (µmol/L)		10.0	15.0			9.0
Direct bili (µmol/L)						2.0
# Local lab results						

CEC Adjudication Summary: Baseline elevated ALT 89; AST 73. ALT rose to 535 and AST to 232 and peak alkaline phosphatase of 342 from baseline of 85. Hepatitis serologies negative. ALT fell to 77, bilirubin stayed normal. Probable drug-related.

FDA Medical Reviewer Assessment: Agree with the CEC. This pattern of liver function abnormalities has been reported in association with the administration of amoxicillin/clavulanate and generally resolves without any specific treatment. This patient was not considered by the CEC to meet the criteria for possible drug-related

clinically significant hepatic injury, most likely due to the fact that she was asymptomatic.

Hepatic Laboratory Analyte Elevations from Baseline to Post-Therapy

This section provides the FDA medical reviewer assessment of hepatic laboratory data obtained in Study 3014. A more comprehensive review of this data can be found in the review of Study 3014 done by George Rochester, Ph.D.

Table 17 shows ALT values obtained during the course of Study 3014 (post-therapy at Day 17-22 and late post-therapy as indicated in the table footnote below) in subjects with normal baseline hepatic function. These tests were collected in a usual care setting at various time-points in an unstructured fashion.

TABLE 17

	Post-Therapy		Late Post-Therapy	
Changes in ALT	TEL (N=7708)	AMC (N=7516)	TEL (N=664)	AMC (N=659)
≤1 x ULN	7158 (92.9%)	7044 (93.8%)	585 (88.1%)	607 (92.1%)
>1 to ≤2 x ULN	488 (6.3%)	433 (5.8%)	57 (8.6%)	42 (6.4%)
>2 to ≤3 x ULN	35 (0.5%)	22 (0.3%)	6 (0.9%)	4 (0.6%)
>3 to ≤5 x ULN	12 (0.2%)	8 (0.1%)	4 (0.6%)	3 (0.5%)
>5 to ≤ 8 x ULN	8 (0.1%)	7 (0.1%)	4 (0.6%)	0 (0.0%)
>8 x ULN	7 (0.1%)	2 (0.0%)	8 (1.2%)	3 (0.5%)

Tel = telithromycin, AMC = amoxicillin/clavulanic acid, ULN = upper limit of normal
Note: Denominator based on number of subjects with a valid assay
*Some subjects had laboratory tests conducted at visit 3 (late post-therapy, from Day 30 to approximately 6 months post-treatment) due to missing protocol-defined laboratory or as part of abnormal value follow-up.

MO Comment: There was no difference between treatment groups with regard to low level elevation of ALT. However, ALT elevations of ≥3 x ULN occurred more commonly in the telithromycin treatment group, although it is important to note the degree of transaminase elevation is not predictive of the degree of hepatocellular damage. Also, there was a higher rate of subjects with persistent elevations of ALT at the late post-therapy visit in the telithromycin treatment group.

Table 18 shows post-therapy AST values in subjects with normal baseline hepatic function.

TABLE 18

	Post-Therapy	
Changes in AST	TEL (N=7570)	AMC (N=7390)
≤1 x ULN	7264 (96.0%)	7129 (96.5%)
>1 to ≤2 x ULN	267 (3.5%)	227 (3.1%)
>2 to ≤ 3 x ULN	19 (0.3%)	20 (0.3%)
>3 to ≤5 x ULN	10 (0.1%)	12 (0.2%)
>5 to ≤ 8 x ULN	5 (0.1%)	1 (0.0%)
>8 x ULN	5 (0.1%)	1 (0.0%)
Tel = telithromycin, AMC = amoxicillin/clavulanic acid, ULN = upper limit of normal Note: Denominator based on number of subjects with a valid assay		

MO Comment: The AST changes mirror those for ALT, with a higher incidence of AST elevations >5 x ULN in the telithromycin treatment group.

Table 19 shows the frequency of post-treatment ALT elevations in telithromycin-treated subjects with normal baseline LFTs according to the duration of exposure to the drug.

TABLE 19

	Post-Therapy	
Changes in ALT	TEL 7-10 Days (N=3024)	TEL 5 days (N=4684)
≤ 1 x ULN	2779 (91.9%)	4379 (93.5%)
>1 to ≤2 x ULN	210 (6.9%)	278 (5.9%)
>2 to ≤3 x ULN	19 (0.6%)	16 (0.3%)
>3 to ≤ 5 x ULN	7 (0.2%)	5 (0.1%)
>5 to ≤ 8 x ULN	4 (0.1%)	4 (0.1%)
>8 x ULN	5 (0.2%)	2 (0.0%)
Tel = telithromycin, AMC = amoxicillin/clavulanic acid, ULN = upper limit of normal Note: Denominator based on number of subjects with a valid assay		

MO Comment: There was a trend toward a higher level of ALT elevation (ALT >3 X ULN) with increasing duration of telithromycin exposure.

Table 20 shows the frequency of elevations in hepatic analytes at post-therapy and late post-therapy, irrespective of baseline hepatic analyte values.

TABLE 20

	Post-therapy		Late follow-up	
Analyte Status	TEL n/N (%)	AMC n/N (%)	TEL n/N (%)	AMC n/N (%)
ALT >3 x ULN	94/10661 (0.9)	81/10359 (0.8)	47/1087 (4.3)	28/1122 (2.5)
AST >3 x ULN	48/10450 (0.5)	45/10159 (0.4)	30/1070 (2.8)	17/1097 (1.5)
Total bilirubin >3 x ULN	2/10039 (0.0)	2/9784 (0.0)	1/1027 (0.1)	0/1033 (0.0)
ALT ≥3 x ULN and total bilirubin ≥1.5 x ULN	3/9991 (0.0)	5/9723 (0.0)	0/1026 (0.0)	2/1027 (0.2)
Alkaline phos. ≥3 x ULN	4/10809 (0.0)	1/10535 (0.0)	0/1094 (0.0)	1/1126 (0.1)
Tel = telithromycin, AMC = amoxicillin/clavulanic acid, ULN = upper limit of normal Note: Denominator based on number of subjects with a valid assay				

As noted in the CDER-PHRMA-AASLD Conference 2000 Clinical White Paper, the combination of pure hepatocellular injury (transaminase elevation without significant ALK elevation) and jaundice is of concern, since hepatocellular injury severe enough to interfere with bilirubin excretion must involve a large fraction of the liver cell mass.[2] As noted, this combination has frequently been predictive of serious liver injury leading to death or requiring transplant. Therefore, subjects with laboratory elevation of the transaminases and total bilirubin in the absence of alkaline phosphatase elevation were scrutinized. Three subjects in the telithromycin treatment group were noted to have ALT ≥3 x ULN and total bilirubin ≥1.5 ULN versus five subjects in the amoxicillin/clavulanate treatment group at post-therapy. The three subjects in the telithromycin group had concomitant elevations in alkaline phosphatase; subject #2004 002 had gallstones, subject #3440 001 had a presumptive diagnosis of autoimmune hepatitis by the investigator, and subject #3146 003 had acute hepatitis B. Three out of the five subjects in the amoxicillin/clavulanate group had concomitant elevations in alkaline phosphatase (subjects #0050 015, #0211 104, and #0627 004) with all subjects recovering near to pretherapy/entry values (< 2x ULN). The other two amoxicillin/clavulanate-treated subjects did not have associated elevations in alkaline phosphatase; however, subject #1129 179 had a history of hepatitis C and subject #1564 004 had a history of substantial alcohol use and daily consumption of ibuprofen. Additionally, at late post-therapy two amoxicillin/clavulanate subjects (subjects #0194 060 and #2326 004) met this criterion with no subjects noted in the telithromycin group. Both of these subjects, however, had simultaneous elevations in alkaline phosphatase levels and had resolution of abnormalities at extended follow-up within the six-month study period.

MO Comment: The following summary shows the degree of elevation of each hepatic parameter for those patients with ALT ≥3 x ULN and total bilirubin ≥1.5 x ULN noted above, as well as the most likely reason for these elevations.

[2] www.fda.gov/cder/livertox/clinical.pdf

Post-Therapy

Telithromycin:
#2004 002: Cholecystitis and cholestasis, Day 23
ALT 270 (8 x ULN), AST 162 (5 x ULN), ALK 461 (3.0 x ULN), Tbili 104 (5 x ULN)
#3146 003: Acute hepatitis B, Day 19
ALT 2345 (69 x ULN), AST 1056 (31 x ULN), ALK 146 (1.38 x ULN), Tbili 38.0 (1.8 x ULN)
#3440 001: Drug-related (study vs pravistatin) or passed gallstone, Day 18
ALT 969 (15 x ULN), AST 1357 (37 x ULN), ALK 285 (2.1 x ULN), Tbili 30.78 (1.8 x ULN)

Amoxicillin/Clavulanate:
#0050 015: Metastatic adenocarcinoma, Day 18
ALT 211 (5 x ULN), AST 151 (4 x ULN), ALK 197 (1.6 x ULN), T bili 44.8 (2.6 x ULN)
#0211 104: Probable alcoholic hepatitis, Day 28
ALT 220 (5 x ULN), AST 270 (8 x ULN), ALK 246 (1.9 x ULN), Tbili 31.0 (1.48 x ULN)
#0627 004: Probable drug-induced injury, Day 19
ALT 234 (5 x ULN), AST 95 (3 x ULN), ALK 146 (1.1 x ULN), Tbili 32 (1.52 x ULN)
#1129 179: History of hepatitis C, Day 21
ALT 129 (4 x ULN), AST 214 (6 x ULN), ALK 98 (0.92 x ULN), Tbili 32 (1.52 x ULN)
#1564 004: Extensive alcohol history, Day 18
ALT 131 (3 x ULN), AST 71 (2 x ULN), ALK 55 (0.43 x ULN), Tbili 32 (1.52 x ULN)

Late Post-Therapy

Amoxicillin/Clavulanate:
#0194 060: Late onset symptomatic hepatitis, inv assoc amox/clav, Day 43
ALT 227 (5 x ULN), AST 108 (3 x ULN), ALK 303 (2.4 x ULN), Tbili 44 (2.1 x ULN)
#2326 004: Cholestatic hepatitis, Day 28
ALT 571 (10 x ULN), AST 348 (8 x ULN), ALK 182 (1.5 x ULN), Tbili87.2 (5.1 x ULN)

This summary indicates that patient #0627 004 in the amoxicillin/clavulanate treatment group had minimal elevation in alkaline phosphatase and therefore seems to satisfy the criteria for serious hepatic damage.

Labeling Recommendations

The following excerpts regarding hepatotoxicity are taken from the Sponsor's proposed labeling contained within the amendment to NDA 21-144.

ADVERSE REACTIONS

Liver and biliary system: increased liver enzymes (ALT, AST), abnormal liver function tests, abnormal hepatic function, increased transaminases. In clinical

trials, observed liver enzyme elevations were generally asymptomatic and returned to baseline or near baseline levels with discontinuation of telithromycin. Rates of transaminase increases to 3 x ULN were similar to those seen with comparators. Clinically overt or symptomatic hepatic injury was uncommon.

MO Comment: The comparator agent in Study 3014, Augmentin®, has specific labeling regarding potential for hepatotoxicity in both the WARNINGS and ADVERSE REACTIONS section of the label. However, information in the WARNINGS section recommends caution in treatment of patients with hepatic dysfunction and rarely, reports of death. At this point in time, however, the data available from Phase 3 studies and Study 3014 for telithromycin indicate that the statements listed in the Applicant's proposed label are reflective of the known hepatic events associated with telithromycin. Study 3014 demonstrated similar findings for patients with hepatic impairment (predominantly hepatitis) and without a history of hepatic impairment. It may be reasonable to include incidence rates of transaminase elevations noted in — and Phase 3 studies.

Study 3014 – Hepatic Adverse Events Conclusions

1. Study 3014 was designed primarily to capture safety data, in particular adverse events of special interest including hepatic, in a large number of patients many of whom were at increased risk of having adverse events. Issues in study design and conduct limit the strength of the conclusions that can be drawn. These include:

- Lack of a standardized laboratory protocol for follow-up of hepatic adverse events of special interest (AESIs), leading to inconsistent testing of patients with these events.

- Delays in CEC assessment of hepatic AESIs, hindering the CEC's ability to request additional testing (for example, liver biopsy).

- Ambiguity in the criteria used by the hepatic CEC to adjudicate the hepatic safety endpoint of possible drug-related clinically significant hepatic injury, without consistent documentation of these criteria.

- Findings of significant GCP violations at study sites inspected by the Division of Scientific Investigations (see medical team leader memorandum by Dr. David Ross).

2. The distribution of subjects with HAESIs was balanced between treatment groups (0.91% for telithromycin versus 0.82% for amoxicillin/clavulanate). Possible drug-related HAESIs were distributed similarly, with the FDA review showing 80 events

occurring in the telithromycin group (0.66% of 12159 safety evaluable patients,) and 63 events occurring in the amoxicillin/clavulanate group (0.53% of 11978 safety evaluable patients). In the 39 subjects with clinically symptomatic HAESIs, possible relationship to study drug was noted in 15/20 (75%) of the telithromycin treatment group and in 11/19 (55%) amoxicillin/clavulanate treatment group as determined by the FDA medical reviewer. The symptoms noted most commonly were fatigue and nausea.

3. There were six events assessed by the FDA medical reviewer that represented possible drug-related clinically significant hepatic events, with four in the telithromycin-treated group and two in the amoxicillin/clavulanate-treated group. However, all four of the possible drug-related clinically significant hepatic events in the telithromycin group were confounded by other factors such as alternative medical diagnoses (pyelonephritis and chronic cholecystitis) or other medications (pravistatin and levofloxacin). There were no cases of hepatic failure or death related to hepatic causes in the telithromycin treatment group.

4. Two subjects, one in each treatment group, were treated by investigators with prednisone for drug-related hepatotoxicity. The diagnoses given to these patients by the local investigator were possible autoimmune hepatitis in the telithromycin-treated patient and cholestasis in the amoxicillin/clavulanate-treated patient. The case of possible autoimmune hepatitis in a telithromycin-treated patient was not captured by the CEC definition for clinically significant hepatic injury due to lack of clinical symptoms. This patient is of concern since the possibility exists that the autoimmune phenomenon resulted from drug administration, but without a histopathologic diagnosis, this cannot be established. Of note, a telithromycin-treated patient described in the original NDA had evidence of drug-induced hepatitis, with a subsequent biopsy nine months later showing chronic hepatitis consistent with autoimmune hepatitis.

5. There was no apparent difference in the incidence of low-level elevation of ALT in either treatment group, although there was a tendency for higher elevations of ALT to be noted in the telithromycin group, with an increased incidence of persistence of ALT elevation noted at the late post-therapy visit.

6. Three subjects in the amoxicillin/clavulanate treatment group had elevation of ALT to $\geq$3 x ULN and total bilirubin $\geq$1.5 x ULN in the absence of elevation of ALK. Two of these subjects had alternate explanations for these abnormalities based on pre-existing disorders (hepatitis C, alcohol use history), however, the third patient had possible drug-related hepatic injury. There were no subjects with these parameters observed in the telithromycin treatment group.

7. Longer exposure (7-10 days versus 5 days) to telithromycin was also associated with a higher incidence of higher levels of ALT elevation (>3 x ULN).

8. Information from Study 3014 and the integrated safety database from all telithromycin clinical studies does not address the potential for hepatotoxicity in patients receiving longer courses of therapy (Phase III studies used a maximum treatment duration of 10 days) or repeated short course therapy. Both of these practices are common in the community.

Appendix A: CRF Hepatic Events of Interest Form

HMR3647A/3014 Site number | Subject number | Subject initials | AE number **Hepatic**

Events of Interest Evaluation Form

A. Clinical investigation for _____
(Diagnosis/syndrome of AE)

1. **Associated signs/symptoms:** ☐ *tick if "none"*
   1☐ fatigue 4☐ jaundice 5☐ rash or pruritis 7☐ dark urine
   2☐ nausea 3☐ fever 6☐ abdominal *(right upper quadrant abdominal pain)*
   Did symptoms begin more than 5 days after starting therapy? N☐ No Y☐ Yes
2. **Specify if any history of the following:** *(tick all that apply and quantify amount)*
   1☐ alcohol use _____ 4☐ Herbal _____
   2☐ acetaminophen use _____ 5☐ Homeopathic _____
   3☐ corticosteroid use _____ 6☐ over-the-counter drug use _____
3. **Specify if patient has any history of viral hepatitis, other liver disease, or abnormal liver tests** N☐ No Y☐ Yes
   (If YES, please obtain results.)
4. **Specify if patient has any contacts with similar symptoms in the same time period.** N☐ No Y☐ Yes
5. **Specify if patient does have evidence of uncontrolled heart failure at the time of the event.** N☐ No Y☐ Yes
6. **Specify if patient has a history of cancer.** N☐ No Y☐ Yes
   Known metastases? N☐ No Y☐ Yes
7. **Has there been any suspected sepsis or hypotension associated with the underlying infection?** N☐ No Y☐ Yes
8. **Is there a clinical suspicion of acute gallstones?** N☐ No Y☐ Yes

B. Procedures/Laboratory evaluations:

Please perform and provide results (lab reports) for the following:

1☐ transaminases, alkaline phosphatase and bilirubin *(total and fractionated)*
2☐ hepatitis A, B, and C titers
3☐ white blood cell count with differential
4☐ prothrombin time

If any of the following labs were performed, please provide results:

5☐ autoimmune tests *(ANA, anti-mitochondrial, anti-smoother muscle antibodies, anti-DNA antibodies)*
6☐ ultrasound or CT scan
7☐ liver biopsy

C. Comments: _____

Date subject evaluated: ___/___/___
(dd) (mmm) (yyyy)

* ***Please fax this form along with AE CRF page and/or SAE/ER form (as appropriate) to PPD at 1-888-529-3580 within 24 hours if a serious adverse event, otherwise within 5 days.***

hepatic events- 06/2001

Appendix B: CEC Hepatic Adjudication Form

HMR3647A/3014 Site number | Subject number | Subject initials | AE number — **Events of Interest Adjudication Form**

Final Judgement

Reported adverse event of interest *(as described by investigator)* _____

[1] **Has sufficient case information been provided?** ..... N☐ No* Y☐ Yes

If NO, indicate reason:* ☐ Lab data lacking ☐ Clinical information lacking** ☐ Other**

***Specify required information:* _____

_____

[2] **Does this case represent one of the defined events of interest?** ..... N☐ No* Y☐ Yes

**If NO, provide explanation:* _____

[3] **Does this case report represent one of the confirmed below** *(as defined in the CEC manual)?* N☐ No Y☐ Yes*

**(answer only one)*

☐ Clinically overt significant hepatic injury
☐ A likely malignant ventricular arrhythmia
☐ Blurred vision
☐ Vasculitis

[4] **Has a compatible temporal relationship been established?** ..... N☐ No* Y☐ Yes

**If NO, provide reason for why relationship cannot be established:*

**(answer only one)*

☐ Event onset prior to study drug administration
☐ Delayed time to onset excludes study drug as cause
☐ ALT recovery outside of specified period *(hepatic only)*
☐ Other *(specify in section 7)*

[5] **Have compelling alternative explanations been excluded?** ..... N☐ No* Y☐ Yes

**If NO, indicate the likely alternative explanation for the event:*

**(Please mark only one category and one diagnosis within the selected category)*

☐ **Hepatic**		☐ **Cardiac**
☐ acute viral hepatitis	☐ Acute gallstones	☐ Acute myocardial infarction within 7 days of the event
☐ acute alcohol ingestion	☐ malignant neoplasm	☐ Hypokalemia
☐ Decompensated heart failure		☐ Hypomagnesemia
☐ Other well defined hepatic processes*		☐ Other active underlying cardiac disease*
☐ **Visual**		☐ **Vasculitis**
☐ Other ophthalmologic disease as a likely explanation*		☐ Other active disorder as a likely explanation*

**specify in section 7*

[6] **Has the safety endpoint been confirmed** *(i.e., responses 1-5 answered 'yes')?* ..... N☐ No Y☐ Yes

[7] **If there are additional comments, please provide below:**

_____

_____

_____

Chairman signature: _____ **Date:** ___/___/2000 (dd) (mmm) (yyyy)

finaljudgement- 11/30/01

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

/s/

Janice Pohlman
2/28/03 03:52:25 PM
MEDICAL OFFICER

David Ross
2/28/03 04:12:08 PM
MEDICAL OFFICER

Janice Soreth
3/3/03 03:27:12 PM
MEDICAL OFFICER

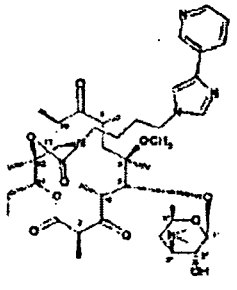
Medical Officer's Review of the Hepatic Effects of Ketek (Telithromycin) NDA 21-144

Identifying information

Aventis Pharmaceuticals Inc. (Applicant)
399 Interpace Parkway
P.O. Box 663
Parsippany, NJ 07504

Submission/review dates
Date of submission: February 28, 2000
CDER stamp date: March 1, 2000
Date review begun: November 13, 2000
Date of submission for the Major Clinical Amendment: February 28, 2001
Date review completed: May 18, 2001

Drug Identification
Generic name: telithromycin
Proposed trade name: Ketek
Other names used during development: HMR 3647
Chemical name: 11,12-dideoxy-3-de [(2,6-dideoxy-3-C-methyl-3-O-methyl-alpha-L-ribo-hexopyranosyl) oxy]6-O-methyl-3-oxo-12, 11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-H-imidazol-1-yl]butyl]imino]]erythromycin
Chemical Structure:



Molecular Formula: $C_{43}H_{65}N_5O_{10}$ Molecular weight: 812.30
Pharmacologic category: ketolide antimicrobial agent
Dosage form: tablet Strength: 400 mg
Route of administration: oral

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Telithromycin - Hepatic Effects

Executive Summary

In preclinical studies in rats, dogs, and monkeys, the main site for organ toxicity for telithromycin was the liver with the kidney as a second target organ. Electron microscopic examination of selected tissues (hepatocytes, bile duct epithelium, and renal epithelium) found that telithromycin was stored in lysosomes. Telithromycin is primarily metabolized by the liver by cytochrome P450 3A4 (CYP 3A4) and to a lesser extent by cytochrome P450 1A.

In phase I studies, several telithromycin treated patients experienced hepatic adverse events. There was a clustering of events (elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST)) in elderly subjects receiving a single 2000 mg dose of telithromycin (the highest dose received by elderly subjects). The elevations occurred between 7 to 17 days after the last dose of telithromycin. All three of these elderly patients had negative serologic evaluations for Hepatitis A, B, and C. These patients also underwent serologic testing at the time of the event for cytomegalovirus (CMV), Epstein-Barr virus (EBV), Herpes Simplex virus (HSV), and toxoplasmosis. One of the subjects had a serology that was positive for CMV IgG and IgM and another of the three had a serology positive for EBV IgG and IgM. However, consideration of all of the serologic information in the patient group in which these events are occurring does not provide convincing evidence that these events are due to either CMV or EBV. The possibility remains that these may be drug-related events with a one to two week latency period. In the single dose studies of 2400 mg in young subjects, no hepatic adverse events were reported. There was one hepatic adverse event in the single dose studies of young subjects receiving 3200 mg. In the highest doses studied in multiple dose studies of telithromycin (1600 mg qd and 1200 mg po qd), no hepatic adverse events were noted. In examining these results it is important to consider that the design of the phase I studies may limit the degree to which such studies can be expected to provide evidence of drug-induced hepatic toxicity.

In the comparative phase III clinical studies, the proportion of subjects experiencing hepatic adverse events was similar between telithromycin and its comparators. This is true for both "all Treatment Emergent Adverse Events (TEAEs)"* and for "possibly-related TEAEs". In the non-comparative studies of telithromycin, hepatic TEAEs were reported more frequently than in the comparative studies. This was largely the result of a marked increase in the proportion of subjects in the non-comparative CAP Study 3000 reporting hepatic TEAEs. The absence of a comparator group in these studies limits the extent to which any conclusions regarding causality can be made. In the comparative studies, the proportion of subjects discontinuing study medication because of hepatic

* TEAE is a Treatment Emergent Adverse Event defined as any on-treatment adverse event that was not present before treatment and became more intense (increased in severity) or frequent during the treatment period as determined by the investigators. The treatment period encompassed the period from the first day of study medication to 7 days (or three days for clinical pharmacology trials) after the last day of study medication.