diagnosis of myasthenia gravis. In most of these cases, it does not appear that a diagnosis of myasthenia gravis was considered. There was one patient (200311799EU) who experienced severe bilateral ptosis after the first dose of telithromycin. The report states that "tests for botulism and myasthenia gravis were negative." It does not state exactly what tests were done to evaluate for myasthenia gravis. Since 10-20% of patients with myasthenia gravis have a negative result on the most common diagnostic test (anti-ACh antibodies), it is still possible that this patient actually had underlying myasthenia gravis which remained undiagnosed. No such testing was reported for the other 5 patients.

Table 8 shows all symptoms for patients who were likely or possibly experienced a telithromycin-associated myasthenic exacerbation.

Table 8. Myasthenic Symptoms in Patients with Likely and Possible Telithromycin-associated Myasthenic Exacerbation †

Symptoms	Likely Teli-Assoc (N=13 patients)	Possibly Teli-Assoc (N=6 patients)	Total
Respiratory Arrest	6*	0	6
Muscle Weakness/ Fatigue	4	3	7
Dysarthria	4	0	4
Deglutition Disorder	2	0	2
Ptosis	2	2	4
Dyspnea	1	0	1
Dysphagia	1	1	2
Diplopia	1	2	3

* Patient 200211064EU died as a result of respiratory arrest.
† Patients may have had more than one symptom.

Medical Officer Summary:
Post-marketing data has identified a group of patients who experienced severe worsening of myasthenic symptoms after exposure to telithromycin. Several of these patients required intubation and one died. Based on this information, it is reasonable to recommend that patients with myasthenia gravis be warned of the potential for exacerbations with administration of Ketek.

Visual Adverse Events Associated with Telithromycin – Integrated Overview

Early during Phase 1 development of telithromycin, there were subjects who complained of visual adverse events associated with ingestion of telithromycin. During controlled Phase 3 clinical trials, a higher incidence of visual adverse events was observed in telithromycin-treated patients vs. comparator-treated patients. Visual adverse events from phase 1 studies, Phase 3 studies, and post-marketing adverse events are consistent with a disorder of accommodation as the primary disturbance. Drug-associated disturbance of visual accommodation is not common and has not been described before with antibiotics. Therefore, a detailed attempt was made to understand and characterize this adverse event. This section includes a review of analyses of telithromycin-associated visual events.

Available data used to characterize the visual adverse events associated with telithromycin exposure are derived from the following sources: Phase 1 studies, controlled Phase 3 studies, uncontrolled Phase 3 studies, study 3014, study 5001 (intensive monitoring post-marketing data), and spontaneous post-marketing data.

Phase 1 Studies

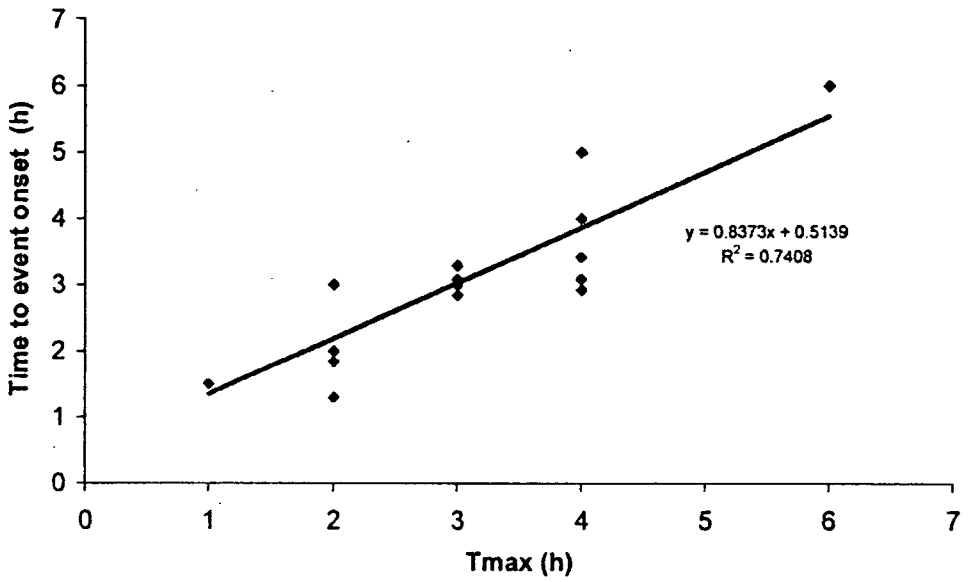
Data from Phase 1 studies suggested that the incidence of telithromycin-associated visual adverse events was related to total dose. **Table 9** shows that the overall incidence of visual adverse events increased with increasing dose. Visual adverse events were seen to occur at an incidence of 41.7% when subjects received a 3,200 mg dose of telithromycin (4 times the dosage used in Phase 3 clinical trials).

Table 9. Number (%) of subjects with visual treatment-emergent adverse events in Phase I Studies 1008, 1030, 1032, 1046, 1049, 1059, 1064: Pooled visual MedDRA term equivalent population								
	Placebo	Telithromycin (mg)						
	N=138	400 N=18	800 N=88	1200 N=14	1600 N=80	2000 N=16	2400 N=101	3200 N=24
Visual TEAEs[1]	1 (0.7%)	-	-	-	9 (11.3%)	4 (25%)	26 (25.7%)	10 (41.7%)
Blurred vision	1 (0.7)	-	-	-	7 (8.8)	3	22 (21.8)	4 (16.7)
Abnormality of accommodation	-	-	-	-	-	0	4 (4.0)	3 (12.5)
Diplopia	-	-	-	-	2 (2.5)	0	1 (1.0)	-
Eye disorder	-	-	-	-	-	1	1 (1.0)	2 (8.3)
Abnormal vision	-	-	-	-	-	0	-	1 (4.2)

Studies 1059 and 1064 attempted to further evaluate occurrence of visual adverse events. Study 1059 was a randomized, double blind, placebo-controlled, three-way, crossover study in which telithromycin at either 800 mg or 2400 mg, or placebo, was administered as a single dose to 15 younger patients (aged 18-40 years) and 15 older patients (aged 50-64 years). Ophthalmic examinations, plasma concentrations, and tear fluid concentrations were performed. Study 1064 was a randomized, double blind, 2-way, crossover study in which either telithromycin at 2400 mg or placebo was administered as a single dose, and plasma concentration and ophthalmic examinations performed. Twenty-four subjects aged 19 to 64 years were enrolled and treated.

Of the combined study patients receiving 2400 mg of telithromycin (N=22), there were 9 who experienced a visual adverse event. Attempts to correlate onset of visual adverse events with plasma concentrations revealed that the time to onset of the visual adverse event was more closely related to Tmax than Cmax. Figure 1 shows this observation.

Figure 1 - Relationship between Tmax and time to onset of visual TEAE



Medical Officer Comment: Amongst a group of subjects who all ingested the same amount of telithromycin (2400 mg), there appeared to be a relationship between onset of visual adverse events and Tmax (time to maximum concentration) but not Cmax (maximum concentration). In individual subjects who experience telithromycin-associated visual adverse events, time to onset of the events correlates with time to maximum concentration of drug.

Incidence of Telithromycin-associated Visual Adverse Events

The overall incidence of telithromycin-associated visual adverse events varied according to the source data from which the incidence was calculated. In general, the incidence of visual adverse events increased as the level of follow-up increased. For instance, the incidence was highest in controlled Phase 3 studies where the level of patient follow up was highest. By contrast, the post-marketing data, which was collected in a passive manner, had the lowest incidence of visual adverse events. **Table 10** lists the incidences of telithromycin-associated visual adverse events according to source data.

Table 10. Rates of Telithromycin-associated Visual Adverse Events According to Data Source

Data Source	Type of Data	Incidence of Patients with Telithromycin-associated Visual Adverse Events (%)
Phase 3	Controlled Studies	30/2072 (1.1%)
Study 3014	Safety study	88/12,159 (0.72%)
Phase 3	Uncontrolled Studies	7/1770 (0.4%)
Study 5001	Intensive Monitoring Post-marketing study	60/ 29,439 (0.2%)
Post-marketing	Spontaneous passive post-marketing data	316/ [redacted]

Medical Officer Comment:
It is likely that incidence of telithromycin-related visual adverse events seen in the Phase 3 controlled studies most closely represents the actual incidence, because the Phase 3 studies were blinded and employed the closest observation of study subjects. It is a common finding that, among a group of studies, the incidence of adverse events declines among studies as the thoroughness of patient follow-up declines. Confirmation of this can be found by comparing the incidences in the data sources of all adverse events (grouped). The pattern closely resembles the pattern seen for the visual adverse events. For controlled Phase 3 studies, the rate of <u>any</u> adverse event was 49.9% (1,348/2,702) while the rate for uncontrolled Phase 3 studies was 35.1% (622/1,770), the rate for Study 3014 was 23.1% (2807/12,159), the rate for Study 5001 was 4.1% (1,204/29,439), and the rate for the post-marketing data was [redacted]. It is interesting to note that while Study 3014 had 35.2% less overall adverse event reporting than did the uncontrolled Phase 3 telithromycin-treated patients, it still had 80% more telithromycin-associated visual adverse events than was seen in the uncontrolled phase 3 data. When attempting to describe the true incidence of adverse events, it is not appropriate to combine data which have been collected in different ways. This may result in an underestimation of the incidence of specific adverse events. For example, adverse event data collected from controlled Phase 3 studies should not be combined with adverse event

data collected from uncontrolled studies or post-marketing studies. In addition, it is important to present data from controlled Phase 3 studies separately because this provides clinically useful information to the treating physician by providing a context which, in this case, would be the incidence of visual adverse events in the study drug as compared to the control-treated patients.

Visual Adverse events According to Age

Table 11 shows visual adverse events by age in controlled and uncontrolled Phase 3 data. For both controlled and uncontrolled Phase 3 data, the majority of patients experiencing visual adverse events were under 40 years of age.

Table 11 – Number (%) of subjects with visual TEAE by age group in Phase III studies: Pooled visual MedDRA term population

	Controlled studies		Uncontrolled	Total
Age group (years)	Telithromycin	Comparator	Telithromycin	Telithromycin
	N=2702	N=2139	N=1770	N=4472
<20	1/146 (0.7)	1/140 (0.7)	0/102 (0)	1/248 (0.4)
>20 - <30	14/503 (2.8)	1/355 (0.3)	3/322 (0.9)	17/825 (2.1)
>30 - < 40	6/596 (1.0)	0/456 (0)	3/411 (0.7)	9/1007 (0.9)
>40 – < 50	5/493 (1.0)	3/358 (0.8)	1/343 (0.3)	6/836 (0.7)
>50 – < 60	1/402 (0.2)	0/300 (0)	0/314 (0)	1/716 (0.1)
>60 – <70	1/336 (0.3)	2/265 (0.8)	0/166 (0)	1/502 (0.2)
>70	2/226 (0.9)	0/265 (0)	0/112 (0)	2/338 (0.6)

Source: Table T-1, pg. 00254

Medical Officer Comment:
Because the primary mechanism of telithromycin-associated visual adverse events is thought to be one of a disturbance of accommodation, it is not surprising that the majority of patients experiencing this type of event are below the age of 40 years old. This is because after the age of 40, a person's loss of the ability to accommodate (which occurs gradually throughout life) exceeds their reserve. Thus, people's ability to accommodate declines after the age of 40. For people over the age of 40 years old who have begin to lose or have already lost the ability to accommodate, it can be expected that their incidence of telithromycin-associated visual adverse events will be lower.

Table 12 shows the age ranges for patients experiencing telithromycin-associated visual adverse events according to data source.

Table 12. Visual Adverse Event Rates According to Age and Data Source						
Age (years)	Phase 1†	Contr. Phase 3	Uncontr. Phase 3	Study 3014	Study 5001	Post-marketing data
Total	28.1% (9/32)	1.1% (30/2702)	0.4% (7/1770)	0.72% (88/12,152)	0.2% 60/29,439	316/
≤ 40	31.3% (5/16)	1.7% (21/1245)	0.72 % (6/835)	0.76% (29/3823)	0.33% (39/11790)	(180/
> 40	25% (4/16)	0.62% (9/1457)	0.12% (1/935)	0.7% (59/8329)	0.12% (20/17368)	(106/
Age Unknown (number)	0	0	0	0	1	30

* calculated as a percentage of overall exposure since demographics of exposed population not known

† Studies 1059 and 1064; patients received 800mg or 2,400 mg (or three times the standard dose)

Medical Officer Comment:

The data in **Table 12** above confirm that in multiple data sources telithromycin-associated visual adverse events occur at a higher rate in patients under age 40. This age related finding is plausible and expected since patients under the age of 40 have a greater ability to accommodate and therefore, are more likely to experience disturbances in accommodation. Only the data from Study 3014 is inconsistent with this finding.

Visual Adverse Events by Gender

In phase 1 and 3 clinical trials, Study 3014, as well as post-marketing data, there is larger percentage of females who experienced visual adverse events than males as is seen in **Table 13**.

Table 13. Percentage of Visual Adverse Events by Gender				
Gender	Phase 1†	Contr. Phase 3	Uncontr. Phase 3	Study 3014
Total	18.8% (6/32)	1.1% (30/2702)	0.4% (7/1770)	0.73% (89/12,159)
Female	33.3% (6/18)	1.5% (21/1385)	0.63% 5/791	1.0% (72/7453)
Male	21.4% (3/14)	0.68% 9/1317	0.2% 2/979	0.36% (17/4776)

† Studies 1059 and 1064; patients received 800mg or 2,400 mg (or three times the standard dose)
* Intensive monitoring post-marketing study
** Gender knot known for 28 patients

For the post-marketing data (spontaneously reported and from the German intensive monitoring study, demographic data are not available to perform this analysis. However, as is seen in **Table 14**, there were larger overall numbers of females with reported telithromycin-associated visual adverse events.

Table 14. Visual Adverse Events by Gender in Post-marketing Data		
Gender	**Study 5001***	**Post-marketing data****
Total	0.2% (60/29,439)	(316/
Female	46	206
Male	14	82

* German intensive monitoring post-marketing data
** Gender not known for 28 patients

Medical Officer Comment: There is no reason to suspect that significantly more Ketek prescriptions were written for females than for males. Thus, it is reasonable to assume

that the difference seen by gender in the post-marketing data is supportive of the gender difference that was seen with the Phase 1 and Phase 3 data.

Telithromycin-Associated Visual Adverse Events by Age and Gender

Since the data suggest that telithromycin-associated visual adverse events occur more frequently in females and in people under 40 years old, it is of interest to know what the observed incidence of visual adverse events was by gender and age. **Table 15** shows this.

Table 15. Incidence and Relative Risk of Visual Adverse Events According to Gender and Age

Gender	Uncontr. Phase 3	Contr. Phase 3	Contr. Phase 3 Comparators	Relative Risk of Visual AE's in Contr. Phase 3 Studies
Total	0.4% (7/1770)	1.1% (30/2702)	0.28% (6/2139)	3.9
Female (total)	0.63% (7/791)	1.5% (21/1385)	0.18% (2/1096)	8.3
Female ≤40	1.3% (5/373)	2.1% (14/682)	0.0% (0/524)	22.1*
Female >40	0.0% (0/418)	1.0% (7/703)	0.35% (2/572)	2.9
Male (total)	0.2% (2/979)	0.68% (9/1317)	0.38% (4/1043)	1.8
Male ≤40	0.2% (1/462)	1.2% (7/563)	0.48% (2/416)	2.5
Male >40	0.19% (1/517)	0.27% (2/754)	0.33% (2/627)	0.84

* RR calculated using exact method

Medical Officer Comment: This analysis of visual adverse events by age and gender indicates that in controlled phase 3 data, the increased risk of telithromycin-associated visual adverse events in the following populations (ordered highest to lowest risk): females ≤40 (RR 22.1), females > 40 (RR 2.9), males ≤ 40 (RR 2.5), males>40 yo (RR 0.84). In phase 3 controlled clinical trials, the greatest difference between telithromycin- and comparator-treated patients was seen in females ≤ 40 years of age. There did not appear to be a difference between telithromycin- and comparator-treated patients in visual adverse events in males over 40 years of age.

The same analysis by age and gender, when performed on data from 3014, produced results which are not consistent with what was seen in all other data. **Table 16** shows the results of this analysis for data from Study 3014.

Table 16. Incidence of Telithromycin-associated Visual AEs by Age and Gender in Study 3014	
Gender	Study 3014 Telithromycin
Total	0.73% (89/12,159)
Female (total)	1.0% (72/7453)
Female ≤ 40 yo	0.98% (24/2440)
Female > 40 yo	0.96% (48/5013)
Male (total)	0.36% (17/4776)
Male ≤ 40 yo	0.5% (7/1,405)
Male > 40 yo	0.3% (10/3,371)

Medical Officer Comment: This analysis shows no difference in Study 3014 between women over 40 years old and women under 40 years old in terms of incidence of telithromycin-associated visual adverse events. Study 3014 was the only data source not to show a difference in overall incidence of visual adverse events by age category (over 40 y.o. vs. under 40 y.o.). This finding not only disagrees with all other data but it also is inconsistent with the known mechanism of telithromycin-associated visual adverse events. Since the visual adverse event associated with disturbance of accommodation, and since patients over the age of 40 years of age do not have the ability to accommodate to the same degree as do those under the age of 40 years of age, it is understandable that all other data show an increase in the rate of telithromycin-associated visual adverse events for people 40 years old and younger.

Visual Adverse Events by Severity and Serious Criteria

Severity of visual adverse events in Phase 3 clinical trials and Study 3014 are included in **Table 17**.

Table 17. Number (%) of subjects with visual TEAEs by intensity in Phase III studies and Study 3014: Pooled visual MedDRA term population

	Controlled studies		Uncontr	Total	Study 3014	
Intensity	Teli	Comparator	Teli	Teli	Teli	Amox/Clav
	N=2702	N=2139	N=1770	N=4472	N=12,159	N=11,978
All pooled visual TEAEs	30 (1.1)	7 (0.3)	7 (0.4)	37 (0.8)	88 (0.7)	6 (0.1)
Mild	18 (0.7)	6 (0.3)	5 (0.3)	23 (0.5)	62 (0.5)	4 (<0.05)
Moderate	10 (0.4)	1 (<0.05)	2 (0.1)	12 (0.3)	19 (0.2)	2 (<0.05)
Severe	2 (0.1)	0	0	2 (<0.05)	7 (0.1)	0 (<0.05)

Medical Officer Comment: Patients with telithromycin-associated visual adverse events in Phase 3 clinical trials were assessed as having moderate to severe intensity in 37.8% of patients having visual adverse events (40% in controlled phase 3 studies and 28.6% in uncontrolled phase 3 studies). In study 3014, the incidence of moderate to severe visual adverse events was 29.5% amongst patients having visual adverse events. It is important to note that no systematic method was used for assessing the severity of visual adverse events which calls into question the significance of this variable. In addition, it is important to note that severity or intensity of a visual adverse event may often have little to do with the significance of the visual adverse event. For example, a mild intensity visual adverse event may be quite significant if it occurs in an airplane pilot, a butcher, or a school bus driver. At the same time, a severe intensity event may be insignificant if it occurs in a debilitated nursing home resident who is confined to the bed. The significance of the intensity of a visual adverse event is not intrinsic to the event alone and instead involves aspects which may be unrelated to the effect of the drug itself such as the activities and/or occupation of the patient suffering the adverse event. This must be considered in a setting where a drug, such as telithromycin, is expected to be used in a large number of patients who are likely to be engaging in normal activities of daily living during therapy.

Amongst those experiencing a visual adverse event, the rates of serious adverse events in phase 3 clinical trials and in study 3014 were low (1/37 and 3/88, respectively). Amongst those experiencing a visual adverse event, the rate of serious visual adverse events in the post-marketing database and study 5001 was much higher (83/289 and 14/60 respectively).

Medical Officer Comment: The higher rates of serious visual adverse events in the post-marketing databases might be the result of reporting bias, since the more severe an adverse event is, the more likely it will be reported in the post-marketing setting. An assessment of whether the phase 3 data is accurate with regard to seriousness cannot be

performed because detailed information regarding the visual adverse events was not collected in a systematic fashion. The primary serious criterion to which telithromycin-associated visual adverse events may qualify as serious includes those adverse events which "result(s) in persistent or significant disability/incapacity." No data was collected which would allow for an assessment as to whether any of the phase 3 visual adverse events might qualify as serious under this category. Since 37.8% of phase 3 visual adverse events were categorized as moderate to severe in intensity, it is possible that there might be a higher number of visual adverse events which might reasonably considered as "serious."

Visual Adverse Events/ Cases of Interest

Assessment of the post-marketing is limited for the purposes of determining rates but it is useful in establishing a range of severity of adverse events. Review of the post-marketing visual adverse events revealed numerous reports of visual adverse events which contained descriptions of a dramatic and serious nature (please refer to post-marketing visual adverse event section for examples). Phase 3 clinical data did not contain the sort of descriptive data to allow for an assessment.

Time to Onset, Duration, and Resolution of Visual Adverse Events

The primary data used to analyze these parameters (time to onset, duration, and resolution) included data from phase 3 studies and Study 3014. Data allowing for assessment of time to onset, duration, and resolution of visual adverse events were collected differently in the different data sets. Phase 3 studies did not collect data to allow for an assessment of these parameters in hours as a unit of measure. Therefore, these parameters were calculated in days by using dates of onset and resolution.

Data allowing for a determination of each parameter using hours as a unit of measure was collected for study 3014. However, there were numerous deficiencies in this process:

1. Data were typically collected on study days 17-24, and not during the actual adverse event.
2. For a significant proportion of patients (33% or 29/89) complete data was not collected. This occurred because for 10 patients, data collection was incomplete. One patient was not identified until after analysis of 3014 was completed by the sponsor. For the other patients, the visual symptom experienced was not included in the pre-specified definition in the study protocol.
3. There was no pre-determined methodology for evaluating these patient during the course of the visual adverse event. Such a methodology might have included mandatory ophthalmological examination and the recording of events as they occurred. This would have allowed for more accurate data collection.

Because of the missing data, the sponsor conducted an analysis using imputed data in place of the missing data. The rules of this analysis are contained in the sponsor's Integrated Overview of Visual Events on page 192. The results from this analysis are contained in **Table 18**.

Table 18. Onset from prior dose and duration of visual episode (in hours) in Study 3014: Pooled visual MedDRA term population including imputed data

	Total		Continued		Discontinued	
	TEL N=88	AMC N=6	TEL N=61	AMC N=4	TEL N=27	AMC N=2
Onset in hours						
N	88	6	61	4	27	2
Median	1.0	2.0	1.0	37.0	2.0	1.0
Range	0 - 312	0 - 96	0 – 312	0 – 96	0.25 - 24	0, 2
Duration (hours)						
N	87	6	60	4	27	2
Median	11.75	36.0	15.75	36.0	5.75	25
Range	0.083 - 336	2 - 72	0.083 – 336	16 – 72	0.167 – 47.75	2, 48

(from Table 26, applicant's integrated overview of visual events, page 92)

Medical Officer Comment: In trying to understand the duration of visual adverse event episodes and onset of visual adverse events, it is problematic that such a large amount of data is missing. The method of imputation for the missing data generally attempted to be conservative. For example, if duration data (in hours) were missing for a specific patient, then 24 hours was used as the duration, assuming the episode began while the patient was on therapy. If the patient's episode began after therapy ended, then the duration was calculated using the date to determine number of days which was then multiplied by 24 hours. For time to onset, if data were missing, then a time to onset of 0 hours was used for those visual events occurring during therapy. This would be likely to result in an underestimation of the time to onset.

Table 19 gives a representation of time of onset and duration of visual adverse events in phase 3 clinical trials. Since hours were not recorded during these studies, event onset and duration was calculated using dates and represented in terms of days.

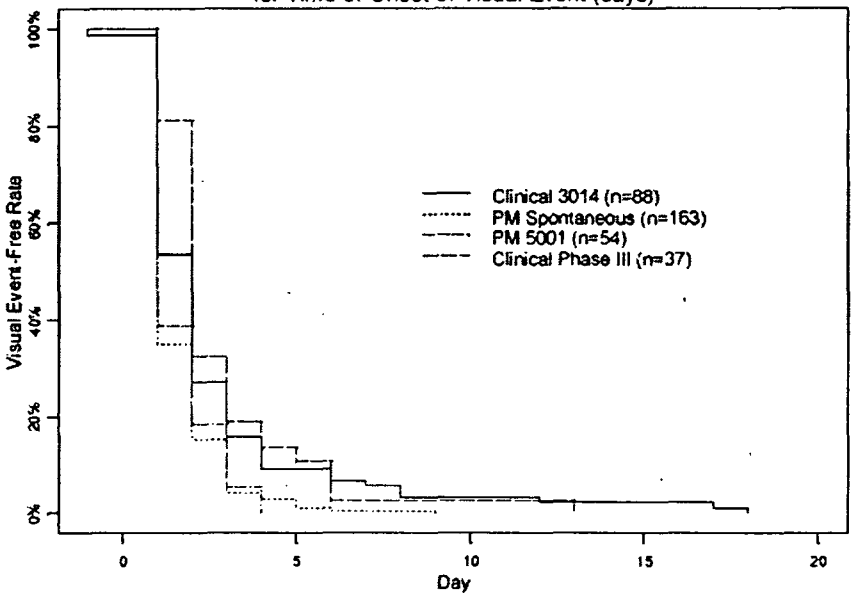
Table 19. Time of onset and duration of visual TEAEs (in days) in Phase III studies: Pooled visual MedDRA term population

	Total		Continued		Discontinued	
Statistic	TEL N=37	Control N=7	Tel N=31	Control N=7	TEL N=6	Control N=0
Day of onset						
N	37	7	31	7	6	0
Median	2	3	2	3	2	-
Range	1 – 13	1 – 16	1 – 13	1 – 16	1 – 5	-
Duration (days)						
N	35	6	29	6	6	0
Median	2	2	2	2	4.5	-
Range	1 – 12	1 – 4	1 – 12	1 – 4	3 – 8	-

(from Table 13, applicant's Integrated Overview of Visual Adverse Events. Page 76.)

Figure 2 below is a Kaplan-Meier curve for time to onset of telithromycin-associated visual adverse events in clinical phase 3 data, Study 3014, Study 5001, and spontaneous post-marketing reports. (Applicant's integrated overview of visual events, page 153)

Figure 2 Pooled Target Visual Terms - Kaplan-Meier Curves (Telithromycin) for Time of Onset of Visual Event (days)



Medical Officer Comment: This curve in **Figure 2** above shows that approximately 65% of patients who experience a visual event will do so within the first two days according to clinical phase 3 data. That still leaves a substantial proportion of patients who will go on to experience a telithromycin-associated visual adverse event on treatment day 3 (15%) and beyond (20%). The other data sources are roughly consistent with this finding. Since 35% of patients who experience telithromycin-associated visual adverse events are likely to do so after 3 or more days of therapy, it can reasonably be expected that such events may occur almost at any time during treatment, which most often runs between 5-7 days.

Resolution of Symptoms On and Off Therapy

Of patients in Phase 3 clinical studies who experienced telithromycin-associated visual adverse events, there were some whose visual adverse events were reported to have resolved while therapy was continued and others whose visual adverse events resolved only after cessation of therapy. **Table 20** contains an analysis of the patient-reported resolution of symptoms on and off therapy in Phase 3 clinical trials.

Table 20. Incidence of Visual Adverse Symptom Resolution by Duration in Days for Events Resolving On Therapy and Post-Therapy: Phase 3 Clinical Trials

	Study Day of Symptom Resolution			
	Days 1-2	Days 3-4	Days 5-7	Day 10 or more
Resolved On Therapy (N=21)	23.8% (5/21)	61.9% (13/21)	14.4% (3/21)	0
Resolved After Stop of Therapy (N=16)	25% (4/16)	37.5% (6/16)	6.25% (1/16)	31.3% (5/16)

Of the 37 patients with telithromycin-associated visual adverse events, 21 of 37 (or 56.8%) were reported to have resolved on therapy.

Medical Officer Comment: The majority of patients who reported resolution of symptoms did so only after several days of therapy. Since the treatment course of telithromycin is most commonly between 5-7 days, continuation of therapy in patients with a visual adverse event most likely will result in continuation of the visual adverse event for the majority of the treatment course. In addition, it is very important to recognize that patient report of improvement in visual adverse events was not verified by ophthalmologic examination. This is important because of the phenomenon of adaptation, which was seen with voriconazole. Despite ophthalmologic evidence of ongoing visual events, many patients reported improvement in symptoms after several days while being treated with voriconazole. It is not known if this phenomenon occurs with telithromcyin-associated visual adverse events. It is interesting to note that among patients whose symptoms resolved only after cessation of therapy, there was a large percentage (31.3%) who resolved after prolonged periods of time (day 10 or more). It is possible that these patients represent a group that is more susceptible to this adverse event or are less able to adapt to the visual changes. Other possible explanations include: an individual variability or drug interaction effect on pharmacokinetics that could result in exposure differences, potential age effect on time to resolution, or gender effect. It is not possible at this time to understand these sorts of differences amongst patients who experienced a telithromycin-associated visual adverse event.

Table 21 contains an analysis of the patient-reported resolution of symptoms on and off therapy in Study 3014

Table 21. Incidence of Visual Adverse Symptom Resolution by Duration in Days for Events Resolving On Therapy and Post-Therapy: Study 3014					
	Study Day of Symptom Resolution				
	Days 1-2	Days 3-4	Days 5-7	Days 8-9	Day 10 or more
Resolved On Therapy (N=28)	32.1% (9/28)	53.6% (15/28)	10.7% (3/28)	3.6% (1/28)	0
Resolved After Stop of Therapy (N=60)	16.7% (10/60)	18.3% (11/60)	33.3% (20/60)	3.3% (2/60)	28.3% (17/60)

Medical Officer Comment: Compared to phase 3 clinical trials, study 3014 had a larger overall percentage of patients whose symptoms resolved after stop of therapy rather than on therapy. This is possibly explained by the fact that of those experiencing visual adverse events in study 3014, more (30.7% or 28/88) discontinued therapy as a result of visual adverse events than in phase 3 studies (16.2% or 6/37).

Impact on Activities of Daily Living

There was no study conducted which adequately assessed what impact telithromycin-associated visual adverse events may have had on activities of daily living. The visual adverse event form for Study 3014 had one single yes/no type question regarding possible effect on activities of daily living, while Study 5001 had a single question asking how seriously the visual event affected the patient's activities. No detailed questions were asked to assess possible impact of the visual event on specific activities such as reading, driving, negotiating stairs, working, writing, or cooking.

Table 22 show what was reported for effect of telithromycin on activities of daily living.

Table 22. Impact on activity of visual AEs: Pooled visual MedDRA term population

	Number of patients (%)		
Activity	**3014 N=75**	**5001 N=60**	**PMS N=207**
Total with impact on activity	33 (44)	14 (23.3)	51 (24.6)
Reading	7 (9.3)	6 (10.0)	31 (15.0)
Driving	5 (6.7)	3 (5.0)	6 (2.9)
Working	5 (6.7)	1 (1.7)	7 (3.4)
Walking	0	0	3 (1.4)
Other categories	1 (1.3)	7 (11.7)	24 (11.6)

Table 80, applicant's Integrated Overview of Visual Events, page 159.

Medical Officer Comment: These data show that among those experiencing a visual adverse event, there were patients whose activities of daily living were affected. Since the information about potential impact on daily living was not collected in a systematic and detailed way, it is not possible from these data to determine the full impact that telithromycin-associated visual events might have on activities of daily living. It is not clear how or if investigators explained to patients what types of information was of interest with regard to activities of daily living; the protocol contained no method for doing so. For these reasons, the data **Table 22** are not useful in understanding the true rate of patients with telithromycin-associated visual events who experienced an impact on activities of daily living. It is most useful in understanding that such an impact does occur with this particular adverse event. Because patients taking this drug will, to a large degree, be continuing to participate in activities of daily living, such as driving, working, and walking, it can be assumed that many of these patient's activities are likely to be affected.

Discontinuation Due to Visual Adverse Events

Table 23 shows the percentage of patients who discontinued therapy due to a visual adverse event.

Table 23. Number (%) of subjects with serious visual TEAEs and visual TEAEs resulting in Discontinuation

	Pooled visual MedDRA term population			
	Phase III	**3014**	**5001****	**PMS**
Total number of Visual AEs	N=37	N=88	N=60	N=162*
Visual TEAEs resulting in discontinuation	6	27 (0.2)	29	152
Rate of discontinuation among patients with visual adverse events	16.2% (6/37)	30.7% (27/88)	48.3% (29/60)	93.8% (152/162)

* information was missing for 212 reports of visual adverse events.
** intensive monitoring, passive reporting post-marketing study

Medical Officer Comment: Depending on the data source examined, the rate of discontinuation of telithromycin in patients who experienced a telithromycin-associated visual adverse event ranged from 16.2% to 93.8%. It is difficult to estimate what the actual rate of discontinuation would be in a usual use setting based on these data. The discontinuation rate in the post-marketing data may be so high because more severe cases have a higher likelihood of being reported. In addition, the discontinuation rate for patients in the Phase 3 studies might be somewhat lower than in a usual care setting because of the degree of monitoring and close follow-up by investigators.

Sequelae

The clinical trials that were performed are unable to answer the question of whether rare sequelae might occur in patients who experienced telithromycin-associated visual adverse events. There were two phase 1 studies (Studies 1059 and 1964) in which patients given

high doses of telithromycin (2,400mg) were followed with detailed ophthalmic examinations to document resolution of symptoms. In these studies, visual symptoms were documented as having resolved. However, the limitation of these studies is that only a small number of patients (N=24 for patients receiving 2,400 mg) were studied and, therefore, the studies may not have been able to detect rare examples of prolonged or non-resolving symptoms.

There are a small number (N=8) of poorly documented cases from the spontaneous reporting post-marketing data base who appear to have experienced non-resolving visual adverse events for an extended period of time after cessation of therapy. (see post-marketing review of visual adverse events). Other than these cases, there are no available data to assess whether or not there are possible long-term sequelae associated with telithromycin induced visual adverse events.

Medical Officer Comment: Because of the poor quality of follow-up data and the poor understanding of the pathophysiology of telithromycin-associated visual adverse events, it is unclear at this time whether the potential exists for long-term sequelae. Since this adverse event is newly recognized, it will be important in the future for the applicant to make every attempt to collect data which may improve our understanding of the possibility of sequelae. It is possible that the small number of poorly documented reports collected from the post-marketing data base could potentially be a signal indicating the existence of rare cases of prolonged visual disturbance resulting from exposure to telithromycin. It is reassuring that in phase 1 and 3 data, patients have reported resolution of symptoms. However, the phase 1 and 3 database is relatively small and would not be expected to detect rare events. In order to address the potential for sequelae, the applicant should conduct careful post-marketing assessments of the visual adverse events, including aggressive follow-up of reports where outcome has not completely resolved.

Public Health Impact of Telithromycin-associated Visual Adverse Events

When attempting to assess the potential impact of telithromycin-associated visual adverse events on public health, it is important to distinguish between rates and overall numbers of events. In controlled phase 3 trials, telithromycin-associated visual adverse events occurred at a rate of 1.1% overall. This rate is low when compared to other drugs such as voriconazole which has a visual adverse event rate of approximately 30%. However, to assess the possible public health impact of a particular drug associated adverse event, consideration of drug exposure is also important.

Telithromycin is a drug that is proposed for use in respiratory tract infections including ABS, AECB, and CAP. According to IMS data, there were [redacted] prescriptions written for azithromycin and clarithromycin in the U.S. last year. In addition, there were a total of [redacted] prescriptions written for antibiotics for the treatment of ABS. Given these figures and for the purposes of assessing potential public health impact, it is reasonable to estimate that telithromycin might eventually be prescribed to [redacted] patients per year. Based on a 1.1% rate of visual adverse events, this would be expected to result in [redacted] patients with telithromycin-associated visual adverse events.

By contrast, although voriconazole may have a higher rate of associated visual adverse events, the total number of patients affected may be less. This is because the number of patients with invasive aspergillosis and esophageal candidiasis is much smaller than the number of patients with respiratory tract infections. For example, the number of cases of invasive aspergillosis annually in the United States from 1996-2001 ranged from 5,822 – 11,405.[15] Therefore, in patients treated with voriconazole for aspergillosis, the number of patients who might experience voriconazole-associated visual adverse events is estimated at 1,746-3,421 over a 5-year period if all of them were treated with voriconazole. Esophageal candidiasis, although more common than invasive aspergillosis, is still much less common than respiratory tract infections. Furthermore, fluconazole remains a very effective and safe treatment. Therefore, it is estimated that, overall, there will be more telithromycin-treated patients than voriconazole treated patients who will experience drug associated visual adverse events despite the fact that voriconazole's visual adverse event rate is much higher than that of telithromycin.

An additional consideration in assessing the potential public health impact is the potential effect of such visual adverse events on the patients experiencing them. Voriconazole is likely to be used in the setting of a seriously ill patient population. This population of patients, which includes those with invasive aspergillosis, AIDS, organ transplant, and cancer, is very likely to have significant limitations to their activities of daily living. By contrast, the majority of patients treated with telithromycin, including those with ABS or AECB, are likely to be much more active with less limitations on their activities of daily living. Telithromycin-treated patients are much more likely to be engaging in activities such as driving and, therefore, will be at increased risk as a result of the visual adverse events.

Medical Officer Summary of Visual Toxicity of Telithromycin

Data from phase 1, 3, and post-marketing have identified an unusual drug-associated visual adverse syndrome involving interference with the ability to visually accommodate. Telithromycin-associated visual adverse events included a variety of visual complaints but most often involved blurred vision, diplopia, and difficulty focusing. There were several severe post-marketing reports of telithromycin-associated visual adverse events affecting activities of daily living and, in some cases, resulting in incapacitation. Most often these events lasted from several hours to a few days and had an onset which was unpredictable and sudden. A small number of reports were identified in which patients reported visual adverse events of prolonged duration without further follow up. Because telithromycin will be used in many cases for relatively mild infections (acute bacterial sinusitis and acute exacerbation of chronic bronchitis), and because treated patients will often be engaging in activities of daily living, such as driving, it is important to include information in the product label which is as informative and visible as possible. Such labeling information should warn patients and prescribing clinicians about the possibility and nature of these visual adverse events as well as the potential outcomes and event

[15] Clark TA, Hajjeh RA. Recent trends in the epidemiology of invasive mycoses. Curr Opin Infect Dis. 2002 Dec;15(6):569-74.

course. The range of severity of telithromycin-associated visual adverse events includes cases which meet the regulatory definition of serious. It is reasonable to include in the label a warning regarding the possibility of visual adverse events when administering telithromycin.

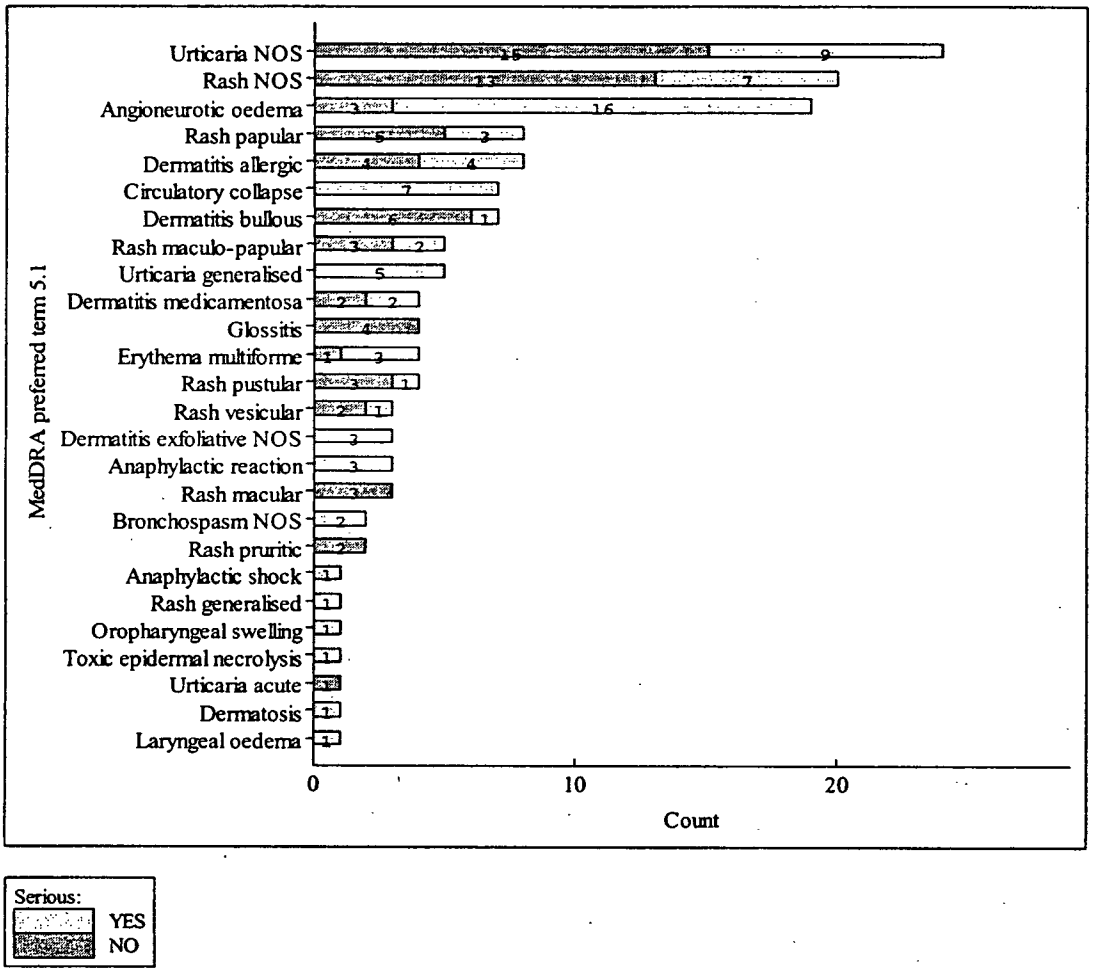
Reports of Post-marketing Gastrointestinal Bleeding

Interest in a possible association of gastrointestinal bleeding originated from two cases of hemorrhagic esophagitis which were reported in two young patients. All post-marketing reports were reviewed for any case of gastrointestinal bleeding. In total, there were 20 patients with post-marketing reports of gastrointestinal bleeding in the post-marketing database. Detailed review of these cases revealed no particular pattern. The two initial cases of hemorrhagic esophagitis are possibly duplicate reports of one patient with a history of depression on an SSRI. There was no mention of possible suicide attempt in that patient and no information regarding possible caustic ingestion. There was one additional case of erosive esophagitis in a 20 year-old patient reported from — The patient developed erosive esophagitis after the first day of therapy with telithromycin. The rest of the patients

Post-marketing Allergic Reactions

Graph 18 shows all potentially allergic reactions in the post-marketing database. The most common allergic reactions include urticaria, rash, and angioneurotic edema. All serious events were reviewed. Many of the events were either poorly documented or inaccurately described.

Graph 18. Adverse Events Potentially Involving Allergic Reactions



There was one reported case of toxic epidermal necrolysis (200311450FR), however, this case was poorly documented and appears to possibly have been erythema multiforme. The patient was reported as having not been hospitalized and there were no mucosal lesions and no report of sloughing skin.

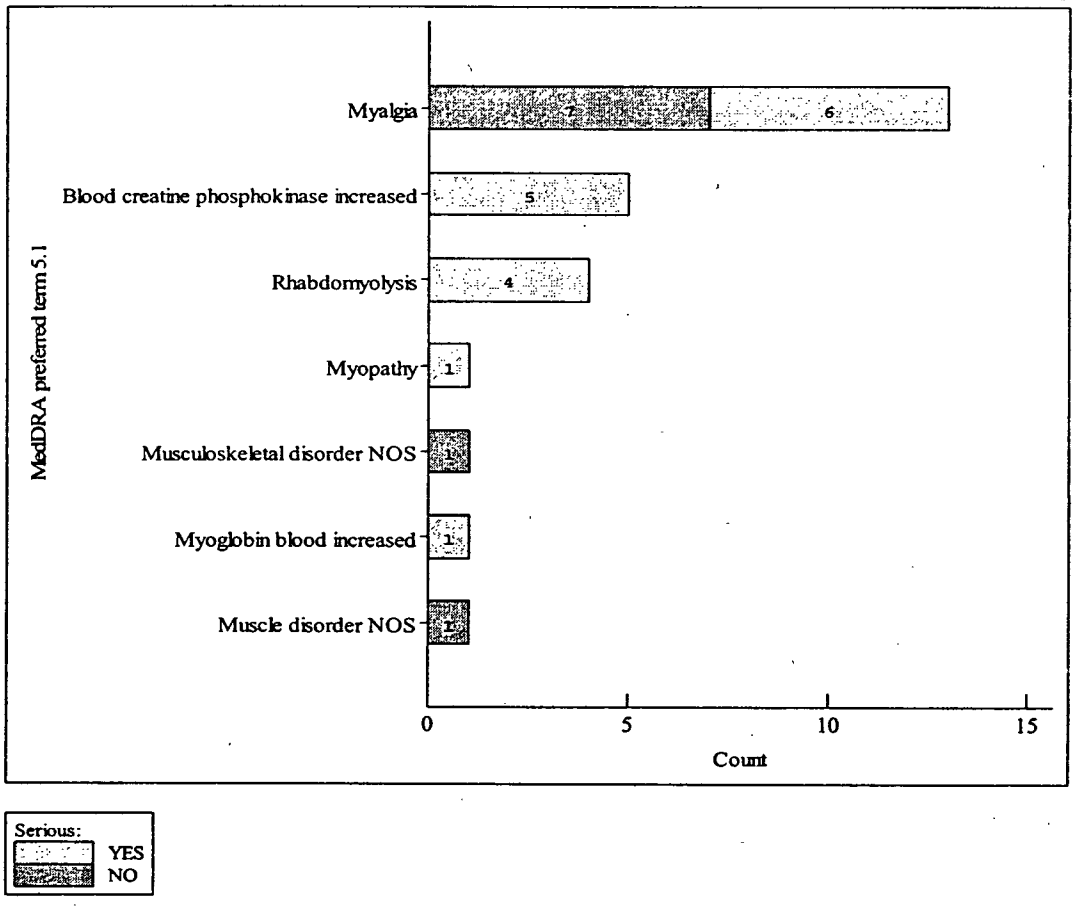
Medical Officer Comment: The numbers and severity of cases reported for a post marketing database of → . does not indicate an unusually large safety signal. The

types of allergic reactions reported are consistent with what has been described for other antibiotics.

Rhabdomyolysis

The post-marketing data base was examined specifically for cases of rhabdomyolysis because phase 1 studies indicated that telithromycin may cause significant elevations in HMG-CoA reductase inhibitor levels. All post-marketing preferred terms were searched for events which could possibly indicate a case of rhabdomyolysis. These terms are included in the **Graph 19**.

Graph 19. Adverse Events Possibly Related to Rhabdomyolysis



All of these cases were reviewed and evaluated as possible cases of rhabdomyolysis. Concomitant medications were reviewed to determine if there were possible cases that resulted from a drug interaction between telithromycin and an HMG-CoA reductase inhibitor. Review of these reports revealed two cases of clear rhabdomyolysis (200212530DE and 200310523DE) but neither of these has a clear cause and neither appears to be related to possible interaction with an HMG-CoA reductase inhibitor. There

are several cases of patients with hypercholesterolemia who complained of muscle symptoms, but these cases lacked information regarding CK measurements or statin use.

Review of Safety Data from Study 5001 and Review of 5 Month Bridging PM Data

An intensive monitoring study was conducted in Germany. In this study, passively collected post-marketing data were evaluated and reports of particular interest were followed up with pre-determined questionnaires aimed at obtaining more detail information.

A five month bridging report was provided which covered new post-marketing data from August 2003 through December 2003.

Medical Officer Comment: Data from both of these sources were reviewed. These data were consistent with the findings of the main collection of post-marketing data. No new safety signals or safety concerns were identified from these sources.

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

/s/

Charles Cooper
3/31/04 06:03:54 PM
MEDICAL OFFICER

Please Sign

John Alexander
3/31/04 06:08:46 PM
MEDICAL OFFICER

MEDICAL OFFICER
ADDENDUM TO EFFICACY REVIEW:
NDA 21-144 RESUBMISSION

Date of Submission: October 17, 2003
Date Review Completed: March 22, 2003

Applicant: Aventis Pharmaceuticals Incorporated
200 Crossing Blvd.
P. O. Box 6800
Bridgewater, NJ 08807-0800

Drug Information

Proprietary Name: Ketek™
Established Name: Telithromycin
Drug Class: Ketolide
Formulation: 400-mg oral tablets

Executive Summary

This document is an addendum to the efficacy review for Ketek™ (telithromycin) tablets by Dr. John Alexander. This addendum summarizes the clinical outcomes for cases of community-acquired pneumonia (CAP) due to *Streptococcus pneumoniae* resistant to one or more antibiotics. These cases were collected from four active-controlled and four open-label studies. Clinical cure rates for patients with CAP due to multi-drug resistant *Streptococcus pneumoniae* were 38/47 (80.1%) in the intent-to-treat population and 33/36 (91.7%) in the evaluable population. These cure rates were similar to the cure rates for CAP due to *Streptococcus pneumoniae*, regardless of antibiotic susceptibility. Aventis Pharmaceuticals, Inc. has provided substantial evidence to support a claim for mild-to-moderate community-acquired pneumonia due to multi-drug resistant *Streptococcus pneumoniae*.

In response to the approvable letter dated January 24, 2003, analyses of pathogen-specific outcomes for patients with CAP, acute bacterial sinusitis, and acute exacerbation of chronic bronchitis (AECB) and subgroup analysis of steroid use in AECB were submitted. This addendum summarizes the pertinent results from these analyses.

Clinical Review

I. Introduction and Background

Ketek™ (telithromycin) is an oral ketolide antibiotic developed by Aventis Pharmaceuticals, Inc. In NDA 21-144 for Ketek™, the applicant seeks approval for the treatment of community acquired pneumonia (CAP), acute bacterial sinusitis (ABS), and acute exacerbation of chronic bronchitis (AECB).

This document serves as an addendum to the efficacy review by John Alexander, MD, MPH. Dr. Alexander's clinical review summarizes the studies of CAP and ABS and reviews the cases of CAP due to penicillin-resistant and macrolide-resistant *Streptococcus pneumoniae*. This addendum reviews the efficacy data submitted in response to the approvable (AE) letter of January 24, 2003. The response to this AE letter was received on October 17, 2003. This addendum review will refer to the AE letter response as the 3rd Ketek™ submission. Charles K. Cooper, M.D., reviewed the safety data in the 3rd Ketek™ submission. The reader should refer to Dr. Cooper's review for information on the safety of Ketek™.

In the approvable letter of January 24, 2003 the following requests for additional information pertaining to the efficacy of telithromycin.

- For each indication, provide analyses of clinical outcome at the test-o-cure visit by pre-therapy pathogen for each bacterial pathogen included in labeling. These analyses should present results for both the MITT and per protocol populations. In the MITT population analysis, patients with indeterminate or failure outcomes should be treated as failures. Provide a sensitivity analysis wherein indeterminate outcomes are treated as missing. Present these analyses for each controlled and uncontrolled study separately. The comparator result should be included whenever applicable. In addition, provide aggregate results for each indication...
- Provide subgroup analyses for patients with concomitant corticosteroid use in each of the three AECB studies. Clinical outcome at the test-of-cure visit should be described for patients who received concomitant oral or inhaled corticosteroids and those who did not. Exclude patients who received only topical corticosteroids. Provide a discussion of the results of these subgroup analyses.

The applicant provided the requested analyses in the submission dated October 17, 2003.

Since the approvable letter, the agency has granted a claim for community acquired pneumonia due to MDRSP to Factive®. In order to determine whether telithromycin would qualify for a similar claim the applicant was asked to provide additional analyses. These analyses of clinical outcome in CAP patients with drug resistant *S. pneumoniae* were submitted on February 3, 2004.

In this addendum, the data submitted for a labeling claim for multi-drug resistant *Streptococcus pneumoniae* (MDRSP) in the setting of community acquired pneumonia are reviewed. As used in this review, MDRSP is defined as an isolate of *Streptococcus pneumoniae* that is resistant to at least two of the following drug classes: penicillin; macrolides; second generation cephalosporins; tetracyclines; and TMP-SMX. The main focus of this review is the

labeling of Ketek™ for MDRSP in patients with community acquired pneumonia. This review will also address labeling for other pathogens in patients with CAP, and labeling for AECB and ABS indications.

II. Clinically Relevant Findings from Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and other Consultant Reviews

Andrew Yu, Ph.D., performed the chemistry review for the 3rd Ketek™ submission, as well as the original NDA. The reader should refer to that review for further details. Microbiology and biopharmaceutics reviews of the 3rd Ketek™ submission were performed by Mr. Harold Silver and Jenny Zheng, Ph.D., respectively.

III. Human Pharmacokinetics and Pharmacodynamics

Jenny Zheng, Ph.D., conducted the clinical pharmacology review for the original submission and resubmission. Telithromycin is metabolized by the cytochrome P450 system, namely CYP3A. There were a number of drug interactions of note. The 3rd Ketek™ submission included the final study reports for clinical pharmacology studies of the interactions of simvastatin with telithromycin and clarithromycin. The reader should refer to the clinical pharmacology review of Jenny Zheng, Ph. D. for further details.

IV. Description of Clinical Data and Sources

The applicant submitted efficacy analyses dated October 17, 2003 in response to the approvable letter of January 24, 2003. This submission was reviewed for clinical outcome by pathogen for patients with CAP, AECB and ABS. This submission also contained a sub-groups analysis of patients with AECB who received steroids. The applicant submitted an efficacy analysis regarding MDRSP specifically on February 3, 2004.

A literature search was performed on February 17, 2004. Some of the available literature was addressed in previous reviews. There were no articles that addressed the use of ketolides as treatment for CAP secondary to MDRSP. The published literature does not add significantly to this review.

V. Clinical Review Methods

Previous FDA findings on the efficacy of Ketek™ were reviewed by looking at efficacy reviews by Dr. John Alexander and other clinical reviewers. Documents related to the approval of gemifloxacin for CAP due to MDRSP were also referenced to ensure consistency in the definition of MDRSP and the outcome analyses.

The listings and tables submitted were reviewed. The CRFs not reviewed in the previous efficacy analysis were reviewed. The information provided came from studies 3000, 3001, 3006, 3009OL, 3010, 3012, and 4003. NCCLS standards were used to determine the breakpoints for antibiotic resistance. For this addendum, the case report forms for additional cases of CAP due to MDRSP were reviewed. The outcome data for these patients were added to the existing database of CAP patients with PRSP or ERSP maintained by Dr. Alexander. Analyses were performed of cases of CAP due to MDRSP and are described in the following section of this document.

The analyses of clinical outcome by pathogen for the CAP, AECB and ABS studies were provided by the applicant. The analyses were reviewed by the medical officer and pertinent findings are described in the following section of the review.

VI. Integrated Review of Efficacy

Analysis of CAP due to MDRSP

The overall cure rate for CAP due to *S. pneumoniae* in the PPb population was 93.6%, 88.9% for the bmITT population. The number of *S. pneumoniae* isolates was low in individual studies. In the uncontrolled studies, the cure rate for CAP due to *S. pneumoniae* was 94.4% for the PPb population, and 87.4% for the bmITT population.

For CAP due to MDRSP strains, the clinical cure rate reported by the applicant was 91.9% (34/37) in the PPb population, and 80% (40/50) in the bmITT population. The numbers in the controlled studies were small thus a meaningful rate for the comparator-treated patients could not be obtained.

In the medical officer analysis, 56 CAP patients had isolates resistant to one or more antibiotics that were treated with telithromycin. Only 8 of the isolates were resistant to a single drug (all erythromycin). Of the remaining isolates, which are all MDRSP by definition, the clinical cure rate was 38/47 (80.1%). One patient, 3000/101/1365, was considered to have an indeterminate outcome by both the applicant and the medical officer. This patient was excluded from the analysis. This number is comparable to the figures provided by the applicant using the bmITT population. The difference may be that patients with isolates intermediate to penicillin may have been counted as MDRSP by the applicant. In the PPb population, the clinical cure rate for CAP patients with MDRSP was 33/36 (91.7%).

In patients that were found to be bacteremic, the cure rates reported by the applicant were slightly lower. For all *S. pneumoniae*, the clinical cure rate of bacteremic patients was 88.2% (67/76) in the PPb population, and 77.2% (71/92) in the bmITT population. For the MDRSP population, the cure rates of bacteremic patients were 84.6% (11/13) and 68.8% (11/16), respectively. [The bacteremia outcomes in this paragraph are from the applicant's analysis in a submission on 2/3/2004.]

Clinical Outcome for patients with CAP due to antibiotic-resistant S. pneumoniae treated with telithromycin – bmITT Population

Antimicrobial	Clinical Cure Rate	%
Penicillin[+]	23/31	74.2
Cefuroxime[+]	23/30	76.7
Erythromycin[*]	36/44	81.8
Tetracycline/doxycycline	15/20	75.0
TMP/SMX[+]	27/35	77.1

**: This includes 8 isolates that are resistant to erythromycin only, 7 were clinical cures.*
+: One patient was considered to have an indeterminate outcome and was excluded from these analyses.

Clinical Outcome for patients with CAP due to antibiotic-resistant S. pneumoniae treated with telithromycin – PPb Population

Antimicrobial	Clinical Cure Rate	%
Penicillin	20/23	86.9
Cefuroxime	20/22	90.9
Erythromycin[*]	32/36	88.9
Tetracycline/doxycycline	11/13	84.6
TMP/SMX	24/27	88.9

**: this includes 8 isolates that are resistant to erythromycin only, 7 were clinical cures*

Penicillin resistance – From all CAP studies, there were a total of 32 patients with penicillin-resistant *S. pneumoniae*, one of whom was excluded because of an indeterminate outcome. All of the penicillin-resistant strains were MDRSP. Of these, 23 were treated successfully.

Cefuroxime – There were 31 patients with isolates resistant to cefuroxime, one of which was excluded because of an indeterminate outcome. There were also 3 with intermediate strains. Twenty-three patients were clinically cured. All these isolates fit the criteria for MDRSP.

Erythromycin resistance – From all CAP studies, there were a total of 44 isolates that were resistant to erythromycin. Of these, 8 isolates were resistant to erythromycin only. There were no intermediate strains. Overall, 36 of 44 patients were cured. All eight patients with isolates resistant to erythromycin only were considered clinically evaluable. The clinical cure rate was 7/8.

Tetracycline – There were 24 isolates that showed some resistance to tetracycline (4 intermediate). All tetracycline intermediate and resistant strains were MDRSP. Of the 20 resistant isolates, 15 were clinically cured. This group of isolates contains isolates tested for resistance to either tetracycline or doxycycline.

TMP/SMX – There were 36 isolates that showed resistance to TMP/SMX, one of which was excluded because of an indeterminate outcome. Eight isolates were intermediate strains. All of the isolates were MDRSP strains. Of these patients, 27 were clinically cured.

Of the isolates provided, there were 6 isolates that were resistant to all five antibiotics. All of these patients were treated with telithromycin. Four (66.7%) of the patients treated with telithromycin achieved clinical cure. By the applicant's evaluation, 1 patient was a clinical failure, and one was indeterminate. From a review of the CRFs by the reviewer, the indeterminate would appear to be a clinical failure as well.

Analysis of Telithromycin Activity against Other Pathogens

In the approvable letter issued on January 24, 2003, there was also a concern regarding the lower clinical cure rates observed in patients with *H. influenzae*. In all controlled CAP studies the cure rate for the bmITT population was 76.5% as compared to 85.3% in the comparator groups. In the uncontrolled CAP studies, the cure rate was 82.7%. Even lower cure rates were seen when comparing CAP due to *S. aureus*. The cure rates in the bmITT population with CAP due to *S. aureus* were 77.8% (14/18) in telithromycin treated patients, and 93.3% (14/15) in comparator patients. A similar cure rate for telithromycin treated patients was seen in the uncontrolled studies, 72.7% (40/55) for patients with CAP due to *S. aureus*.

(M.O. Comment: Overall there were lower cure rates seen for CAP patients with *S. aureus* in the controlled studies. The number of patients in controlled studies was low, but the low cure rate was similar to what was seen in the uncontrolled studies. Given that pneumonia due to *S. aureus* is usually severe and treated parenterally, it is not recommended that *S. aureus* be included in the pathogens under the CAP indication.)

The following tables show the cure rates in the CAP patients with specific pathogens. The tables separate the controlled and uncontrolled studies. Only patients receiving 7-10 days of telithromycin were included in these analyses.

CAP cure rates in bmITT population with missing treated as failure (controlled)

Organism	Telithromycin	Comparator
S. pneumoniae	82.6% (90/109)	76% (79/104)
H. influenzae	76.5% (65/85)	85.3% (64/75)
M. catarrhalis	78.9% (15/19)	64.3% (9/14)
S. aureus		

**Efficacy Analysis page 60*

CAP cure rates in bmITT population with indeterminate treated as failure (uncontrolled)

Organism	Cure Rate	%
S. pneumoniae	235/269	87.4
H. influenzae	211/255	82.7
M. catarrhalis	42/56	75.0
S. aureus		

**Efficacy Analysis page 64*

CAP cure rates in PPb population (controlled)

Organism	Telithromycin	Comparator
S. pneumoniae	93.6% (73/78)	90% (63/70)
H. influenzae	83% (39/47)	95.5% (42/44)
M. catarrhalis	85.7% (12/14)	77.8% (7/9)
S. aureus		

**Efficacy Analysis page 41*

(M.O. Comment: The above table provides the pathogen specific outcomes for CAP

CAP cure rates in PPb population (uncontrolled)

Organism	Cure Rate	%
S. pneumoniae	204/216	94.4
H. influenzae	145/157	92.4
M. catarrhalis	31/35	88.6
S. aureus		

**Efficacy Analysis page 44*

The following tables provide clinical cure rates in bmITT and PPb populations with AECB due to specific pathogens. All the trials were comparator controlled. Cure rates were somewhat lower for telithromycin treated patients with *H. influenzae* in the PPb population than for comparator patients. However, the rates were similar in the bmITT analysis. There were few patients with *S. aureus* as the baseline pathogen.

AECB cure rates in bmITT population with indeterminate treated as failure (controlled)

Organism	Telithromycin	Comparator
S. pneumoniae	82.8% (24/29)	79.2% (19/24)
H. influenzae	73.1% (57/78)	70.8% (51/72)
M. catarrhalis	90.9% (30/33)	80.5% (33/41)
S. aureus		

**Efficacy Analysis page 156*

AECB cure rates in PPb population (controlled)

Organism	Telithromycin	Comparator
S. pneumoniae	81.5% (22/27)	78.9% (15/19)
H. influenzae	73.3% (44/60)	84.9% (45/53)
M. catarrhalis	93.1% (27/29)	85.3% (29/34)
S. aureus		

**Efficacy Analysis page 152*

(M.O. Comment: The above table provides the pathogen specific outcomes for AECB

The following tables provide clinical cure rates in bmITT and PPb populations with ABS due to specific pathogens. The numbers included in the table below include data from controlled trials comparing 5 days of telithromycin to comparator. The results of study 3002 are presented in separate tables. Study 3002 was a dose comparison study of five days versus ten days of telithromycin.

ABS cure rates in bmITT population with indeterminate treated as failure (controlled)

Organism	Telithromycin 5-d	Comparator
S. pneumoniae	82.5% (33/40)	81% (17/21)
H. influenzae	86% (37/43)	83.3% (15/18)
M. catarrhalis	100 % (9/9)	87.5% (7/8)
S. aureus	90% (9/10)	66.7% (2/3)

**Efficacy Analysis page 175*

ABS cure rates in PPb population (controlled)

Organism	Telithromycin 5-d	Comparator
S. pneumoniae	87.1% (27/31)	87.5% (14/16)
H. influenzae	82.4% (28/34)	86.7% (13/15)
M. catarrhalis	100% (7/7)	100% (7/7)
S. aureus	100% (8/8)	66.7% (2/3)

**Efficacy Analysis page 167*

(M.O. Comment: The above table provides the pathogen specific outcomes for ABS [redacted]. The numbers of patients with *S. aureus* or *M. catarrhalis* from the controlled trials are few, but the additional patients with these organisms in study 3002 provide sufficient numbers to support labeling. *S. aureus* was considered a pathogen only if it was isolated by sinus puncture, was present at $\geq 10^4$ CFU, was the sole ABS pathogen, and did not appear to be part of a contaminated culture.)

ABS cure rates in bmITT population with indeterminate treated as failure (Study 3002)

Organism	Telithromycin 5-d	Telithromycin 10-d
S. pneumoniae	78.4% (29/37)	87.9% (29/33)
H. influenzae	93.8% (15/16)	94.4% (17/18)
M. catarrhalis	87.5% (7/8)	87.5% (7/8)
S. aureus	5/6 (83.3%)	66.7% (2/3)

**Efficacy Analysis page 176*

ABS cure rates in PPb population (Study 3002)

Organism	Telithromycin 5-d	Telithromycin 10-d
S. pneumoniae	93.3% (28/30)	89.3% (25/38)
H. influenzae	100% (14/14)	92.3% (12/13)
M. catarrhalis	85.7% (6/7)	75% (3/4)
S. aureus	100% (5/5)	100% (1/1)

**Efficacy Analysis page 168*

Analysis of Telithromycin in AECB with concomitant steroid use

The applicant submitted data regarding the concomitant use steroids in the treatment of AECB. In all AECB studies similar numbers of patients received steroids in each group (telithromycin or comparator), although there was a small difference within the studies. In the mITT population 36.6% of all patients that received telithromycin were given concomitant steroids. In the comparator group, 36.2% received steroids. In the PPc population, the numbers were 36.7% and 36.9% respectively. Overall, the patients that received telithromycin and did not

receive steroids had slightly higher cure rates than those given steroids, but the difference was only a few percent. The following tables present the data.

Cure Rates – mITT (all AECB studies)

	Telithromycin	Comparator
Overall	81%	78.8%
No steroids	82.2%	78.5%
Steroids	79%	79.5%

**Subgroup Analysis of Corticosteroid Use in AECB pages 18-20*

Cure Rates – PPc (all AECB studies)

	Telithromycin	Comparator
Overall	86%	85.8%
No steroids	88.2%	86.6%
Steroids	82.4%	84.4%

**Subgroups Analysis of Corticosteroid Use in AECB pages 15-17*

(MO Comment: Based on the data there does not appear to be a significant interaction between telithromycin and corticosteroid use in the treatment of AECB. This information does not need to be included in the labeling.)

VII. Integrated Review of Safety

The safety review for telithromycin was done by Charles K. Cooper, MD. The reader should refer to that review for any detailed information on the safety of telithromycin. The common adverse events associated with telithromycin include diarrhea, nausea, headache, vomiting, and dyspepsia. Other adverse events reported are prolonged QTc interval, visual effects, and possible hepatotoxicity.

VIII. Dosing, Regimen, and Administration Issues

The dose used in the studies was 800 mg taken orally once a day. The length of treatment for CAP was 7-10 days.

IX. Use in Special Populations

As the number of patients with MDRSP was relatively small, there were not enough patients in any special populations to make any recommendations.

X. Conclusions and Recommendations

The indication for the use of telithromycin in mild to moderate CAP secondary to MDRSP is approvable. The numbers of patients in the studies was adequate. There were similar cure rates between all CAP secondary to *S. pneumoniae* and CAP secondary to MDRSP.

The indication for the use of telithromycin in mild to moderate CAP secondary to *S. aureus* is not approvable. Generally pneumonia secondary to *S. aureus* is a more severe disease treated with parental antimicrobials. There is no intravenous form of telithromycin available.

In reviewing the AECB studies with and without steroids, there was no evidence of the steroids being a confounding factor. The cure rates were similar both with and without steroids indicating that it was not the steroids making the main difference in clinical improvement.

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/s/

Anitra Denson
3/31/04 10:54:36 AM
MEDICAL OFFICER

John Alexander
3/31/04 11:49:24 AM
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Integrated Review of Safety – NDA 21-144 (Ketek (telithromycin))

Patient Accounting, Demographics and Extent of Exposure

Phase 1

Table ISS.1 shows the number of subjects exposed to telithromycin in clinical pharmacology studies. Patients may have been enrolled in more than one study; for example, the 45 subjects in the single IV dose studies received a total of 64 doses of telithromycin when doses received in other telithromycin studies are taken into account.

Table ISS.1. Telithromycin exposure in Phase 1 studies

Regimen	No. of subjects	Dose range (mg)	Mean age, y (range)	Mean no. of doses (range)
Single PO	313	50 – 2400	35.4 (18 – 76)	1
Multiple PO	208	100 – 2000	33.4	8.8 (1-21)
Single IV	45	120 – 2000	37.3 (18 – 76)	1

The vast majority of subjects (>95%) were white; most (>80%) were men. There were 55 subjects aged 65 years or older; 12 subjects with hepatic impairment; and 30 with renal impairment.

After the original NDA submission, the Applicant submitted data from additional clinical pharmacology studies comprising 84 patients. Most of these involved administration of single or multiple oral 800 mg doses of telithromycin. One study, designated 1049, enrolled 24 subjects (age range 53 – 77 years) with underlying cardiovascular disease, who received single telithromycin doses ranging from 800 – 1600 mg.

In 14 drug interaction studies, there were an additional 261 subjects who received multiple oral doses of 800 mg telithromycin. Concomitant medications or foods included ketoconazole, itraconazole, oral contraceptives, cisapride, sotalol, midazolam, digoxin, warfarin, coumadin, simvastatin, theophylline, ranitidine, antacid, paroxetine, or grapefruit juice. Subjects in these studies were healthy adults, generally less than 50 years old.

Medical Officer's Comment

It is important to note that the drug interaction studies, including those involving cardiovascular drugs, enrolled healthy young adults rather than individuals with the diseases for which these drugs are intended.

Phase 2

The Applicant selected dosing for Phase 3 studies on the basis of results from Phase 1 safety and pharmacokinetic studies, as well as pharmacodynamic studies in animal models of infection. Thus, there were no traditional Phase 2 dose-finding studies or proof-of-concept studies, and the safety review will consider only Phase 1 and Phase 3 studies.

Phase 3

The Phase 3 safety database for NDA 21-144 (telithromycin; Ketek™) consisted of all patients who received at least one dose of study treatment and who had at least one post-randomization safety assessment; the cut-off for safety information was 24 November 2000. The original NDA, submitted on 28 February 2000 contained safety information on 2365 telithromycin-treated patients and 1551 comparator-treated patients. A major clinical

amendment submitted on 28 February 2001 contained data on an additional 900 telithromycin-treated and 121 comparator-treated patients. There were 6113 patients enrolled in 13 Phase 3 trials; the safety database comprises data from 4937 patients (3265 telithromycin and 1672 comparator). For the controlled trials within the database, there were 2045 telithromycin-treated patients and 1672 comparator-treated patients. There were 1220 patients in uncontrolled Phase 3 trials.

All telithromycin-treated patients in Phase 3 studies received a daily oral dose of 800 mg; the scheduled duration of therapy ranged from 5-10 days, depending on the indication (actual range 1-15 days). Comparators included amoxicillin 1000 mg tid; amoxicillin/clavulanate 500 mg/125 mg tid; cefuroxime 500 mg bid; penicillin VK 500 mg tid, clarithromycin 250 – 500 mg bid; and trovafloxacin 200 mg qd. Comparators were given orally for 7-10 days.

Table ISS.2 shows patient accounting for the final Phase 3 safety database. Enrolled patients were excluded from the safety database because they did not receive study medication (generally because they were found not to meet inclusion or exclusion criteria after enrollment); because they were enrolled at one of 6 study sites that were excluded from the database because of concerns over data integrity; or because of lack of post-randomization safety assessment.

Table ISS.2. Patient accounting for telithromycin Phase 3 safety database.

Population	All centers	Excluding censored centers
Enrolled	6113	5909
Randomized/assigned	5193	4998
Treated	5169	4985
Safety evaluable	5113	4937

Medical Officer's Comment

The size of the database, like most NDA databases, is small in comparison to the potential population exposure, given that over 80 million treatment courses are written annually in the U.S. for outpatients with upper respiratory tract infections[1]. Thus, this database is not powered to detect rare but serious adverse events that could result in a significant number of adverse reactions post-approval, since events occurring at an incidence of 0.1% or less are not likely to be detected. For example, a fatal adverse event occurring at a rate of 0.001% would most likely not be detected in a database of this size; however, if 8 million telithromycin courses were administered post-approval (10% of the estimated market), 80 deaths from such an adverse event could be predicted.

In general, for controlled studies, the rates of exclusion from the safety database for each reason given above (not treated, not assessed, or studied at censored study site) were comparable for telithromycin and comparator. A total of 48 treated patients (25 telithromycin, 23 comparator) from data-valid sites were excluded from the database because of lack of post-randomization information. Although the majority of these exclusions were due to loss to follow-up or the patient's decision to stop participating in the study, 6 of these exclusions (4

[1] McCaig LF and Hughes JM. Trends in antimicrobial drug prescribing among office-based physicians in the United States. JAMA 1995; 273:214-9.

telithromycin, 2 comparator) were due to patients being discontinued for failure to meet inclusion or exclusion criteria. The sponsor did not provide an explanation for the failure to collect safety information on these patients.

Demographics for patients in Phase 3 controlled and uncontrolled studies are shown in **Table ISS.3** and a summary of age distribution is shown in **Table ISS.4**. Extent of exposure is shown in **Table ISS.5**.

Table ISS.3. Number of subjects (%) for demographic variables: all Phase III studies

Dosing Regimen	No. of Subjects	Sex		Race				Age (yrs)		
		M	F	White	Black	Asian	Other	13-18	>18-<65	≥65
Ketek 5 d	1429	648 (45.3)	781 (54.7)	1282 (89.7)	85 (5.9)	28 (2.0)	34 (2.4)	57 (4.0)	1219 (85.3)	153 (10.7)
Ketek 7-10 d	1836	983 (53.5)	853 (46.5)	1409 (76.7)	313 (17.0)	32 (1.7)	82 (4.5)	38 (2.1)	1579 (86.0)	219 (11.9)
Comparator	1672	785 (46.9)	887 (53.1)	1438 (86.0)	163 (9.7)	26 (1.6)	45 (2.7)	69 (4.1)	1343 (80.3)	260 (15.6)

Table ISS.4. Age distribution in Phase 3 studies

	Ketek 5 d	Ketek 7-10 d	Comparators
Mean age (y) ± SD	41.2 ± 16.1	43.8 ± 16.0	43.7 ± 17.6
Median age (y)	38.0	42.0	41.0
Range	13-86	13-99	13-97

Medical Officer's Comment

There were 372 telithromycin-treated patients (261 in controlled trials) who were 65 years or older in the safety database. Although this may appear to be a sizeable number of elderly patients, it is a relatively small sample in relation to the potential population exposure. This is particular important for this drug since, as discussed below, its pharmacokinetics are altered in elderly patients, potentially increasing the risk for adverse events and/or drug-drug interactions.

Table ISS.5. Extent of exposure in Phase 3 studies.

	Ketek 5 d	Ketek 7-10 d	Ketek total	Comparators
Number of patients	1429	1836	3265	1672
Mean days ± SD	4.9 ± 0.6	8.9 ± 1.8	7.2 ± 2.8	9.8 ± 2.1
Range (days)	1-5	1-15	1-15	1-16

Medical Officer's Comment

In interpreting safety information in relation to duration of telithromycin treatment, it is important to note that telithromycin has a long terminal half-life (9.8 hours); thus, the drug can be detected in serum for some days after therapy has ended. In addition, given the higher concentrations of drug that may accumulate in tissues, end-organ effects could potentially occur even after therapy has been completed.

Table ISS.6 shows the number of patients with medical conditions who may have been at higher risk for telithromycin-associated toxicity. **Table ISS.7** shows the numbers of patients receiving selected concomitant medications with the potential to interact with telithromycin.

Table ISS.6. Pretreatment disease profile of subjects in Phase 3 trials

Pretreatment Disease	Telithromycin			Comparator
	No. in controlled trials (%) (N=2045)	No. in uncontrolled trials (%) (N=1220)	Total (%) (N=3265)	No. of Subjects (%) (N=1672)
Chronic respiratory disease	822 (40.2)	518 (42.5)	1340 (41.0)	654 (39.1)
Cardiovascular disease	408 (20.0)	239 (19.6)	647 (19.8)	341 (20.4)
Ischemic heart disease	87 (4.3)	53 (4.3)	140 (4.3)	89 (5.3)
CrCl <50 mL/min	73 (3.6)	105 (8.6)	178 (5.5)	65 (3.9)
CrCl <80 mL/min	420 (20.5)	391 (32.0)	811 (24.8)	363 (21.7)
Diabetes mellitus	93 (4.5)	58 (4.8)	151 (4.6)	73 (4.4)
Liver Disease	29 (1.4)	18 (1.5)	47 (1.4)	27 (1.6)
Risk factors for torsade de pointes	810 (39.6)	539 (44.1)	1349 (41.3)	670 (40.0)
Abnormal baseline ECG	475 (23.2)	639 (52.4)	1114 (34.1)	437 (26.1)
Increased baseline QTc	102 (5.0)	107 (8.8)	209 (6.4)	104 (6.2)

Table ISS.7. Frequency of concomitant use of drugs with potential for causing drug interactions with telithromycin: Phase III studies

Concomitant medication	Telithromycin			Comparator
	No. in controlled trials (%) (N=2045)	No. in uncontrolled trials (%) (N=1220)	Total (%) (N=3265)	No. of Subjects (%) (N=1672)
Theophylline	29 (1.4)	38 (3.1)	67 (2.1)	34 (2.0)
Anticoagulants	137 (6.7)	136 (11.1)	273 (8.4)	136 (8.1)
Warfarin	13 (0.6)	13 (1.1)	26 (0.8)	8 (0.5)
Cardiac glycosides	6 (0.2)	17 (1.4)	23 (0.7)	8 (0.5)
Antiarrhythmics	8 (0.4)	6 (0.5)	14 (0.4)	7 (0.4)
CYP 3A4 substrates	766 (37.5)	423 (34.7)	1189 (36.4)	643 (38.5)
CYP 2D6 substrates	255 (12.5)	167 (13.7)	422 (12.9)	227 (13.6)
CYP 3A4 inhibitors	207 (10.1)	70 (5.7)	277 (8.5)	164 (9.8)
High potential to prolong QTc	145 (7.1)	17 (1.4)	162 (5.0)	94 (5.5)
CNS-active drugs	172 (8.4)	48 (3.9)	220 (6.7)	154 (9.2)
Statins	48 (2.3)	32 (2.6)	80 (2.5)	50 (3.0)

Medical Officer's Comment

The numbers of patients in Phase 3 trials in some of these at-risk populations are quite small (e.g., patients receiving cardiac glycosides). This is due in part to exclusion criteria built into the Phase 3 trials. Although these criteria were rational from a subject safety viewpoint, they severely limit any conclusions about the risks of administering telithromycin in the general population. In particular, patients with certain major risk factors for torsades de pointes (such as patients with severe hypokalemia or bradycardia) were generally excluded, limiting the amount of data about the safety of telithromycin in such patients.

The Applicant classified a surprisingly high percentage (>40%) of patients in Phase 3 trials as having risk factors for torsades de pointes. It was not clear from the data presented how such risk factors were defined or what their relative significance was. There was a marked discrepancy between this high percentage and the low numbers of patients identified by the safety reviewer as having defined risks for torsades. For example, of patients with sufficient EKG data to allow calculation of changes in QTc, there were only eight telithromycin-treated patients who had a heart rate of less than 50 at baseline, and only two telithromycin-treated patients with a baseline serum potassium level of less than 3 mEq/L.

Other at-risk populations, although not specifically excluded from the Phase 3 trials, were not represented in the safety database to any great extent. For example, there were only three telithromycin-treated patients who received concomitant HIV protease inhibitors. This is a significant limitation since HIV-infected patients have an increased incidence of

pneumococcal infection than the general population and are more likely to receive antimicrobials; in addition, protease inhibitors are metabolized by CYP 3A4 and their clearance is significantly affected by other medications interacting with this system. Thus, there is little information in the database on the safety of telithromycin for a large population likely to receive the medication and who are also on a potentially interacting medication.

Deaths

There were no deaths in Phase 1 studies. There were 11 deaths in Phase 3 trials (7 telithromycin and 4 comparator). Ten deaths occurred in studies of community-acquired pneumonia (CAP); one (in a patient with acute lymphoid leukemia receiving penicillin) occurred in a study of tonsillopharyngitis. The adverse event leading to death occurred on treatment for 5/7 telithromycin patients and 3/4 comparator-treated patients. First-listed causes of death in the telithromycin group included multi-organ failure, heart failure, leptospirosis, Gram-negative septicemia, aspiration, acute myocardial infarction, and pneumonia. First-listed causes of death in the comparator group included asthma, lung carcinoma, pneumonia, and acute lymphoid leukemia. None of the deaths were assessed as being related to study drug.

Narratives for each death as supplied by the sponsor are as follows:

Deaths in Telithromycin-treated patients

Subject 0703/1466 in Study 3000 was a 57-year-old white male who started treatment for CAP with 800 mg telithromycin daily on 24 Nov 1998. On —, the subject developed gastritis with nausea and vomiting. On —, the onset of acute leptospirosis, confirmed by serological tests, was recorded in association with renal failure, hemolytic anemia, sepsis, and liver insufficiency. On —, the subject developed adult respiratory distress syndrome (ARDS), with worsening pneumonia and sepsis. Study medication was discontinued on — due to the events of acute leptospirosis and ARDS. Subsequent antimicrobial therapy was started on — to treat the pneumonia. The subject died on —, with the primary cause of death listed as ARDS and acute leptospirosis. Relevant medical/surgical history included hypertension and total hip replacement in 1977. The pretherapy chest x-ray showed left lower lobe consolidation with infiltrates. Retrospective serology was positive for *Chlamydia pneumoniae*.

Medical Officer's Comment

The patient's presentation and course are consistent with leptospirosis (either in the acute phase or immune phase); the diagnosis was apparently made by serology, although no titers are provided. Given this, it is reasonable to exclude a relationship between death and administration of telithromycin. Of note, a week after discontinuation of telithromycin, the patient received cisapride and nifedipine; the pharmacokinetics of both of these drugs could potentially be altered by telithromycin via interactions with CYP 3A4. There is no data to indicate whether drug-drug interactions could have influenced the patient's course, although the timing argues against the occurrence of such interactions.

Subject 0803/1520 in Study 3000 was a 65-year-old white male who started treatment for CAP with 800 mg telithromycin daily on 8 Dec 1998. Treatment with study medication was completed on 16 Dec 1998. At the end of treatment visit on —, the subject's clinical status had returned to the preinfection state. On —, the subject presented with a nonpruritic rash on upper and lower extremities, which a skin biopsy confirmed as leukocytoclastic vasculitis. Urinalysis showed microscopic hematuria and chest x-ray showed bilateral infiltrates, which were identified in the chest CT scan as pleural fluid. On —

the posttherapy assessment of clinical outcome was cure. On this day, however, the subject became hypotensive and ECG and serum creatine kinase indicated an acute myocardial infarction. On [redacted] (the posttherapy/TOC visit), the clinical assessment was failure. The subject died on [redacted] with the primary cause of death listed as gram-negative septicemia. Relevant medical/surgical history included stroke in 1993, COPD since 1994, hypertension since 1993, CHF since [redacted] 1998, respiratory insufficiency from [redacted] 1998, CAD, diabetes mellitus since 1993, partial gastrectomy in 1976, thymectomy in 1996, aortobifemoral bypass on [redacted] 1998, and chronic osteomyelitis of the left foot since [redacted] 1998.

Medical Officer's Comment

The diagnosis of leukocytoclastic vasculitis is interesting, since this disorder is frequently due to immunologic reactions to drugs. Concomitant medications included ofloxacin and clindamycin (discontinued 12/8/98), aspirin, atenolol, furosemide, and salbutamol. While any of these could have induced a drug reaction, the temporal relationship between timing of telithromycin therapy and the appearance of the eruption suggests, but does not prove, a causal relationship. Although the rash started after telithromycin had been discontinued, it is important to note that telithromycin has a long half-life and detectable serum concentrations were most likely present at the time of onset of the eruption. Leukocytoclastic vasculitis is a necrotizing disorder and could potentially have affected viscera, including the GI tract, predisposing the patient to Gram-negative sepsis via bowel leakage.

Subject 1002/027 in Study 3001 was a 71-year-old white female who started treatment for CAP with 800 mg telithromycin daily on [redacted]. At study entry, the subject was admitted to a frail nursing care unit. Pretherapy chest x-ray showed single lobe consolidation on the right side. Sputum cultures were positive for *S. pneumoniae*, beta-lactamase-producing *H. influenzae*, and *S. aureus* (resistant to HMR 3647). On [redacted], the subject's clinical condition worsened (severe lobar pneumonia, with associated hypotension, cyanosis, and altered mental state). Antimicrobial therapy with intravenous gentamicin and Rocephin (ceftriaxone) was started. On [redacted], severe multiorgan failure developed, with circulatory, kidney, and respiratory failure. The subject died on [redacted], with the primary cause of death reported as multiorgan failure (coded using the HARTS dictionary as "ill-defined condition"). The investigator assessed the multiorgan failure as not related to the study medication. The last dose of study medication was taken on [redacted]. Relevant medical/surgical history included COPD since 1990,CAD since 1994, dorsal scoliosis, and surgical intervention for squamous carcinoma of the right cheek in 1994.

Medical Officer's Comment

This death appears to have due at least in part to therapeutic failure of telithromycin. On entry, the patient was tachycardic (140 bpm) and had a blood pressure of 95/70. The case report form does not indicate the patient's oxygenation on study entry. Of note, the patient's creatinine clearance on [redacted] was 16 mL/min. It is not clear that it was appropriate to enroll this debilitated elderly patient with tachycardia and borderline hypotension in a trial of an oral antimicrobial for treatment of community-acquired pneumonia.

Subject 1301/004 in Study 3001 was an 80-year-old white male who started treatment for CAP with 800 mg telithromycin daily on 16 Dec 1998. On [redacted], the subject developed dyspnea and hypotension (BP: 100/70 mm Hg). Intensive medical care was given, but

Subsequently, new information was obtained after the NDA submission, and the cause of death was changed to foreign body in larynx.

Medical Officer's Comment

It is not clear from the case report form on what basis aspiration was established as the primary event in this patient's demise. Of note, the patient developed unexpected renal insufficiency, with the autopsy showing coronary artery disease and cardiomyopathy. The possibility that telithromycin affected cardiac function, leading to renal insufficiency and fluid overload cannot be excluded by the data at hand. It is of interest that the patient was on concomitant theophylline and developed nausea and vomiting, which can be signs of theophylline intoxication; a drug-drug interaction between theophylline and telithromycin cannot be excluded.

Subject 0537/009 in Study 3010 was a 44-year old black male who experienced a serious adverse event of acute myocardial infarction on day 1 of the study. The subject presented with pleuritic chest pain, cough, dyspnea, tachypnea and fever; he was hospitalized and enrolled into the study. Pretherapy/entry chest x-ray revealed consolidation. No causative pathogen for CAP was isolated. Review of the pretherapy/entry ECG indicated evidence of a new myocardial infarction (Q waves in leads V1-V3, ST segment elevations in leads V1-V4, PR segment depressions in lead II, QTc of 470 msec) and sinus tachycardia at 130 beats per minute. The subject died on day 2. The investigator assessed the event as not related to the study.

Medical Officer's Comment

This death is of concern because the patient had a baseline EKG showing QT interval prolongation, raising the possibility that telithromycin, with its effects on cardiac repolarization, may have induced a ventricular dysrhythmia in this patient. Of note, this patient had normal levels of the MB fraction of creatinine phosphokinase and of troponin I.

Deaths in Comparator-treated patients

Subject 0111/004 in Study 3001 was a 52-year-old white male who started treatment for CAP with amoxicillin on 27 Jul 1998. Study medication was discontinued on 3 Aug 1998 due to low creatinine clearance at study entry (exclusion criteria). Subsequent antimicrobial therapy with amoxicillin was started on — to treat the pneumonia. On — the subject experienced bronchospasm and died while being transported to the hospital. The severe asthmatic crisis, which led to the death, was reported as assessed by the investigator to be not related to study medication. No autopsy was performed. Relevant medical history included asthma since 1956 and gastritis since 1998.

Medical Officer's Comment

The length of time between treatment and death argues against any relation between study drug and death in this case.

Subject 1306/008 in Study 3004 was a 55-year-old white female who started treatment for tonsillitis/pharyngitis with penicillin VK on 25 Feb 1999. The last dose of study medication was taken on 27 Feb 1999. On —, the subject had fever and weakness. Pretherapy hematology tests showed elevated leukocytes (215 x10 9 /L). The subject was diagnosed with severe acute lymphoid leukemia. The subject was started on amoxicillin for tonsillitis on — On — ne subject was withdrawn from the study and transferred to another hospital for treatment of acute lymphoid leukemia. On —, 44 days after the last dose

of study medication, the subject died with the primary cause of death reported as acute lymphoid leukemia. The investigator assessed the cause of death as not related to study medication but due to the underlying/concomitant illness. Relevant medical/surgical history included mild perceptive hearing loss and splenectomy in 1997.

Medical Officer's Comment

The length of time between treatment and death, as well as the history of acute lymphoid leukemia, argues against any relation between study drug and death in this case.

Subject 0060/002 in Study 3006 was a 70-year-old white female who started treatment for CAP with clarithromycin on 17 Jul 1998. The subject completed 10 days of treatment with study medication on 26 Jul 1998. The subject died 5 months posttreatment (on —, with the cause of death reported as malignant bronchial neoplasm. Relevant medical/surgical history included schizophrenia since 1978, hypothyroidism since 1995, seizure disorder since 1995, COPD since 1988, constipation since 1995, intestinal pneumatosis since 1997, and small bowel resection in 1997. The subject had been a smoker since 1941, and smoked 50 cigarettes/day at the time of enrollment.

Medical Officer's Comment

The length of time between treatment and death, as well as the history of lung cancer, argues against any relation between study drug and death in this case.

Subject 0386/018 in Study 3006 was a 43-year-old white female who started treatment for CAP with clarithromycin on 28 Jul 1999. Pretherapy sputum culture revealed normal flora. The subject completed 10 days of treatment with study medication on 6 Aug 1999. On 9 Aug 1999, the subject developed worsening pneumonia. Subsequent antimicrobial therapy with ceftriaxone was started on 9 Aug 1999 to treat the pneumonia. On —, the subject was hospitalized for worsening pneumonia with associated dyspnea, tachypnea, hyperventilation, increased sputum production, chest pain, nausea, increased rales and rhonchus, and mild pleural effusion. Antimicrobial therapy with clindamycin, cefotaxime, ceftazidime, and amikacin was started to treat the pneumonia. The subject died on —, with the primary cause of death as pneumonia (organism not identified). Relevant medical/surgical history included diabetes mellitus since — 1999 and a breast biopsy in 1994.

Medical Officer's Comment

This patient most likely suffered relapse from her pneumonia; this death should be regarded at least in part as being due to therapeutic failure of clarithromycin.

Patients may have had multiple causes of death listed in addition to the first-listed cause. For telithromycin-treated patients, 6/7 deaths had a primary or secondary cardiovascular cause listed. None of the deaths in comparator-treated patients had a cardiovascular cause listed. Details of deaths related to cardiovascular causes may be found in the cardiovascular safety section of this review.

Nonfatal serious adverse events (SAEs)

In Phase 1 studies, two telithromycin-exposed subjects had SAEs; both of these were post-tonsillectomy patients, one of whom had epistaxis and the other of whom had surgical site hemorrhage. In neither case was the SAE felt to be related to telithromycin.

In controlled Phase 3 trials, 40/2045 (2.0%) of telithromycin-treated patients had nonfatal serious adverse events (SAEs), while 41/1672 (2.5%) of comparator-treated patients had nonfatal

SAEs. Eight telithromycin-treated patients and 4 comparator-treated patients had nonfatal SAEs possibly related to study drug. **Table ISS.8** shows possibly related nonfatal SAEs in Phase 3 trials.

Table ISS.8. Nonfatal SAEs possibly related to study drug in Phase 3 controlled trials.

	Telithromycin (N=2045)	Comparators (N=1672)
Any SAE	8 (0.4%)	4 (0.2%)
Allergic reaction	2 (0.1%)	1 (0.1%)
Liver damage	2 (0.1%)	0 (0.0%)
Gastroenteritis	1 (<0.1%)	0 (0.0%)
Pseudomembranous colitis	1 (<0.1%)	1 (0.1%)
Erythema multiforme	1 (<0.1%)	0 (0.0%)
Vomiting	1 (<0.1%)	0 (0.0%)
Dyspnea	0 (0.0%)	1 (0.1%)
Gastrointestinal disorder	0 (0.0%)	1 (0.1%)

In uncontrolled trials, 40/1220 (3.3%) of telithromycin-treated patients had a nonfatal SAE. Four (0.3%) of these were assessed as being possibly related to telithromycin: gastroenteritis, vasculitis, hepatitis, and leukopenia.

A discussion of serious cardiovascular SAEs may be found in the cardiovascular safety section of this review. For a discussion of hepatic SAEs, please refer to the review of hepatic safety by Dr. Edward Cox.

Adverse events

The Applicant defined the term **adverse event** as "any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in a clinical study that may impair the well being of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g., that require unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study).

The Applicant defined the term "treatment-emergent adverse event" as follows:

"All on-treatment events were classified as treatment-emergent or non-treatment-emergent. The following definitions were used:

- "Treatment-emergent adverse events (TEAEs) include any on-treatment adverse event that was not present before treatment or was 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. In addition, any on-treatment adverse event considered possibly related to study medication by the investigators that led to permanent discontinuation of study medication, or resulted in death, was considered treatment-emergent. This group of adverse events is of primary interest.
- "Possibly related treatment-emergent adverse events are those treatment-emergent adverse events the investigators reported as "possibly related" to study medication and those on-treatment adverse events with missing causality."

Table ISS.9 shows the incidences of the most common TEAEs in Phase 3 controlled trials.

Table ISS.9. Incidence of TEAEs by decreasing frequency in Phase 3 controlled trials

	Telithromycin (n=2045)	Comparators (n=1672)
Diarrhea	295 (14.4%)	167 (10.0%)
Nausea	184 (9.0%)	73 (4.4%)
Headache	118 (5.8%)	118 (7.1%)
Dizziness	91 (4.4%)	48 (2.9%)
Vomiting	67 (3.3%)	40 (2.4%)
Dyspepsia	50 (2.4%)	30 (1.8%)
Abdominal pain	40 (2.0%)	26 (1.6%)
Abnormal LFTs	32 (1.6%)	25 (1.5%)

Other TEAEs of note in controlled trials included taste perversion (telithromycin 1.8%, comparators 2.2%), gastrointestinal pain (telithromycin 1.5%, comparators 0.8%), flatulence (telithromycin 1.7%, comparators 0.8%) and blurred vision (telithromycin 0.7%, comparators 0.1%).

Table ISS.10. shows the incidence of the most common drug-related TEAEs in controlled Phase 3 trials.

Table ISS.10. Incidence of drug-related TEAEs by decreasing frequency in Phase 3 controlled trials

	Telithromycin (n=2045)	Comparators (n=1672)
Diarrhea	272 (13.3%)	158 (9.4%)
Nausea	166 (8.1%)	64 (3.8%)
Dizziness	73 (3.6%)	26 (1.6%)
Vomiting	57 (2.8%)	24 (1.4%)
Headache	45 (2.2%)	51 (3.1%)
Dyspepsia	39 (1.9%)	20 (1.2%)
Abdominal pain	32 (1.6%)	19 (1.1%)
Abnormal LFTs	23 (1.1%)	18 (1.1%)

Table ISS.11 shows the incidence of the most common drug-TEAEs in uncontrolled Phase 3 trials.

Table ISS.11. Incidence of drug-related TEAEs by decreasing frequency in Phase 3 uncontrolled trials

	Telithromycin (n=1220)
Diarrhea	88 (7.2%)
Nausea	44 (3.6%)
Headache	14 (0.7%)
Dizziness	9 (1.1%)
Vomiting	23 (1.9%)
Dyspepsia	5 (0.4%)
Abdominal pain	12 (1.0%)
Abnormal LFTs	35 (2.9%)
Vaginal moniliasis	16 (1.3%)
Taste perversion	12 (1.0%)

Table ISS.12 shows the incidences of the most common TEAEs by sex in Phase 3 controlled trials.

Table ISS.12. Incidence of TEAEs by sex in Phase 3 controlled trials

	Men		Women	
	Telithromycin (n=949)	Comparators (n=785)	Telithromycin (n=1096)	Comparators (n=887)
Diarrhea	124 (13.1%)	80 (10.2%)	171 (15.6%)	87 (9.8%)
Nausea	58 (6.1%)	22 (2.8%)	126 (11.5%)	51 (5.7%)
Headache	52 (5.5%)	50 (6.4%)	66 (6.0%)	68 (7.7%)
Dizziness	35 (3.7%)	23 (2.9%)	56 (5.1%)	25 (2.8%)
Vomiting	17 (1.8%)	16 (2.0%)	50 (4.6%)	40 (2.7%)
Dyspepsia	14 (1.5%)	146 (1.8%)	36 (3.3%)	16 (1.8%)
Vaginal moniliasis	0 (0.0%)	0 (0.0%)	29 (2.6%)	32 (3.6%)
Taste perversion	12 (1.3%)	15 (1.9%)	24 (2.2%)	22 (2.5%)
Abdominal pain	18 (1.9%)	7 (0.9%)	22 (2.0%)	19 (2.1%)
Dry mouth	12 (1.3%)	12 (1.5%)	20 (1.8%)	8 (1.5%)
Abnormal LFTs	21 (2.2%)	18 (2.3%)	11 (1.0%)	7 (0.8%)

Medical Officer's Comment

The incidence of diarrhea, nausea, vomiting, and dizziness were increased in women treated with telithromycin relative to comparator.

Table ISS.13 shows the incidence of the most common treatment-emergent events in patients 65 years and older in Phase 3 controlled trials.

Table ISS.13. Incidence of TEAEs in patients 65 y and older in Phase 3 controlled trials

	Telithromycin (n=257)	Comparators (n=260)
Diarrhea	32 (12.5%)	31 (11.9%)
Nausea	17 (6.6%)	8 (3.1%)
Headache	9 (3.5%)	9 (3.5%)
Dizziness	9 (3.5%)	6 (2.3%)
Abnormal LFTs	7 (2.7%)	3 (1.2%)
Dyspepsia	6 (2.3%)	1 (0.4%)
Abdominal pain	5 (1.9%)	3 (1.2%)
Vomiting	3 (1.2%)	4 (1.5%)

Telithromycin is metabolized by cytochrome CYP3A4; phase I data show that the C_{max} and AUC for telithromycin are markedly increased when it is co-administered with a CYP3A4 inhibitor (see the Cardiovascular safety section). It was therefore of interest whether intake of 3A4 inhibitors affected the incidence of adverse events in telithromycin-treated patients. **Table ISS.14** shows the most common TEAEs in controlled trials according to whether or not patients received a concomitant medication that inhibited CYP3A4. For a number of these TEAEs, the absolute incidence was increased in telithromycin-treated patients who received a concomitant 3A4 inhibitor, compared to telithromycin-treated patients who did not receive an inhibitor. In addition, the incidence of these TEAEs was increased in telithromycin-treated patients who received an inhibitor relative to comparator-treated patients who received an inhibitor.

The analysis in Table ISS.14 should be regarded as exploratory and interpreted cautiously, since patients were not randomized on the basis of CYP3A4 inhibitor intake; therefore other variables not controlled for in this analysis could account for the observed differences.

Table ISS.14. Incidence of TEAEs in controlled trials by intake of 3A4 inhibitors

	Received 3A4 inhibitor		Did not receive 3A4 inhibitor	
	Telithromycin (n=207)	Comparators (n=164)	Telithromycin (n=1838)	Comparators (n=1508)
Diarrhea	34 (16.4%)	9 (5.5%)	261 (14.2%)	158 (10.5%)
Nausea	21 (10.1%)	5 (3.0%)	163 (8.9%)	68 (4.5%)
Headache	12 (5.8%)	12 (7.3%)	106 (5.8%)	106 (7.0%)
Dizziness	13 (6.3%)	6 (3.7%)	78 (4.2%)	42 (2.8%)
Vomiting	14 (6.8%)	6 (3.7%)	53 (2.9%)	34 (2.3%)
Abnormal LFTs	3 (1.4%)	0 (0.0%)	29 (1.6%)	25 (1.7%)
Abdominal pain	6 (2.9%)	5 (3.0%)	34 (1.8%)	21 (1.4%)
Dyspepsia	10 (4.8%)	2 (1.2%)	40 (2.2%)	28 (1.9%)

There was no clear increase in TEAEs in patients on other classes of medications; however, given the small numbers of patients in controlled trials who received some potentially interacting medications (e.g., stains), it is difficult to draw firm conclusions regarding the likelihood of clinically relevant interactions. Similarly, in patients with diabetes, severe renal

impairment, or hepatic dysfunction at baseline, there did not appear to be an increased incidence of TEAEs; however, given the relatively small numbers of patients in these populations, this finding should be interpreted cautiously.

Discontinuations

In Phase 3 controlled trials, discontinuations due to adverse events occurred in 98/2045 (4.8%) of telithromycin-treated patients and 73/1672 (4.4%) of comparator-treated patients. **Table ISS.15** shows the most common reasons for discontinuation in controlled trials.

Table ISS.15. Incidence of study drug discontinuation for specific AEs in Phase 3 controlled trials

	Telithromycin (n=2045)	Comparators (n=1672)
Any	98 (4.8%)	73 (4.4%)
Diarrhea	20 (1.0%)	13 (0.8%)
Vomiting	19 (0.9%)	9 (0.5%)
Nausea	18 (0.9%)	10 (0.6%)
Abnormal LFTs	5 (0.2%)	5 (0.3%)
Gastroenteritis	3 (0.1%)	2 (0.1%)
Gastrointestinal pain	2 (0.1%)	2 (0.1%)
Dyspepsia	2 (0.1%)	1 (0.1%)
Allergic reaction	5 (0.2%)	2 (0.1%)
Abdominal pain	5 (0.2%)	3 (0.2%)
Dizziness	5 (0.2%)	1 (0.1%)
Abnormal vision	2 (0.1%)	0 (0.0%)
Blurred vision	1 (<0.1%)	0 (0.0%)
Prolonged QT interval	1 (<0.1%)	1 (0.1%)

In uncontrolled trials, discontinuations due to adverse events occurred in 31/1220 (2.5%) of telithromycin-treated patients. **Table ISS.16** shows the most common reasons for discontinuation in uncontrolled trials.

Table ISS.16. Incidence of study drug discontinuation for specific AEs in Phase 3 uncontrolled trials

	Telithromycin (n=1220)
Any	31 (2.5%)
Diarrhea	3 (0.2%)
Vomiting	3 (0.2%)
Abnormal LFTs	2 (0.2%)
Gastrointestinal pain	2 (0.2%)
Infection	2 (0.2%)
Pleural effusion	2 (0.2%)
Allergic reaction	1 (0.1%)
Nausea	1 (0.1%)
Dyspepsia	1 (0.1%)

Cardiovascular Safety

In vitro *and preclinical data*

For a full discussion of *in vitro* and preclinical data, please refer to the pharmacology/toxicology review by Dr. Terry Peters and the clinical pharmacology review by Dr. Jenny Zheng. *In vitro*, telithromycin blocks repolarization of myocardial cells, in part by inhibiting the rapid component of the delayed rectifying current (IK_r), with an inhibition constant similar to that of a number of quinolones and macrolides. Consistent with its ability to induce IK_r blockade, telithromycin also increases action potential duration in isolated rabbit Purkinje fibers (**ISS.17**).

Table ISS.17. Percentage increase in action potential duration of rabbit Purkinje fibers, stimulated at 60 pulses per minute, induced by telithromycin and comparator macrolides

		% increase in APD at (μM)						
Test agent		0.1	0.3	1	3	10	30	100
Telithromycin	APD_{50}	-3.1	2.3	11.4	21.3	33.7	73.7	164.0
	APD_{90}	0.1	3.2	7.0	13.9	24.5	60.3	148.7
Clarithromycin	APC_{50}	-	-	-	13.4	30.4	49.5	72.6
	APD_{90}	-	-	-	6.1	15.7	31.8	58.4
Erythromycin	APD_{50}	-	-	-	3.5	9.8	24.2	58.5
	APD_{90}	-	-	-	3.1	9.0	21.9	57.5
Roxithromycin	APD_{50}	-	-	-	3.8	10.0	16.2	30.8
	APD_{90}	-	-	-	3.0	9.1	22.4	39.5

Of note, telithromycin markedly potentiates sotalol-induced prolongation of action potential duration. Although the telithromycin concentration at which this effect occurs (8 mg/L) is significantly greater than the mean telithromycin C_{max} (~2 mg/L), it should be kept in mind that there is substantial variability in telithromycin pharmacokinetics, with a maximal C_{max} in phase I studies of [redacted] (see below under Pharmacokinetic Variability in Special Populations). In addition, rat studies have demonstrated myocardial telithromycin concentrations up to 7.7 times those in plasma. Because tissue concentrations are physiologically more relevant to drug effects on cardiac repolarization, conclusions about apparent clinical safety margins extrapolated from *in vitro* free drug concentrations may be misleading.

In dog studies, intravenous infusion of a single dose of telithromycin caused a rapid increase in QT_c (QT interval corrected by Bazett's formula[2]) by 30 msec, within 1 minute after administration, as well as an increase in heart rate. Although Bazett's formula overcorrects the QT interval at higher heart rates, analysis of QT_f (QT interval corrected by Fridericia's formula[3]) also showed prolongation of the QT interval by of telithromycin, by 16 – 31 msec. Clarithromycin increased the QT_c interval by a lesser amount (17 msec) and did not affect heart rate. A multiple oral dose study of telithromycin in dogs showed significant QT prolongation (27-30 msec) at high doses (100 mg/kg/d).

[2] $QT_c = QT/(RR\ interval)^{1/2}$

[3] $QT_f = QT/(RR\ interval)^{1/3}$

Clinical Pharmacology

Medical Officer's Comment

The clinical pharmacology section of this review draws largely on the work of the clinical pharmacology review by Dr. Jenny Zheng; please refer to Dr. Zheng's review for a full discussion of clinical pharmacology and biopharmaceutic issues.

Standard pharmacokinetic parameters for oral telithromycin are given in **Table ISS.18**. Clinical pharmacology concerns of particular importance with regard to cardiovascular safety include the following:

- Drug exposure may be significantly increased in the elderly and renally or hepatically impaired patients.
- Drug-drug interactions: telithromycin exposure may be significantly increased by co-administration of a CYP 3A4 inhibitor such as ketoconazole. In addition, telithromycin may inhibit clearance of other drugs metabolized by 3A4, potentially increasing the risk of toxicity from those agents.
- Cardiac repolarization effects: telithromycin prolongs the QT interval in a concentration-dependent fashion.
- The potential for these factors to act in an additive or synergistic fashion, leading to an increased risk of torsades de pointes..

Table ISS.18. Summary of oral telithromycin pharmacokinetics

PK Assessments in Healthy Subjects	PK Parameters After 800 mg QD (Unless Noted) Expressed as Mean (CV)
Absorption and Systemic Bioavailability (Study 1044)	Absolute Bioavailability: Young: 57.3% (31); Elderly 56.6% (20) T_{max}: 2.5–3 hours
Food Effects (Study 1003)	None
Distribution	Protein Binding: 60% – 70% Bound V_{ss} (L): Young subjects:210 (27); elderly subjects: 226 (21) Penetration into tissues: Blister fluid/tonsil secretion/pulmonary tissue/saliva
Metabolism (Study 1009)	Mainly metabolized (22% and 12% unchanged in feces and urine) CYP3A substrate Four metabolites have been identified.
Excretion (Study 1009)	Urine: 12% Unchanged telithromycin Feces: 22% Unchanged telithromycin
	Single dose: C_{max} (mg/L)= 1.90 (42); range: $AUC_{0-\infty}$(mg·h/L)= 8.25 (31) $t_{1/2}$ (h): 7.16 (19) CL/F (L/h): 102.3 (31) range: CLr/F_{0-24}: (L/h): 12.32 (17) Multiple doses: C_{max} (mg/L)= 2.27(31); range: $AUC_{0-\infty}$(mg·h/L)= 12.5 (43); range: $t_{1/2}$ (h): 9.81 (20) CL/F (L/h): 71.1 (29) range: CLr/F: (L/h): 12.5 (34)
Disposition Kinetics	Nonlinear pharmacokinetics Slightly more than dose proportional Increases in AUC and C_{max} after 400 mg, 800 mg and 1600 mg. Accumulation factor was about 1.5 after multiple doses.
Significant Interactions	CYP3A4 inhibitor: ↑ telithromycin by ketoconazole/itraconazole ↔ telithromycin by grapefruit juice CYP3A4 substrate: ↑ cisapride /↑ simvastatin CYP2D6 substrate: ↔paroxetine CYP1A2 substrate: ↑ theophylline CYP2C9 substrate: ↔ warfarin Others: ↑ digoxin / ↔ oral contraceptive (ethinylestradiol) Gastric pH: telithromycin not changed by ranitidine and Maalox
Renal impairment	AUC and C_{max} not significantly changed after single dose. No dose adjustment recommended by sponsor.
Hepatic Impairment	AUC and C_{max} are comparable but $t_{1/2}$ ↑ significantly. No dose adjustment recommended by sponsor.
Effects of Age on PK	AUC and C_{max} increased by 100% in elderly after multiple doses but no dose adjustment recommended by sponsor.
Effects of Gender on PK	None

1. Phase I data QT_c prolongation and pharmacokinetics in normal subjects

a) Dose-response relationship

Two studies (1030 and 1046) demonstrated that telithromycin and placebo treatments are associated with significantly different maximal changes in QT_c. These studies also demonstrated that the time at which the maximal change in QTc occurred in telithromycin-treated patients may have been later than the time at which maximal serum concentrations were reached.

Study 1030

This phase I study was designed to study changes in QT_c intervals in telithromycin-treated subjects. Four treatment groups were included in this study:

Group A: A four-period, double-blind, randomized, placebo-controlled treatment group. Eight healthy young subjects received a single oral dose of telithromycin. Each subject received 3 incremental single doses of telithromycin (1600, 2000, 2400 mg) and 1 placebo dose. During each period, 6 subjects received active treatment (at one or more dose strengths) and 2 subjects received placebo.

Group B: A double-blind, parallel, randomized, placebo-controlled treatment group. Eight healthy young subjects received telithromycin (1600 mg) once a day for 5 days. Each subject was randomly allocated to 1 of 2 treatments (telithromycin: 6 subjects or placebo: 2 subjects).

Group C: Identical design to group A, except that 8 elderly (aged 60 years to 85 years) male and postmenopausal female subjects were enrolled. Each subject received 3 incremental single doses of telithromycin (1200, 1600, 2000 mg).

Group D: Identical design to group B, except that 8 elderly (aged 60 years to 85 years) male and postmenopausal female subjects were enrolled. Subjects received placebo or 1200 mg telithromycin once a day for 5 days.

Resting EKGs and blood samples for pharmacokinetic measurements were obtained at various timepoints after telithromycin or placebo dosing. For groups A and C, mean ΔQT_c and ΔQT_f values were calculated at each sample collection time. The maximal means are shown in **Table ISS.19**. The maximum mean ΔQT_c occurred at 1.5 hours in young subjects after single telithromycin doses of 1600 mg, 2000 mg and 2400 mg, with values of 20 ms, 18 ms and 28 ms, respectively. The corresponding ΔQT_c after placebo was 4 ms. The differences between treatments and placebo were statistically significant. In elderly subjects, the mean maximum ΔQTc occurred at 4 hours after single doses of 1200 mg, 1600 mg and 2000 mg, with values of 12 ms, 18 ms and 19 ms, respectively. The corresponding ΔQT_c after placebo was -3 ms. The differences between treatments and placebo were statistically significant.

In the multiple dose groups (B and D), when telithromycin was compared with placebo, no statistically significant difference in ΔQT_c between telithromycin and placebo was found after repeated doses of 1600 mg in young subjects or 1200 mg in elderly subjects. However, it should be noted that in these groups, the placebo and treatment arms were parallel instead of crossed over. Because of normal inter-individual variability in QT_c, a design using control subjects different than those exposed to test drug may have decreased power to detect a difference in QT_c intervals.

Table 1SS.19. Mean (±SD) maximum changes in QT_c, QT_f and heart rate after telithromycin treatment.

	Treatment A				Treatment B	
	Placebo	1600 mg	2000 mg	2400 mg	Placebo	1600 mg
Number of subjects	8	8	8	7	2	6
Mean maximum ΔQT_c [a]	4 (18)	20 (14)	18 (10)	28 (19)	0 (1)	17 (17)
Mean maximum ΔQT_f [a]	3 (14)	10 (11)	7 (8)	15 (11)	-1 (2)	5 (12)
Mean heart rate increase	0 (7)	9 (5)	10 (7)	13 (7)	1 (4)	11 (5)
	Treatment C				Treatment D	
Parameters	Placebo	1200 mg	1600 mg	2000 mg	Placebo	1200 mg
Number of subjects	8	8	8	8	2	6
Mean maximum ΔQT_c [b]	-3 (8)	12 (15)	18 (17)	19 (11)	-6 (9)	4 (14)
Mean maximum ΔQT_f [b]	3 (5)	13 (11)	12 (15)	12 (7)	-6 (7)	-5 (13)
Mean heart rate increase	-5 (4)	-2 (6)	5 (4)	7 (4)	1 (1)	9 (6)

[a] The mean average QT_c, QT_f, and heart rate (HR) were calculated for each time point at which observations were obtained. The maximum QT_c and QT_f were observed at 1.5 hours after a single dose in treatment A. The maximum QT_c and QT_f were observed at 1.5 hours after the last dose on day 5 for treatment B.

[b] The maximum QT_c and QT_f were observed at 4 hours after a single dose in treatment C. The maximum QT_c and QT_f were observed at 1.5 hours after the last dose on day 5 for treatment D.

Of note, in treatment group C, the maximum serum telithromycin concentration was observed at 2 hours after dosing for all doses, while the maximum QT_c was observed at 4 hours after dosing.

Medical Officer's Comment

Although these changes are small, they are consistent with a dose-related (and by inference, concentration-related) effect of telithromycin on QT interval. As noted above, Bazett's formula tends to overcorrect the QT interval at higher heart rates. However, analysis using a more conservative correction formula (Fridercia's formula) that is more independent of heart rate also shows an effect of telithromycin on the QT interval.

Study 1046

This was a double-blind, randomized, placebo-controlled, 3-period cross-over study, with 2 escalating single oral doses of telithromycin (2400 mg and 3200 mg) and an interspersed single placebo dose. Twenty-four healthy young subjects (12 men and 12 women, mean age 29 ± 7 years) were studied. Resting EKGs and blood samples for pharmacokinetic measurements were obtained at various timepoints after telithromycin or placebo dosing.

Changes in ΔQT_c and ΔQT_f were calculated at each sample collection time. The maximal mean telithromycin concentration was observed at 4 hours (range, 1-6 h) after dosing with 2400 mg telithromycin and at 3 h (range 1.5-6 h) after dosing with 3200 mg telithromycin.

The maximal mean ΔQT_c occurred at 4 hours with the values of 17 ms and 17 ms, respectively, after telithromycin 2400 mg and 3200 mg. The corresponding ΔQT_c for placebo was –7 ms. There was a statistically significant difference between both of the telithromycin doses (2400 mg and 3200 mg) and placebo. However, no statistically significant difference was found in ΔQT_f between placebo and treatment groups (2400 mg telithromycin and 3200 mg

telithromycin), possibly because of the small sample size. It should be noted that the mean telithromycin C_{max} was about 3.29 mg/L after oral administration of 2400 mg telithromycin, which was lower than the mean telithromycin C_{max} of 5.98 mg/L obtained in Study 1030. The mean telithromycin C_{max} was only 4.41 mg/L after a 3200 mg oral dose. Therefore, although a higher dose (3200 mg) was studied, the observed C_{max} values were not as high as expected.

Medical Officer's Comment

The failure to achieve higher concentrations with the 3200 mg dose may have limited the power of this study to detect concentration-related changes in QTc

b) Population concentration response

Data from 7 Phase 1 studies (Study 1030, 1031, 1032, 1037, 1041, 1045, 1046) were pooled to explore the potential relationship between ΔQT_c, ΔQT_f, and telithromycin concentration. Both ΔQT_c and ΔQT_f showed statistically significant correlations with telithromycin concentration (**Figures 1** and **2**). Similar results were obtained using a naïve pooled method and a linear mixed effects method.

Medical Officer's Comment

Although both regression analyses show substantial variability, increasing telithromycin concentrations are clearly associated with increases in the duration of the QT interval. This is true whether one uses Bazett's formula or Fridericia's to correct for heart rate. The slope of the regression line using Bazett's formula is 3.90; since the Cmax for telithromycin is ~ 2 mg/L, this predicts a mean increase in QTc of approximately 7.8 msec; given the potential for increased concentrations in special populations, this regression lines raises the possibility of significantly greater increases in QTc in such populations.

The Applicant attempted to use the Phase 1 dataset to define a correction formula more independent of heart rate than these two formulae. Although this is a rational approach, the derived formula has not been validated in any other population, raising questions as to its meaning. Of note, however, the Applicant's derived correction formula also shows a concentration-dependent effect of telithromycin on QT interval duration.

2. QT_c prolongation and pharmacokinetics in patients with cardiac disease

Study 1049

This dose-escalation study was conducted in 24 subjects with underlying cardiac disease to assess the effects of telithromycin on QT_c in high-risk patients. It was a double-blind, randomized, placebo-controlled, 4-way crossover study. During 4 different study periods, subjects received telithromycin 800 mg or telithromycin 1600 mg as single oral doses, clarithromycin 500 mg twice daily for one day, or placebo as a single dose treatment.

The mean ΔQT_c was calculated at each time point when EKGs were recorded. The mean maximal serum telithromycin concentration was observed at 1.5 hours after dosing with 800 mg telithromycin and 2 hours after dosing with 1600 mg telithromycin. The maximal mean ΔQT_c occurred at 4 hours, with values of 2, 5, 7, and 12 ms after placebo, 800 mg telithromycin, 500 mg clarithromycin and 1600 mg telithromycin, respectively. No statistically significant difference in ΔQT_c was found between placebo and 800 mg HMR or 500 mg clarithromycin, but a statistically significant difference was found in ΔQT_c between placebo and 1600 mg telithromycin. However, significant time and time by treatment interaction were found for ΔQT_c,

indicating comparisons should be made between treatments at each time. ΔQT_c at 2 hours after dosing with 800 mg telithromycin and 1600 mg was statistically significantly different from placebo; respective changes from baseline for these doses were 8.91 and 17.15 msec greater than changes for placebo. For 1600 mg, there were also statistically significant differences at timepoints ranging from 1.5 to 8 hours after dosing. There were no statistically significant differences for 800 mg at other time points. The correlations between ΔQT_c and telithromycin or clarithromycin concentrations are shown in **Figures 3** and **4**. ΔQT_c was correlated with telithromycin and clarithromycin concentrations.

It is important to note that this was a single-dose study employing a relatively small sample, using subjects without active infection. Multiple doses may lead to a greater effect on QT_c because of accumulation (see below under Pharmocokinetic Variability in Special Populations).

Medical Officer's Comment

This study was reviewed by Dr. Maryann Gordon of the Division of Cardiorenal Drug Products. She concluded that

> " . . . there is most likely a drug effect on cardiac repolarization manifested by a concentration related lengthening of the QTc interval. Further exploration of this issue with higher doses and longer duration of treatment is strongly encouraged."

The Medical Officer concurs with Dr. Gordon's conclusion. Of note, there was no change in mean heart rate in the subjects receiving telithromycin, supporting the use of Bazett's formula. Even when Fridericia's formula was used, telithromycin showed a concentration-dependent effect on QT duration.

3. QT_c prolongation in drug-interaction studies (Study 1041 - cisapride)

Because of the well-described association of cisapride with QT prolongation, the applicant conducted Study 1041 to explore the potential for pharmacokinetic drug-drug interactions between cisapride and telithromycin. This study was a single blind with respect to telithromycin only, randomized, complete two-period crossover design. The study consisted of two parts and four treatments.

Part I: Treatment A: once daily oral doses of placebo for 7 days followed by a single 20 mg (2 x 10 mg) dose of cisapride on day 7.

Treatment B: placebo on day 1, once daily oral doses of 800 mg telithromycin (2 x 400 mg) on days 2 through 7, and cisapride 20 mg (2 x 10 mg) on day 7.

Part II: Treatment C: once daily oral doses of placebo on days 1 through 6 and cisapride 10 mg (1x10 mg) three times daily (total of 13 doses) on days 2 through 6.

Treatment D: placebo on day 1, then 800 mg telithromycin (2 x 400 mg) once daily on days 2 through 6 concurrently with 10 mg (1 x 10 mg) cisapride three times daily on days 2 through 6 (total of 13 doses).

In addition to pharmacokinetic assessment, this study design also allowed for comparison of QT_c prolongation between placebo, 20 mg cisapride, 800 mg telithromycin and 20 mg cisapride coadministered with 800 mg telithromycin. The results showed that telithromycin

increased cisapride AUC and C_{max} by 150% and 95.2%, respectively. Further, it appears that the QT prolongation effect of telithromycin is similar to the effect of cisapride **(Figures 5 and 6)**.

4. Pharmacokinetic variability in special populations

Since the regression analyses shown below demonstrate that ΔQT_c and ΔQT_f are associated with plasma telithromycin concentration, it is important to understand the variability of telithromycin pharmacokinetics and factors affecting telithromycin concentrations.

1. The mean C_{max} was 1.99 mg/L after a single oral dose of 800 mg telithromycin (n=232 from 11 phase 1 studies (Study 1003, 1006, 1004, 1044, 1008, 1009, 1005, 1015, 1016, 1031, 1014)). The largest C_{max} was — mg/L. The accumulation factor after multiple doses was about 1.5.
2. In Phase 3 studies, telithromycin concentrations as high as — (Study 1051) and — mg/L (Study 1052) were observed.
3. The results from study 1005 showed that C_{max} and AUC increased approximately 2-fold in elderly patients when compared to young subjects after multiple doses of 800 mg telithromycin.
4. It was shown in study 1015 that C_{max} and AUC were similar between healthy subjects and hepatic impaired patients after a single oral dose of 800 mg telithromycin. However, this study also showed that renal function was increased and appeared to compensate for impaired hepatic function, so that observed C_{max} and AUC values were similar to the values in healthy subjects. Potential accumulation of telithromycin could be problematic for hepatically impaired patients with decreased renal function.

5. Potential for drug interactions with 3A4 inhibitors

Telithromycin is a CYP 3A substrate. The potential for drug-drug interactions with a CYP3A inhibitor, ketoconazole, was studied by the applicant in study 1045. The results showed that ketoconazole increased the mean C_{max} and AUC of telithromycin after multiple doses by 52% and 95%, respectively. Ketoconazole increased telithromycin concentrations and telithromycin-associated QT_c prolongation **(Table ISS.20)**.

Table ISS.20. Maximum QT_c after once-daily oral dosing with 800 mg telithromycin alone, 400 mg ketoconazole alone, 800 mg telithromycin concomitantly with 400 mg ketoconazole, or placebo

Parameter	Treatment	Mean	N	Comparison	Estimated Difference	(90% CI) around the difference	P-value
Maximum QT_c (msec)	A	410.4	11	A-D	3.344	(-2.3, 9.00)	0.322
	B	413.4	14	B-D	6.388	(0.92, 11.9)	0.057
	C	417.5	11	C-D	10.493	(4.80, 16.2)	0.004
				C-A	7.149	(1.42, 12.9)	0.043
				C-B	4.105	(-1.5, 9.67)	0.220
	D	407.0	12				

A = Telithromycin 800 mg once daily for 5 days

B = Ketoconazole 400 mg once daily for 7 days

C = Telithromycin 800 mg once daily for 5 days and ketoconazole 400 mg once daily for 7 days

D = Placebo

6. Summary: Pharmacokinetics

Phase 1 studies showed that telithromycin is associated with concentration-dependent QT_c prolongation. In some studies, there was a lag between the time of maximal serum telithromycin concentration and the time of the maximal effect on QT_c. Telithromycin concentrations are affected by several factors such as age, hepatic function, and coadministration of CYP 3A inhibitors. Observed telithromycin concentrations were variable. The maximal concentration observed in Phase 3 studies was 9.9 mg/L.

Figure 1. Regression analysis of ΔQT_c vs. concentration by linear and linear mixed effect models (Data are from 7 phase 1 studies)

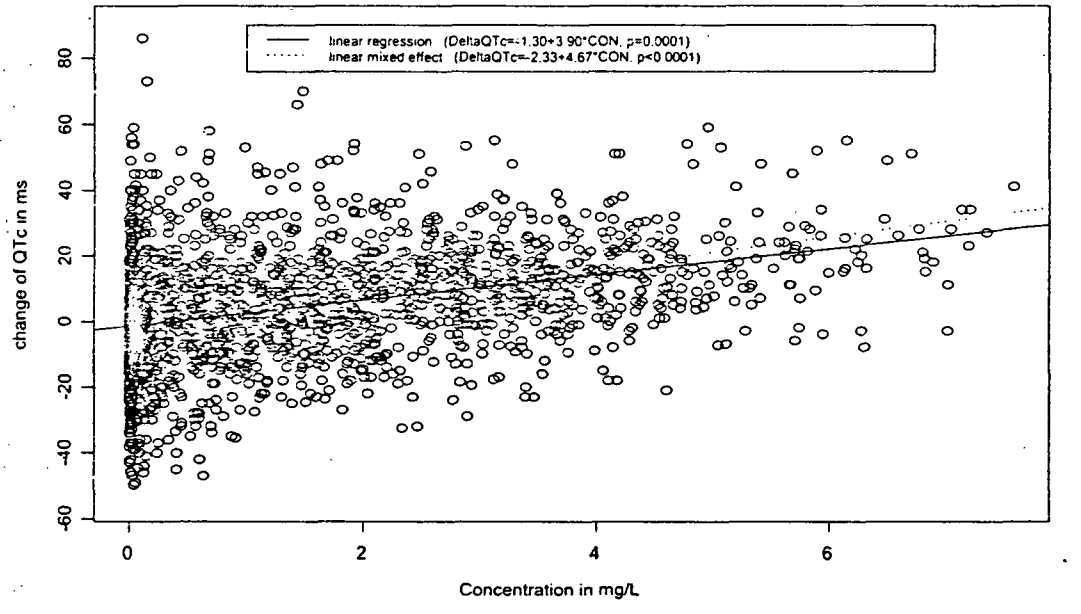

Figure 2. Regression analysis of ΔQT_f vs. concentration by linear and linear mixed effect models (Data are from 7 phase 1 studies)

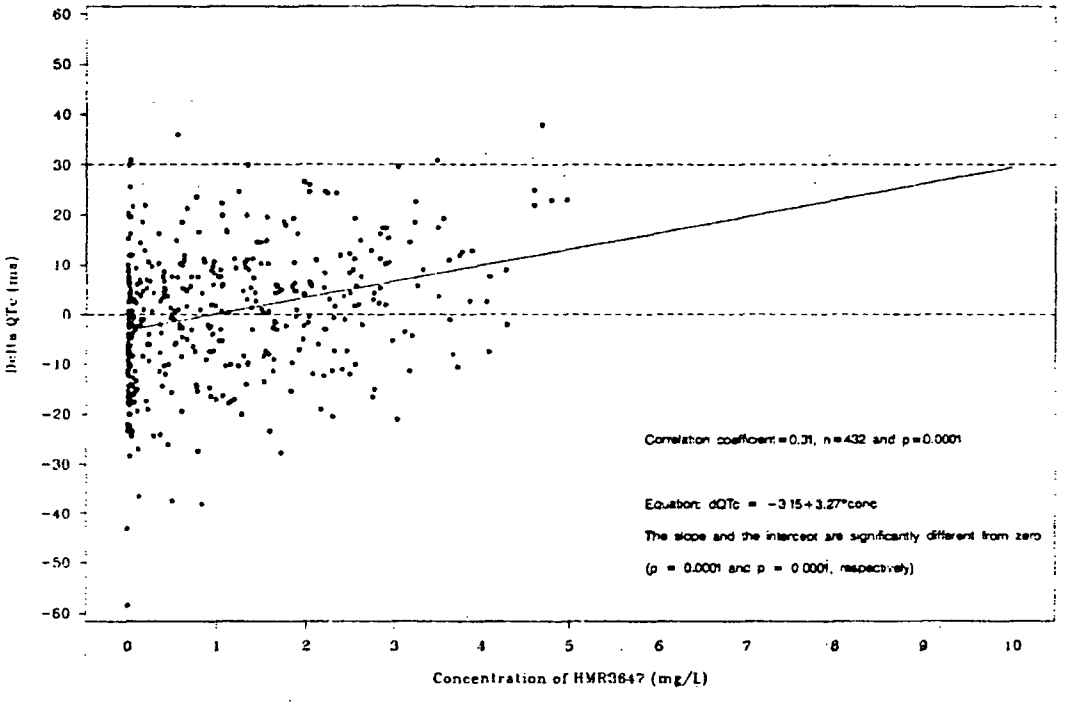

Figure 3. Correlation between plasma concentration and ΔQT_c when 800 mg and 1600 mg telithromycin were administered as a single doses