Table ISS.29. Hepatic TEAE's (MedDRA Preferred Terms) in all integrated completed controlled telithromycin Phase 3 studies (excluding 3014)

	Number (%) of Subjects			
	All TEAE's		Possibly Related TEAE's	
	N=2702	N=2139	N=2702	N=2139
Preferred Term	**Teli**	**Comparator**	**Teli**	**Comparator**
LFT's NOS abnormal	28 (1.0)	26 (1.2)	19 (0.7)	18 (0.8)
ALT increased	21 (0.8)	17 (0.8)	16 (0.6)	14 (0.7)
Transaminase NOS increased	6 (0.2)	3 (0.1)	6 (0.2)	3 (0.1)
AST increased	10 (0.4)	6 (0.3)	9 (0.3)	5 (0.2)
Alkaline Phosphatase increased	6 (0.2)	3 (0.1)	1 (0.0)	3 (0.1)
LDH increased	5 (0.2)	3 (0.1)	2 (0.1)	1 (0.0)
GGT increased	5 (0.2)	3 (0.1)	1 (0.0)	3 (0.1)
Hepatocellular damage	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Hepatic Function Abnormal NOS	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
Jaundice NOS	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Bilirubinemia	1 (0.0)	1 (0.0)	1 (0.0)	1 (0.0)
Hepatitis NOS	2 (0.1)	1 (0.0)	2 (0.1)	1 (0.0)
Hepatic pain	1 (0.0)	0 (0.0)	1 (0.0)	0 (0.0)
Hepatomegaly	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Hepatic cyst	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Gallbladder pain	1 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Cholelithiasis	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis	0 (0.0)	1 (0.0)	0 (0.0)	0 (0.0)
Cholestasis	2 (0.1)	0 (0.0)	2 (0.1)	0 (0.0)
Total number of hepatic events*	91 (3.4)	69 (3.2)	63 (2.3)	50 (2.3)

*A subject may have had more than one hepatic TEAE.

In the controlled studies, the proportion of subjects discontinuing study medication because of hepatic TEAEs was similar for telithromycin and comparator-treated subjects. The proportion of patients discontinued from the non-comparative studies because of hepatic TEAEs was similar to that observed in the controlled studies.

Serious Hepatic Adverse Events

There were no additional serious hepatic adverse events in the three new Phase 3 studies (studies 3012, 3013, and 4003). There were three serious hepatic adverse events in telithromycin-treated patients, which were described in the original Advisory Committee Briefing Document from April 26, 2001. These serious hepatic adverse events are described below.

In the comparative studies, there were 2 serious hepatic AEs reported in telithromycin-treated subjects and one serious hepatic AE reported in a comparator-treated patient. In the non-comparative studies, there was one additional serious hepatic AE in a telithromycin-treated patient. (Case narratives for the four patients with serious hepatic AEs are provided in Appendix A.) There were reasonable alternative explanations for one of the serious hepatic AEs in the telithromycin-treated patients and for the only comparator-treated patient with a serious hepatic AE. The two other serious hepatic AEs in telithromycin-treated subjects were plausibly related to telithromycin therapy. The first of these two events occurred in a 76-year-old female with community-acquired pneumonia (CAP) and a history of hypercholesterolemia and hyperuricemia, maintained chronically on pravastatin 20 mg po qd and allopurinol 20 mg po qd. She experienced isolated asymptomatic elevations of ALT to 13x Upper Limit of Normal (ULN) and AST to 9x ULN on Day 5 of therapy with telithromycin 800 mg po qd in the absence of an elevated total bilirubin (T. Bili.). Telithromycin was discontinued on Day 6 of therapy. Her transaminase abnormalities had nearly resolved by Day 12.

The other serious hepatic AE plausibly associated with telithromycin was as follows:

A 53 year-old male with CAP from a study center in — was enrolled in a non-comparative CAP study. At baseline his ALT was slightly elevated [ALT=81 U/L (normal range (NR) <49)] and his peripheral eosinophil count was 774 cells/10^{-6}L (lab normal range not available). He completed 10 days of telithromycin at 800 mg po qd. Four days after completing therapy, he developed a gastroenteritis-like illness similar to other members of his family, except that the subject's fever persisted. Ten days after completing therapy he had laboratory studies drawn that demonstrated elevations of his ALT to 7x ULN and AST to 5x ULN with eosinophilia. His ALT increased to a peak of 31x ULN and his eosinophils peaked at 2856 cells/10^{-6}L. Serologic evaluations for hepatitis A, B, and C were negative. Throughout the episode his T. Bili. was only mildly elevated (<1.6 x ULN). During this episode of hepatitis, he had a liver biopsy that showed centrilobular hepatic necrosis with eosinophilic infiltration. Other medications that the patient received around the time of this event included inhaled Atrovent, salbutamol, and fluticasone, Nasonex spray (mometasone furoate), and six 500 mg acetaminophen tables over a one week time period. His ALT elevation almost completely resolved in the absence of specific therapy by 6 weeks after initial detection of the hepatic event (AST levels were only infrequently monitored).
Eight months later at a routine follow-up visit, the subject was noted to have an elevated ALT of 1331 U/L in the absence of eosinophilia. Prior to this second event there was no known antecedent exposure to a ketolide or macrolide class agent. Several weeks later he underwent a liver biopsy that showed chronic hepatitis with marked activity and extensive bridging fibrosis. Review of the

pathology from the liver biopsy at the , found the pathologic changes on the first biopsy strongly suggestive of drug-induced liver disease and the second biopsy probably consistent with autoimmune hepatitis.

Hepatic Laboratory Findings

In the review of the original NDA, some differences were seen in the rates of laboratory abnormalities between telithromycin and comparator-treated patients. In particular, for patients in comparative CAP studies with normal ALT, AST, and T. Bili at baseline, there was a greater proportion of telithromycin-treated patients than comparator-treated patients with low-level (between 1x to 3x ULN) elevations in AST. This difference was present for analyses of On-Therapy and Post-Therapy visits and absent for analyses of Late Post-Therapy visits. In the comparative CAP studies, there was a slightly greater proportion of telithromycin-treated patients than comparator-treated patients with low-level ALT elevations at On-Therapy and Post-Therapy visits. For patients from the comparative CAP studies with normal ALT, AST, and T. Bili. at baseline, T. Bili. elevations were infrequent in both telithromycin- and comparator-treated patients. The numbers of patients experiencing elevations in excess of 3x ULN were small in both treatment groups.

Tables ISS.30.A-C show analyses of laboratory abnormalities integrating data from the two new controlled studies (3013, 4003). The results of these analyses are similar to those from the analysis of the original NDA data. There were no significant changes in the previously identified trends after incorporation of data from controlled studies 3013 and 4003.

Table ISS.30.A. Changes in ALT by visit in controlled Phase 3 CAP studies in subjects with normal ALT, AST, and T. Bili. at baseline, All Integrated controlled database

	On-Therapy				Post-Therapy[a]				Late Post-Therapy[b]			
Changes in ALT	**Ketek**		**Comp**		**Ketek**		**Comp**		**Ketek**		**Comp**	
	N= 544		**N= 418**		**N= 378**		**N= 337**		**N= 295**		**N= 221**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
< ULN	478	(87.9)	376	(90.0)	328	(86.8)	304	(90.2)	272	(92.2)	203	(91.9)
> ULN to ≤ 2x ULN	55	(10.1)	38	(9.1)	45	(11.9)	29	(8.6)	19	(6.4)	15	(6.8)
> 2 to ≤ 3x ULN	7	(1.3)	3	(0.7)	5	(1.3)	3	(0.9)	3	(1.0)	3	(1.4)
> 3 to ≤ 5x ULN	4	(0.7)	0	(0)	0	(0.0)	1	(0.3)	1	(0.3)	0	(0.0)
> 5 to ≤ 8x ULN	0	(0.0)	1	(0.2)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
> 8x ULN	0	(0.0)	0	(0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Number of patients lacking lab data for visit	31		35		197		116		280		232	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

APPEARS THIS WAY
ON ORIGINAL

Table ISS.30.B. Changes in AST by visit in controlled Phase 3 CAP studies in subjects with normal ALT, AST, and T. Bili. at baseline, All Integrated controlled database

	On-Therapy				Post-Therapy[a]				Late Post-Therapy[b]			
Changes in AST	**Ketek**		**Comp**		**Ketek**		**Comp**		**Ketek**		**Comp**	
	N=545		**N= 418**		**N= 379**		**N= 337**		N= 295		**N= 221**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
< ULN	487	(89.4)	387	(92.6)	354	(93.4)	326	(96.7)	276	(93.6)	203	(91.9)
> ULN to ≤ 2x ULN	52	(9.5)	27	(6.5)	22	(5.8)	11	(3.3)	18	(6.1)	17	(7.7)
> 2 to ≤ 3x ULN	3	(0.6)	2	(0.5)	2	(0.5)	0	(0.0)	0	(0.0)	0	(0.0)
> 3 to ≤ 5x ULN	3	(0.6)	2	(0.5)	1	(0.3)	0	(0.0)	1	(0.0)	0	(0.0)
> 5 to ≤ 8x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
> 8x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Number of patients lacking lab data for visit	30		35		196		116		280		232	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

APPEARS THIS WAY
ON ORIGINAL

Table ISS.30.C. Changes in T. Bili by visit in controlled Phase 3 CAP studies in subjects with normal ALT, AST, and T. Bili. at baseline, All Integrated controlled database

	On-Therapy				Post-Therapy[a]				Late Post-Therapy[b]			
Changes in T. Bili	**Ketek**		**Comp**		**Ketek**		**Comp**		**Ketek**		**Comp**	
	N= 521		**N= 403**		**N= 359**		**N= 326**		**N= 281**		**N= 214**	
	n	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
< ULN	517	(99.2)	401	(99.5)	355	(98.9)	320	(98.2)	280	(99.6)	212	(99.1)
> ULN to ≤ 2x ULN	3	(0.6)	2	(0.5)	4	(1.1)	4	(1.2)	1	(0.4)	1	(0.5)
> 2 to ≤ 3x ULN	0	(0.0)	0	(0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.5)
> 3 to ≤ 5x ULN	1	(0.2)	0	(0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
> 5 to ≤ 8x ULN	0	(0.0)	0	(0)	0	(0.0)	1	(0.3)	0	(0.0)	0	(0.0)
> 8x ULN	0	(0.0)	0	(0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Number of patients lacking lab data for visit	54		50		216		127		294		239	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

Similar analyses in subjects from the comparative Non-CAP studies found the proportion of subjects with elevations in AST, ALT, or T. Bili. to be similar between treatment groups, with the exception that at the Late Post-Therapy visit, there was a greater proportion of comparator-treated patients with low-level elevations in AST. This pattern was also present in the original analysis. Incorporation of data from studies 3013 and 4003 did not result in a change in the previous findings for LFT's in Non-Cap patients. **Tables ISS.31.A-C** provide the results of these analyses.

Table ISS.31.A. Changes in ALT by visit in controlled Phase 3 non-CAP studies in subjects with normal ALT, AST, and T. Bili. at baseline, All Integrated controlled database

	On-Therapy				Post-Therapy[a]				Late Post-Therapy[b]			
Changes in T. Bili	**Ketek**		**Comp**		**Ketek**		**Comp**		**Ketek**		**Comp**	
	N= 1316		**N= 1038**		**N= 1114**		**N= 928**		**N= 511**		**N= 422**	
	N	(%)	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)
< ULN	1234	93.8	99.5	95.9	1047	94.0	854	92.0	479	97.3	394	93.4
> ULN to ≤ 2x ULN	78	5.9	39	3.8	64	5.7	71	7.7	26	5.1	26	6.2
> 2 to ≤ 3x ULN	3	0.2	4	0.4	2	0.2	1	0.1	4	0.8	0	0.0
> 3 to ≤ 5x ULN	0	0.0	0	0.0	1	0.1	2	0.2	1	0.2	2	0.5
> 5 to ≤ 8x ULN	0	0.0	0	0.0	0	0.0	0	0.0	1	0.2	0	0.0
> 8x ULN	1	0.1	0	0.0	0	0.0	0	0.0	0	0	0	0.0
Number of patients lacking lab data for visit	69		59		271		169		874		675	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

Table ISS.31.B. Changes in AST by visit in controlled Phase 3 non-CAP studies in subjects with normal ALT, AST, and T. Bili. at baseline, All Integrated controlled database

	On-Therapy				**Post-Therapy[a]**				**Late Post-Therapy[b]**			
Changes in AST	**Ketek**		**Comp**		**Ketek**		**Comp**		**Ketek**		**Comp**	
	N= 1315		**N= 1041**		**N= 1112**		**N= 926**		**N= 511**		**N= 422**	
	N	(%)	n	(%)	n	(%)	n	(%)	N	(%)	n	(%)
< ULN	1260	(95.8)	1004	(96.7)	1087	(97.8)	901	(97.3)	498	(97.5)	402	(95.3)
> ULN to ≤ 2x ULN	53	(4.0)	33	(3.2)	22	(2.0)	23	(2.5)	8	(1.6)	20	(4.7)
> 2 to ≤ 3x ULN	1	(0.1)	1	(0.1)	1	(0.1)	0	(0.0)	3	(0.6)	0	(0.0)
> 3 to ≤ 5x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.2)	0	(0.0)
> 5 to ≤ 8x ULN	1	(0.1)	1	(0.1)	2	(0.2)	1	(0.1)	1	(0.2)	0	(0.0)
> 8x ULN	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.1)	0	(0.0)	0	(0.0)
Number of patients lacking lab data for visit	70		59		273		171		874		675	

Key: Ketek = telithromycin; Comp = comparators; ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

Table ISS.31.C. Changes in T. Bili by visit in controlled Phase 3 non-CAP studies in subjects with normal ALT, AST, and T. Bili. at baseline, All Integrated controlled database

	On-Therapy				Post-Therapy[a]				Late Post-Therapy[b]			
Changes in T. Bili	**Ketek**		**Comp**		**Ketek**		**Comp**		**Ketek**		**Comp**	
	N=1293		**N= 1010**		**N= 1092**		**N= 912**		**N= 498**		**N= 416**	
	N	(%)	N	(%)	n	(%)	n	(%)	n	(%)	n	(%)
< ULN	1285	(99.4)	1007	(99.7)	1075	(98.4)	905	(99.2)	492	(98.8)	414	(99.5)
> ULN to ≤ 2x ULN	8	(0.6)	3	(0.3)	17	(1.6)	7	(0.8)	6	(1.2)	2	(0.5)
> 2 to ≤ 3x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
> 3 to ≤ 5x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
> 5 to ≤ 8x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
> 8x ULN	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Number of patients lacking lab data for visit	92		87		293		185		887		681	

Key: Teli = telithromycin; Comp = comparators; ULN = upper limit of normal.
Note: Percentages exclude subjects with missing values.
[a] Days 17-21.
[b] Days 31-36.
Note: the population at Late Post-Therapy has a larger number of missing values in part because patients with previous normal lab values were not required to have follow-up laboratory testing at the Late-Post Therapy visit.

In the original NDA analysis, the changes in alkaline phosphatase were similar between telithromycin and comparators in both the CAP and Non-CAP studies. This similarity between telithromycin and comparators was also seen after the incorporation of data from studies 3013 and 4003.

Table ISS.32 shows how many patients from controlled CAP studies who had normal ALT measurements at study entry developed abnormal ALT measurements during treatment and up to 7 days after treatment. This analysis is different than the previously presented analyses, which required that patients have normal ALT, AST, and total bilirubin measurements to be included as normal at

baseline. Since AST is somewhat non-specific for liver injury and can be elevated by numerous causes (including hemolysis during phlebotomy), it is useful to examine patients who had only normal ALT measurements at baseline.

Table ISS.32. Change in on therapy/post-therapy (up to 7 days) ALT measurements in patients with normal ALT measurements at baseline in all integrated controlled CAP studies

ALT from entry to 7 d post-therapy	Telithromycin (N=688)	Comparators (N=523)
Normal	550 (79.9%)	431 (82.4%)
>1x ULN	114 (16.6%)	80 (15.3%)
>2x ULN	15 (2.2%)	9 (1.7%)
>3x ULN	8 (1.2%)	2 (0.4%)
>5x ULN	1 (0.1%)	1 (0.2%)
>8x ULN	0 (0.0%)	0 (0.0%)

Medical Officer Comment: *A greater proportion of telithromycin-exposed patients with normal ALT at baseline in controlled CAP studies developed ALT levels up to 5 times the upper limit of normal than comparator-treated patients. This finding was not seen in non-CAP studies. This pattern confirms what was seen in the original dataset.*

Summary: Hepatic Safety

In Phase 3 studies, the incidence of hepatic adverse events or treatment discontinuation because of a hepatic adverse event was similar between telithromycin and comparator-treated patients. In the comparative studies there were two serious hepatic AEs in telithromycin-treated patients and one serious hepatic AE in comparator treated patients. There was one additional serious hepatic AE from the non-comparative telithromycin studies. One of these serious adverse events in the telithromycin treated group was a patient with a liver biopsy showing recent centrilobular necrosis and eosinophilic infiltration, strongly suggestive of drug-induced liver disease (the patient's baseline labs included an ALT of 81 U/L (NR<49 U/L) and an eosinophil count of 774 cells/10^{-6} L (NR not available)). (Note: Erythromycin estolate, ethylsuccinate, and propionate have been associated with cholestatic hepatitis, sometimes accompanied by fever and eosinophilia. The pathologic changes for some of the cases of trovafloxacin-associated hepatitis were described as centrilobular necrosis and eosinophilic infiltration on liver biopsy). Several months later this patient went on to have an episode of asymptomatic elevations in his ALT and AST and a liver biopsy showing changes consistent with chronic hepatitis, probably autoimmune.

Medical Officer Comment: *Analysis of liver function tests from the comparative Phase 3 studies in patients who were normal at baseline shows a greater proportion of patients with low level elevations of AST and ALT (<5 x ULN) in the telithromycin-treated patients relative to comparator-patients in the CAP studies. The AST and ALT elevations from patients in the CAP studies were present during the On-Therapy and Post-Therapy visits and in a different analysis while on therapy and up to 7 days post-therapy.*

Visual Adverse Events

Vision Blurred (MedDra Preferred Term)
In the original submission, the incidence of blurred vision in controlled studies in telithromycin-treated patients (14/2045 or 0.7%) was higher than in controls (0/1672 or 0.0%). Review of the three new studies revealed an additional 5 patients with blurred vision (three telithromycin, two comparator). The incidence of blurred vision in telithromycin-treated patients in the integrated database was 20/4472 (0.4%) in controlled and uncontrolled studies and was 2/2139 (0.09%) in comparator-treated patients. **Table ISS.33** summarizes details of all patients with blurred vision in telithromycin studies. This adverse event occurred on all telithromycin-treatment regimens: 5 days: 11/1881(0.9%); 7 days: 3/1175 (0.3%) ; 7-10 days: 3/347 (0.9%) ; 10 days: 3/1059 (0.3%) .

Table ISS.33. Subjects with adverse event of blurred vision in all integrated Phase 3 clinical trials

Indication	Treatment (d=days)	Age	Sex	Duration (days)	Intensity	AE On therapy
Acute Sinusitis	Telithromycin 5 d [1]	22	M	1	Moderate	Yes
	Telithromycin 5 d	25	F	1	?	Yes
	Telithromycin 10 d	29	F	6	Severe	Yes
	Telithromycin 10 d	45	F	2	Mild	Yes
Tonsillitis/ Pharyngitis	Telithromycin 5 d	30	F	4	Mild	Yes*
	Telithromycin 5 d	31	F	2	Mild	Yes
	Telithromycin 5 d	22	F	1	Mild	Yes
	Telithromycin 5 d	26	F	2	Mild	Yes
	Telithromycin 5 d	19	F	2	Mild	Yes
	Telithromycin 5 d	36	F	10	Mild	Yes
	Telithromycin 5 d	34	M	1	Mild	Yes
Community Acquired Pneumonia	Telithromycin 5 d	40	M	1	Moderate	Yes
	Telithromycin 7 d	43	F	10	Mild	Yes
	Telithromycin 7 d	25	F	2	Mild	Yes
	Telithromycin 7 d	29	M	2	Mild	Yes
	Telithromycin 7-10 d	42	M	8	Moderate	Yes
	Telithromycin 7-10 d	33	F	2	Mild	Yes
	Telithromycin 7-10 d	36	F	5	Mild	Yes
	Telithromycin 10 d	28	M	**Unknown**	Mild	Yes
	Clarithromycin[3]	69	F	1	mild	Yes
Acute Exacerbation of Chronic Bronchitis	Telithromycin 5 d	54	F	1	Moderate	Yes
	Amoxicillin/clavulanate [2]	47	F	Ongoing	Mild	No**
	Clarithromycin[3]	69	F	3	mild	No

[1]telithromycin 800 mg; [2]amoxicillin 500 mg/clavulanate 125 mg; [3]clarithromycin 500mg
*Study medication discontinued
** Visual problem pre-dated entry into study

Telithromycin-treated females were more likely to experience this adverse event than males, with 15 females vs. 6 males experiencing blurred vision. **Table ISS.34** shows the incidence of blurred vision for females vs. males for controlled studies only.

Table.ISS.34. Incidence of blurred vision by sex in all integrated controlled Phase 3 studies

	Women		**Men**	
Preferred Term	**Telithromycin (n=1385)**	**Comparators (n=1108)**	**Telithromycin (n=1317)**	**Comparators (n=1031)**
Vision Blurred	12 (0.9%)	2 (0.2%)	5 (0.4%)	0 (0.0%)

Telithromycin is metabolized by cytochrome CYP3A4; Phase 1 data show that the C_{max} and AUC for telithromycin are markedly increased when it is co-administered with a CYP3A4 inhibitor. As an exploratory analysis, certain adverse events were examined to determine if

concomitant use of a CYP3A4 inhibitor resulted in an increase in the adverse event rates. **Table ISS.35.** shows the incidence of blurred vision in controlled Phase 3 trials in the presence and absence of a CYP3A4 inhibitor.

NOTE: Since patients were not randomized on the basis of CYP3A4 inhibitor intake, the results of this analysis should be interpreted cautiously.

Table ISS.35. Frequency of blurred vision in all integrated controlled studies by the presence of a CYP3A4 inhibitor

MedDRA Preferred Term	Received CYP 3A4 Inhibitor		Did not Receive CYP 3A4 Inhibitor	
	Telithromycin N=484	Comparators N=424	Telithromycin N=2218	Comparators N=1715
Eye Disorders (SOC)	12 (2.5%)	2 (0.5%)	29 (1.3%)	13 (0.8%)
Vision Blurred	9 (1.9%)	0 (0.0%)	8 (0.4%)	3 (0.2%)
95% CI*	(0.47% , 3.1%)			

* Exact 95% CI for the difference in rates of blurred vision between patients who received CYP3A4 inhibitors and those who did not.

This analysis is consistent with blurred vision being related to telithromycin exposure. Increased drug exposure may have occurred in the presence of a CYP3A4 inhibitor resulting in an increase of the incidence of blurred vision. Phase 1 studies (1059 and 1064) examined telithromycin-associated blurred vision; the incidence of this AE was significantly increased in patients who received 2400 mg of telithromycin (13-50%). (See the review of these studies by Medical Officer Dr. Tom Smith for further details)

All Visual Adverse Events

The sponsor limited their analysis to include only the MedDRA preferred term of "vision blurred" and did not include MedDRA preferred terms for other visual adverse events which occurred while on treatment with telithromycin. When other such AEs are examined, there were an additional 12 patients with visual adverse events that occurred during treatment with telithromycin. **Table ISS.36** summarizes all visual adverse events in telithromycin-treated patients which occurred in Phase 3 studies and includes a breakdown by gender.

Table ISS.36. All Phase 3 visual adverse events by preferred term and gender

MedDRA Preferred Term	No. of Patients	Gender
Vision Blurred	20	14 F, 6 M
Visual Disturbance NOS	6	3 F, 3 M
Visual Acuity Reduced	2	2 F
Vision Abnormal	2	2 F
Accommodation Disorder	1	1 F
Binocular eye movement disorder NOS	1	1 F
Total	32	23 F, 9 M

Medical Officer Comment: *In all Phase 3 studies, the majority of telithromycin-treated patients who experienced a visual adverse event were female (72%). Only 28% of patients who experienced visual adverse events were male.*

Table ISS.37 contains total incidences of telithromycin-associated induced visual AE's incorporating these additional reports.

Table ISS.37. Incidence of treatment emergent visual adverse events*

Study Type	Visual AEs	
	Telithromycin	**Comparator**
Uncontrolled	6/1170 (0.5%)	
Controlled	**26/2702 (1.0%)**	**4/2139 (0.2%)**
Total	32/4472 (0.7%)	4/2139 (0.2%)

* Includes MedDRA preferred terms: Vision blurred, vision abnormal NOS, Visual disturbance NOS, visual acuity reduced, accommodation disorder, binocular eye movement disorder NOS.

Medical Officer Comment: *In all blinded Phase 3 clinical trials, the overall incidence of visual adverse events was 1.0% in telithromycin-treated patients.*

Table ISS.38. Incidence of telithromycin-associated visual AE's in all integrated Phase 3 controlled studies by gender

	Women		Men	
Preferred Term	**Telithromycin (n=1385)**	**Comparator (n=1108)**	**Telithromycin (n=1317)**	**Comparator (n=1031)**
Visual AE*	**19 (1.4%)**	**2 (0.2%)**	**7 (0.5%)**	**2 (0.2%)**

* Includes MedDRA preferred terms: Vision blurred, vision abnormal NOS, Visual disturbance NOS, visual acuity reduced, accommodation disorder, binocular eye movement disorder NOS.

***Medical Officer Comment**: Inclusion of the additional MedDRA preferred terms results in an increase in the overall incidence of visual adverse events to 1.4% in women.*

Table ISS.39 shows the reported severity of visual AEs in the 31 patients treated with telithromycin who experienced such events in Phase 3 clinical trials.

Table ISS.39. Severity of telithromycin treatment emergent visual adverse events in all integrated Phase 3 clinical trials

	Total	**Mild**	**Moderate**	**Severe**
All Phase 3 Clinical Trials*	32 (100%)	19 (59.4%)	11 (34.4%)	1 (3.1%)
Controlled Phase 3 Trials	26 (100%)	16 (61.5%)	9 (34.6%)	1 (4%)

* one patient did not have a determination as to the severity of the visual adverse event

***Medical Officer Comment:** There was no standardized grading system to allow consistent categorization of severity of the visual adverse events.*

Figure ISS.1 shows the distribution of time of onset of the visual adverse events by treatment day for telithromycin-treated patients in all integrated Phase 3 studies.

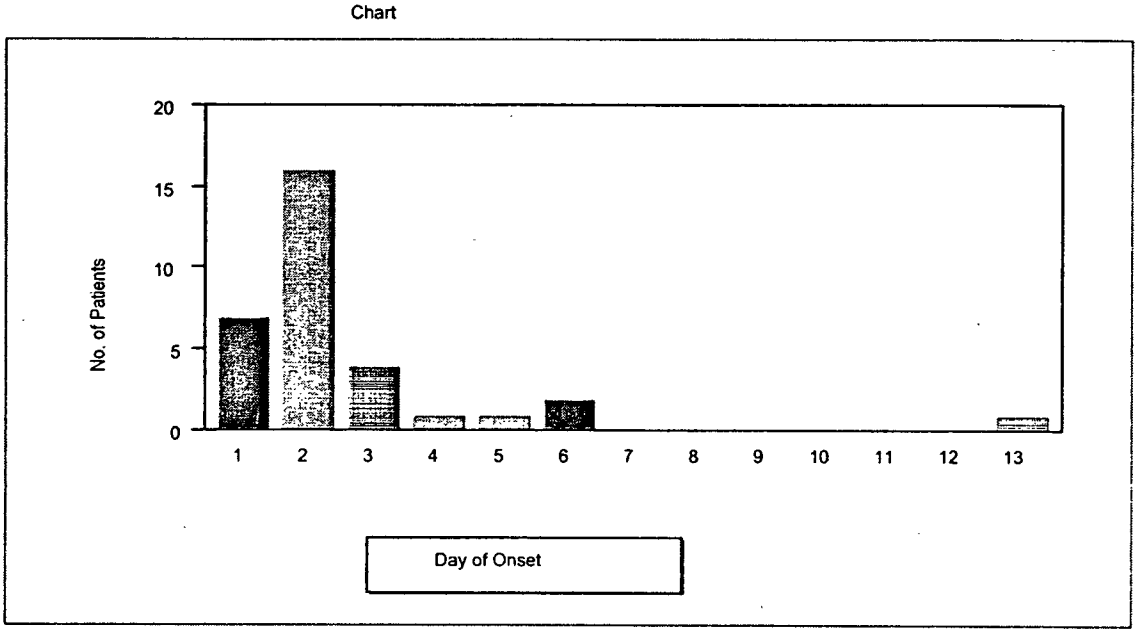
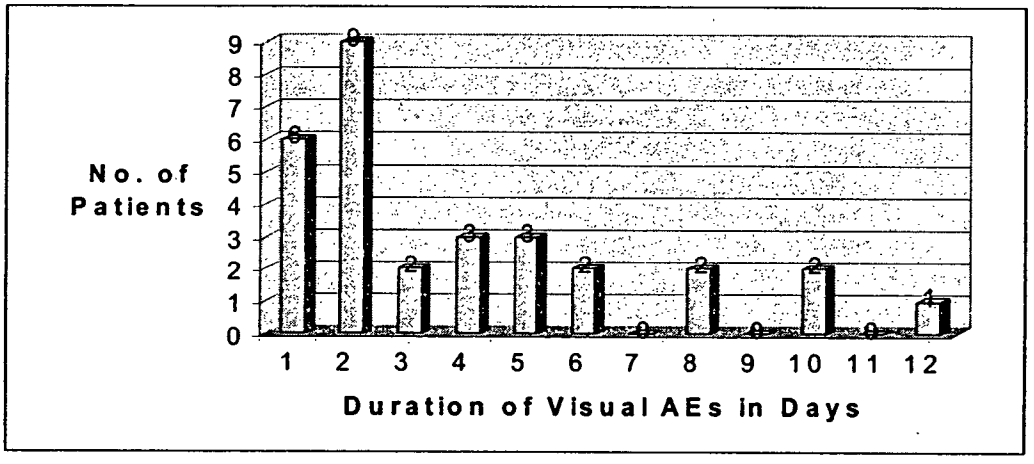


Figure ISS.2 shows the duration of visual adverse events for telithromycin-treated patients in all integrated Phase 3 studies. *



* Two of the patients did not have an end date recorded for their visual adverse event.

The mean age of patients experiencing visual adverse events was 35.6 years. The median age was 32 years and the range was 19-74 years.

Medical Officer Comment: *Visual adverse events were more common in younger patients.*

End of Visual Adverse Events relative to Telithromycin Exposure

Two patients did not have an end date recorded for their visual adverse event (patients 3005.0201.0201002 and 3006.0012.0012010).

Three telithromycin-treated patients with visual adverse events discontinued medication. Two of the patients who discontinued had continued visual complaints for 2 additional days after discontinuation (patients 3005.0197.0197021 and 3006.0374.0374012) and the third had continued visual complaints for one additional day after discontinuation (patient 3008.0209.0209005).

Four telithromycin-treated patients did not discontinue medication but had visual adverse events that continued after completion of therapy. Visual adverse events ended 1 day after completion of study medication for patient 3000.1301.0001503, 2 days after completion of study drug for patient 3009.0298.0298013, 7 days after completion for patient 3006.0027.0027006, and 13 days after completion for patient 4003.3503.3503008. This last patient's visual adverse event actually began two days after completion of study drug.

Three telithromycin-treated patients had visual AEs that ended on the last day of treatment (patients 3008.0264.0264001, 3009.0308.0308016, 4003.3136.3136005).

Twenty out of 32 telithromycin-treated patients experienced resolution of visual adverse events while on therapy. Six of these patients had a duration of visual adverse event of 1 day, 9 had a duration of 2 days, 1 had a duration of 3 days, two had a duration of 4 days, and two had a duration of 6 days.

Summary: Visual Adverse Events

There was a higher rate of visual adverse events in telithromycin-treated patients than in comparator-treated patients. The overall rate of visual adverse events in controlled studies for telithromycin-treated patients was 1.0% vs. 0.2% for comparator-treated patients. Visual adverse events during telithromycin treatment were more common in women than men (1.4% vs. 0.5%) in controlled studies and were more common in younger patients (mean age 35.6 y, median age 32 y). Visual adverse events in telithromycin-treated patients started most commonly on treatment day 2, however, the onset ranged from treatment day 1 to 13. The duration of visual adverse events was most commonly 1-2 days. However, the duration ranged from 1-12 days and 13/30 (43.3%) of patients had visual adverse events that lasted > 3 days. Approximately 39% of patients with visual adverse events in controlled clinical trials had a reported severity of moderate to severe. There was no standardized grading system to allow consistent categorization of severity of the visual adverse events. One telithromycin-treated patient was significantly disabled and discontinued treatment because of a serious adverse event of "accommodation disorder."

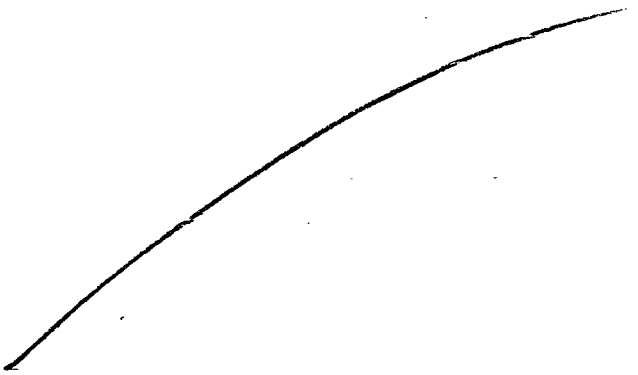
Post-Marketing Safety Data

Telithromycin was approved by the European Union in July of 2001 and has been marketed in several countries, including Germany, France, Italy, Spain, Brazil, Mexico, and Argentina. Approved indications in these countries include CAP, ABS, AECB, and T/P. The FDA has received and reviewed post-marketing safety data submitted by the Applicant up until October 1, 2002, during which time approximately 1 million prescriptions were filled. This post-marketing safety data includes 992 adverse events from 377 patients. The majority of these were reported from Germany (218 patients) and Brazil (79). Italy had adverse events reported from only 25 patients despite having the second highest number of prescriptions sold. Other countries where patients were reported as having adverse events include: Spain (18), France (16), Mexico (8), Peru (4), Columbia (4), Argentina (3), Chile (1), Falkland Islands (1).

Medical Officer: *Disparities in the rates of post-marketing adverse event reporting (lower for Italy than for Germany or Brazil) potentially indicate differences in post-marketing surveillance capabilities. Surveillance data from Italy may be less able to detect safety signals in post-marketing.*

Table.ISS.40. Ketek prescriptions sold by country and month

	Number of Ketek® 5 day unit packs sold							
	Germany	France	Italy	Spain	Belgium	Mexico	Brazil	Other Latin America[a]



Review of post-marketing data focused on adverse events of special interest including cardiac, hepatic, and visual adverse events. All deaths were also reviewed.

Cardiac Post-marketing Adverse Events

There were 37 cardiac adverse events reported from 24 patients. **Table ISS.41** summarizes the most common cardiac adverse events of interest.

Table ISS.41. Most common cardiac adverse events of interest

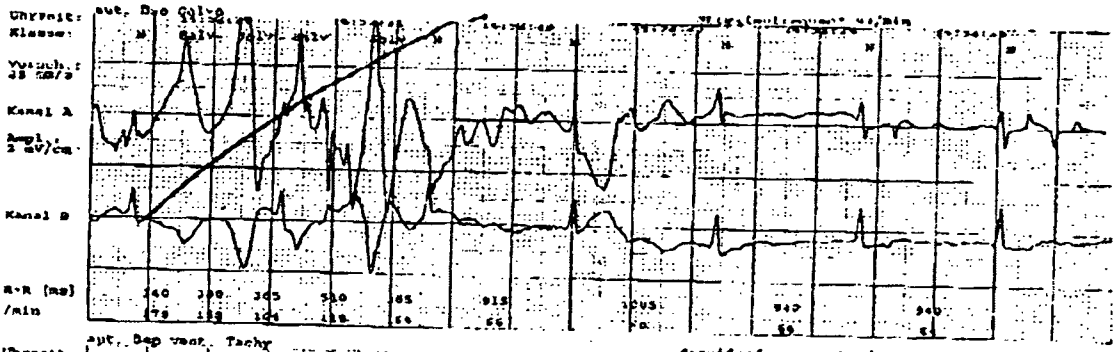
Adverse Event (MedDRA Preferred Term)	Total #	Serious
Tachycardia NOS	8	2
Palpitations	6	1
Cardiovascular d/o NOS	4	2
Atrial fibrillation	1	1
Supraventricular arrhythmia NOS	1	1
Torsades de Pointes	1	1

Because of telithromycin's potential to prolong the QT interval, the case of torsades de pointes was of particular interest and is summarized below.

The patient was a 59-year-old male who was reported as having syncope equivalent, depressed level of consciousness, fatal torsade de pointes, and ventricular fibrillation. He had a past medical history of coronary heart disease, s/p percutaneous transluminal angioplasty with stent implantation after angina pectoris attack in 2001, hypertension, transverse lesion of the cord with "paraplegia TH 5/6 (car accident in 1990), spastic vesical paralysis, adiposity, hypertriglyceridemia, hypercholesterolemia, and manic depressive disease." Concomitant medications included methionin, triamterene, baclofen, isosorbide mononitrate, diazepam, atorvastatin, mirtazapin, metoprolol, amlodipine. The patient started treatment on 5/23/02 with Ketek for sinusitis and tracheobronchitis and on [redacted] he experienced an episode of confusion, retrospectively considered an equivalent of syncope. ECG at that time was normal, as was blood pressure. Ketek was discontinued. On [redacted], the patient lost control while driving his car. He was hospitalized and ECG showed no abnormalities. According to the patient's wife, Ketek was re-administered. The patient was without symptoms until the next afternoon when the patient's telemetry monitor revealed "classic torsade, persisting, finally changing to ventricular fibrillation that results in a zero line." Echocardiography revealed "left venticle at the end of diastole 5.9 cm, posterior wall moderately hypokinetic, ejection fraction 50%, aortic sail closes relatively tight, opening amplitude reduced but sufficiently large. Satisfactory left ventricular function". Laboratory tests on admission revealed the following: CK 530 U/l, CKMB 11 U/l, creatinine 1.4 mg/dl, potassium 3.6 mmol/l, other values within normal ranges. The only ECG data that was available for review from the time of the cardiac arrest were 4 short rhythm strips shown below.

APPEARS THIS WAY
ON ORIGINAL

#1



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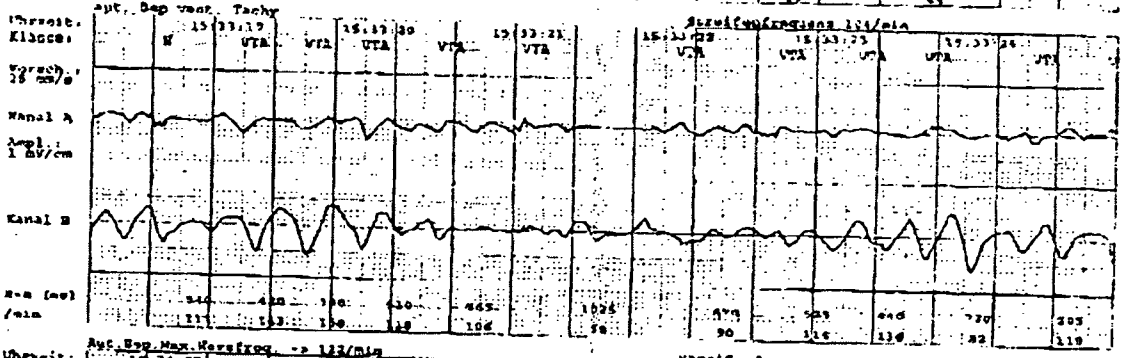

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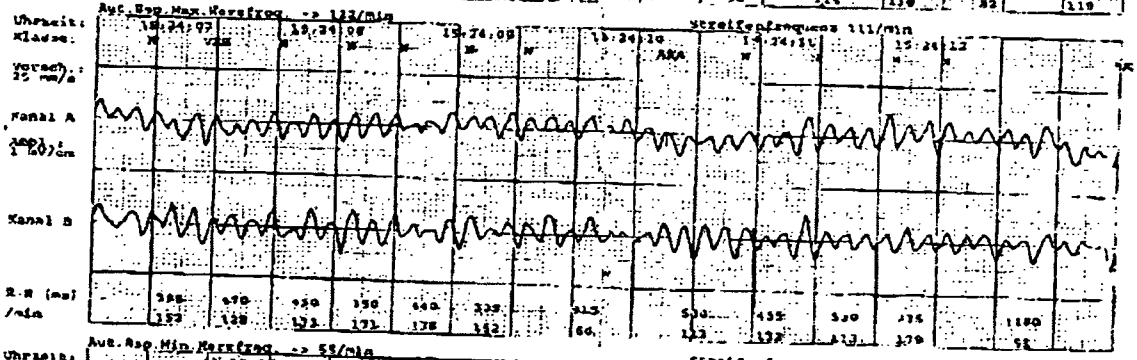

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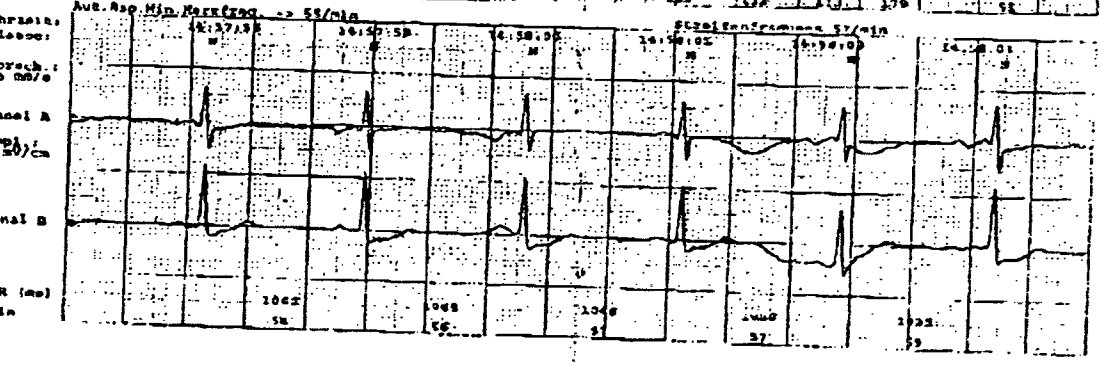

Medical Officer Comment: *The four strips, done on the day of death (———), are not in chronological order and are not concurrent. The correct order as well as time is as follows: #1 at 14:52, #4 at 14:57, #3 at 15:24, and #2 at 15:33. There is a 27 minute gap between strip #4 and strip #3, during which time the malignant rhythm began. Because there is no strip during this time, it is difficult to determine the original fatal rhythm. It is difficult from these strips to determine the length of the QT interval immediately prior to the time of the fatal arrhythmia. Although this case is potentially consistent with torsades de pointes, there is not enough data to make a determination of the existence of torsades or of study drug causality. Review of the other cardiac adverse events did not reveal specific cases of interest that could potentially represent a safety signal for torsades de pointes.*

Hepatic Post-marketing Adverse Events

There were 42 hepatic post-marketing adverse events reported from 18 patients. All of these patients were from Germany. Many of the reports lack narratives or detailed information and some are difficult to understand. There were no deaths related to hepatic post-marketing adverse events; however, there were 6 patients with symptomatic transaminase elevation, including 5 who required hospitalization and three who underwent liver biopsy. Four of these patients had transaminase elevation of >3X ULN and total bilirubin elevation of >1.5X ULN. Three of the four also had elevated alkaline phosphatase levels as well. In all cases, either the treating physician or the reporter suspected possible relationship of telithromycin to the hepatic adverse event. All patients with follow-up information reportedly recovered. These cases of hepatic toxicity had a temporal relationship with telithromycin exposure.

Visual Post-marketing Adverse Events

There were 168 reported post-marketing visual adverse events from 124 patients. **Tables ISS.42a-c** show the reported visual adverse events and the age and gender demographics of the affected patients.

Table ISS.42A. Post-marketing visual adverse events*	
Adverse Event	Total # of Reports
Vision blurred	84
Visual disturbance	42
Accommodation disorder	12
Diplopia	9
Visual acuity reduced	3
Eyelid edema	3
Photophobia	2
Strabismus	2
Miosis	2
Mydriasis	2
Photopsia	1
Bionocular eye movement disorder NOS	1
Eyelid ptosis	1
Lacrimation increased	1
Vitreous floaters	1
Uveitis NOS	1
Blindness	1

Table ISS.42B. Age demographics of patients with post-marketing visual adverse events	
Age Range	Number of Patients
17-30	45
31-40	57
41-50	31
51-60	7
61-70	8
71-80	3
Unknown	17

Table ISS.42C. Gender demographics of patients with post-marketing visual adverse events			
	Female	Male	Unknown
Number	112	52	4

For patients who were reported as having "visual disturbance," the following are examples of the "verbatim descriptions" of the adverse events: "could not see anything"; "severe dimming of sight"; "black before eyes"; "temporary total loss of vision repeated 5 times"; "extreme visual disturbance"; "seeing abnormal color".

The seriousness of the visual adverse event was not reported for 24 of the adverse events. Thirty-six of the visual adverse events were reported as serious, and 108 were reported as not serious.

The nature of some of the reported visual adverse events was quite dramatic and severe. The following narratives are verbatim excerpts from some of the patients with visual adverse events. The nature and severity of these reports is generally not representative of the majority of the reported visual adverse events, but they do provide a reference for the degree of visual AE severity which may occur in patients receiving telithromycin.

Mfr. Report# 200220212GDDC AE: "Visual Lost"
Narrative: Initial Report: This spontaneous report from Brazil involves a 39 yo female patient who received therapy with Ketek 800 mg daily from 10/25/02-10/26/02 for the treatment of sinusitis. There was no mention of relevant history or concommittant drugs. On —— the patient experienced vision loss and cephalgia. She had partial recovery of vision on —— The events are ongoing at the time of this report. The reporter assessed the events as highly probable and medically important. Serious: Yes. †

Mfr report# 200215827DE AE: "Severe Visual Disturbance"
"Source: spontaneous report by physician (internal medicine). Patient: female, 36 years. No information on medical history and concomitant medication. The patient was treated with Ketek orally (indication unknown), first intake on —— One hour later the patient developed severe visual disturbance so that she had to rely on her husband's help. The event resolved after 9 hours. The physician assessed the causal relationship between event and treatment with telithromycin as "highly probable" and the seriousness as "Serious: Yes."

Mfr report #200210800DE AE: "Massive visual disturbance (could not see anything)"
"Source: spontaneous report. Patient: male, 33 years. The patient was treated with Ketek 1 x 400 mg/day orally from 1/13/02 till 1/15/02 for sinusitis and tracheitis; no information on further medication. The patient had no medical history of visual disorders. On —— the patient developed visual disturbance (blurred vision, affecting near and far sight); he was considerably impaired in his activities. The symptoms started increasingly within hours after intake of Ketek and resolved hours after stop of treatment with Ketek (end of event: ——.). The patient was not seen by a specialist. According to physician there was no alternative explanation for the event. He assessed the causal relationship between event and treatment with Ketek as 'highly probable.' Serious: Yes."

Mfr report #200215449GDDC AE: Visual Disorder, Visual Loss"
"Narrative: This spontaneous report from a physician involves a 27 year old female patient who received therapy with telithromycin 800 mg daily from 5/31/02 until 6/2/02 for the treatment of probably mycoplasm cough and expectoration. Relevant medical history includes hypothyroidism and dysrhythmia. Concomitant drugs include salbutamol, betamethasone and thyroxine sodium. On ——, the patient experienced visual disorder with visual loss. She discontinued the treatment with telithromycin. She underwent CAT scan and visual field studies, both were reported to be normal. The patient experienced a complete recovery upon discontinuing drug. The physician assessed the event as highly probable (for causality). Serious: Yes."

Mfr report # 200221623GDDC AE: Visual Disorder, Visual Loss *
"17 yo female who received Ketek 800 mg orally on —— for the treatment of lung infection. The patient experienced blurred vision 30 min after intake of Ketek. The visual loss was a severe blurred vision. It was severe enough to make the patient unable to distinguish her face in a mirror, walk, or eat by herself. It is presumed that the problem was an accommodation problem.

The patient was alone when the event started. The patient's mother arrived 5 hours later and found the patient in bed due to the event. The patient has no history of visual abnormalities. She complained of blurred vision in both distance and near vision. The event lasted 12 hours after the Ketek dose was received. The patient was not only unable to read but was also unable to walk due to the visual abnormality. She had to remain in bed and needed assistance with eating."

† This case occurred after the reporting period but was included because the patient hadn't experienced a complete resolution of the adverse event at the time of the initial report.
* This case occurred after the reporting period, but was included because of its severity.

Myasthenia Gravis Exacerbation

There were a total of five reports of myasthenia gravis or aggravation of myasthenia gravis subsequent to exposure to telithromycin. These cases include one patient (200216097GDDC) who required hospitalization for respiratory failure and one patient (200211064EU) who experienced respiratory failure and died. These cases involved a clear temporal relationship to telithormycin administration and the reporting physicians felt that the myasthenic exacerbations were related to telithromycin exposure.

Medical Officer Conclusions:

Overall

Telithromycin therapy is associated with increased rates of non-serious gastrointestinal adverse events (diarrhea, nausea, and vomiting) when compared to the comparator agents used in the controlled clinical trials. These adverse events occurred in a higher proportion of telithromycin-treated females than males. There were also higher rates of adverse events in those telithromycin treated patients who received a concomitant CYP3A4 inhibitor than those who did not receive a concomitant CYP3A4 inhibitor, although this finding was the result of a post-hoc analysis and therefore, should be interpreted cautiously. Also, based on post-marketing adverse event reports, telithromycin has been associated with exacerbations of myasthenia gravis.

Cardiac Safety

Based on the available Phase 3 data, telithromycin does not appear to cause an increase over the comparators in the number of cardiac adverse events or serious cardiac adverse events. It also does not appear to cause a substantially different change in QTc when compared to the comparators or clarithromycin. This does not preclude the possibility that telithromycin therapy may result in certain cardiac adverse events which are either difficult to detect (such as torsades) or too infrequent to be detected in a Phase 3 database. In addition, the data from these Phase 3 trials do not preclude the potential for telithromycin therapy to result in specific cardiac adverse events when administered

concomitantly with a CYP3A4 interacting drug, since experience with such co-administration is limited.

Hepatic Safety

The available Phase 3 clinical data indicate that telithromycin therapy was associated with higher rates of transaminase elevation than were seen in the comparator drugs. Although this pattern indicates that this drug could be a significant hepatotoxin, it is not definitive evidence of such toxicity. There have been drugs, such as trovafloxacin, which did not have such a pattern and which were later discovered to be significantly hepatotoxic. Conversely, there have been other drugs, such as tacrine, whose pattern of transaminase elevation was much more dramatic than what was seen with telithromycin, but yet have not been associated with permanent or life-threatening hepatotoxicity. Therefore, telithromycin's pattern of transaminase elevation raises the possibility of potential hepatotoxicity but does not allow for a conclusive determination of the extent to which telithormycin may cause liver injury.

Other data in this NDA which pertain to hepatic toxicity include one possible case of non-fatal idiosyncratic liver reaction leading to liver biopsy which was confounded by the possibility that the underlying hepatic process may have been related to an auto-immune mechanism unrelated to drug exposure. There were also six post-marketing cases of symptomatic transaminase elevation, five of which required hospitalization and three of which required biopsies. Because of limited data and confounding, it is difficult to determine the degree to which telithromycin may have contributed to the hepatic events in these post-marketing cases. In total, these cases of possible telithromycin-related hepatotoxicity do not allow for an accurate determination of the degree to which telithormycin causes hepatotoxicity. It is probable that telithromycin's hepatotoxicity will become better defined as larger amounts of post-marketing data become available.

Visual Toxicity

It is clear from the available Phase 3 and post-marketing data that telithromycin therapy is associated with a unique type of visual toxicity which has not been described before in other antibiotics. This toxicity is unique in that its main mechanism is that of an accomodative disorder. It should be noted that older patients, who have lost the ability to accommodate, still have been reported with this adverse event, thus indicating that, at present, a complete understanding of the mechanism of this toxicity is lacking. This visual toxicity is more common in younger patients, females, and possibly those taking a concomitant CYP3A4 inhibitor. Available information indicates that telithromycin-associated visual toxicity may occur at any time during drug administration and may be debilitating. The majority of these events resolve after discontinuation of the drug, however, there have been no attempts to perform long-term assessments of patients with this visual toxicity to determine if there are associated long-term complications. Although the overall rate of these visual adverse events was relatively low at 1.0%, it was higher in females vs. males (1.4% vs. 0.5%). It is important to consider that this drug is likely to be used in large numbers of patients with relatively mild infections (AECB and ABS) and who will likely continue to carry out activities of daily living, such as driving. In such a setting, a rate of visual adverse events on the order of 1.0% is of concern.

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/s/

Charles Cooper
10/15/03 07:00:37 PM
MEDICAL OFFICER

Ketek Safety Review by C. Cooper

David Ross
10/30/03 12:01:59 PM
MEDICAL OFFICER

Janice Soreth
2/27/04 05:01:30 PM
MEDICAL OFFICER

Recommendations:

As additional post-marketing data is collected, a pharmacovigilance plan needs to be designed to aggressively monitor for potential hepatic, cardiac, and visual adverse events. Additional studies should be conducted to assess the potential long-term effects of telithromycin-associated visual toxicity. Labeling should contain information that clearly indicates this drug's ability to cause visual adverse events which could interfere with activities of daily living and could result in danger to the patient depending on what the patient is doing at the time of event onset (e.g., driving).

Medical Officer Review
Visual Effects of Telithromycin

Table of Contents

Executive Summary

1. Background

Blurred vision was reported as an adverse event in an unexpected number of telithromycin recipients in the initial phase 1 and phase 3 studies of this drug. In an approvable letter to the applicant, Aventis Pharmaceuticals, the FDA recommended that Aventis perform additional clinical studies of the effect of telithromycin on various measures of visual function. In addition, the Agency recommended that Aventis perform a large safety study in which particular attention was paid to adverse events of special interest, including visual adverse events.

In its response to the FDA approvable letter, Aventis has submitted reports from two phase 1 safety studies that evaluated the visual effects of high single doses of telithromycin. Aventis also performed a large, comparative, open-label trial of the safety and effectiveness of telithromycin in usual care settings. The present review discusses the phase 1 studies and the subset of patients with visual adverse events in the large safety trial.

2. Phase 1 Studies

2.1. Study 1059: "Mechanism of blurred vision induced by HMR 3647 [telithromycin] at single supraclinical doses (2400 mg) versus therapeutic single dose (800 mg) in a younger and older population of healthy subjects"

This study was a single-center, randomized, placebo-controlled, double-blind, single-dose, three-way crossover study with a one-week washout period between treatments. Two groups of healthy adult subjects were studied:

Group I: 15 subjects 18 to 40 years of age with normal uncorrected vision
Group II: 15 subjects 50 to 64 years of age with presbyopia

Approximately equal numbers of males and females were to be enrolled in each group. Each subject received three treatments: telithromycin 800 mg, telithromycin 2400 mg, and placebo. The order of receipt was randomized, and treatments were administered as single doses with a one-week washout period. Plasma concentrations and amounts of drug in tears were measured and eye examinations were performed at intervals for 24 hours following drug administration.

Four of 15 subjects 18 to 40 years of age and 0 of 15 subjects 50 to 64 years of age reported blurred vision following a 2400 mg dose of telithromycin. Blurring developed 3 to 6 hours following drug administration, lasted 30 minutes to 2 hours, and was described as mild in intensity. Far vision was affected in all four subjects and near vision as well in one. There were no other associated eye symptoms, and no changes were observed from baseline eye examinations. The time of onset of blurring corresponded to the time of peak plasma concentration and amount of drug in tears. No subjects reported blurred vision following an 800 mg dose.

2.2. Study 1064: "Assessment of ophthalmological safety of telithromycin at supraclinical dose (2400 mg) in healthy subjects"

This study was a single-center, randomized, placebo-controlled, double-blind, single-dose, two-way crossover study with a one-week washout period between treatments. Twenty-four healthy adult subjects were studied. At least 35% were to be between 50 and 64 years of age. All subjects were required to have normal uncorrected far vision; a correction for near vision was acceptable for the older subjects. Each subject received two treatments: telithromycin 2400 mg and placebo. The order of receipt was randomized, and treatments were administered as single doses with a one-week washout period. Plasma concentrations were measured until 6 hours following drug administration, and eye examinations were performed at baseline and at 3 hours and 7 days following drug administration.

Twenty-four subjects were enrolled; 18 were 18 to 49 years of age, and 6 were 50 to 64 years of age. Twelve subjects reported blurred vision following the 2400 mg dose of telithromycin. This effect was reported in 5 of 13 males and in 7 of 11 females, and it occurred in both young and older subjects. Blurring developed 1 to 5 hours (median 3 hours) following drug administration and lasted for a median of 2h 50 min. It was most commonly described as difficulty focusing, particularly on distant objects, and was generally described as mild in intensity. Several subjects had concurrent dizziness, nausea, and diarrhea. The time of onset of blurring corresponded to the time of peak plasma concentration.

Eye examinations following drug administration demonstrated no consistent findings attributable to telithromycin, either in those reporting blurred vision or in those exposed but without blurring. There were no changes from baseline in visual fields, color vision, intraocular pressure, anterior chamber angle, or pupil diameter. One subject with blurring had impairment of near visual acuity, decrease in amplitude of accommodation, and impaired near-to-far reaction and response times. Continuous recording of accommodation in all subjects revealed no consistent changes in reaction or response times following drug administration. Tear film stability was reduced in three subjects with blurring and in three without blurring (one following telithromycin, two following placebo). Slit lamp examination was abnormal in one subject with blurring who had a corneal defect believed possibly due to eye rubbing; all remaining slit lamp examinations were normal.

3. Visual Adverse Events in Study 3014: "Randomized, Open-Label, Multicenter Trial of the Safety and Effectiveness of Oral Telithromycin (Ketek™) and Amoxicillin-Clavulanic Acid (Augmentin®) in Outpatients with Respiratory Tract Infections in a Usual Care Setting"

This was a comparative, randomized (1:1 ratio), open-label, multicenter study with the primary objective of characterizing the safety of telithromycin when used for the outpatient treatment of respiratory tract infections. The primary safety outcome measure

was the incidence of particular hepatic, cardiac, vasculitic, and visual adverse events that had been identified in the original NDA submission. Patients with acute sinusitis, acute exacerbation of chronic bronchitis, or community-acquired pneumonia received either telithromycin for 5 to 10 days or amoxicillin-clavulanate for 7 to 10 days. Patients were instructed to notify investigators of any adverse events that occurred. Evaluations of safety and effectiveness were performed at posttherapy follow-up visits between days 17 and 22 and between days 30 and 35. At these visits, investigators determined if patients had serious adverse events or predefined "adverse events of special interest" (AESIs), which necessitated more detailed data collection and follow-up. For AESIs, case data were forwarded to independent Clinical Expert Committees (CECs) to determine whether the reported events met criteria for safety endpoints. The applicant used the CEC endpoint determinations to calculate incidence rates for the AESIs.

The visual AESI was "blurred vision," which was not otherwise defined in the study protocol. The CEC for visual AESIs had a single member, a university-affiliated opthalmologist. The confirmed safety endpoint definition used by the CEC for blurred vision was "all drug-related episodes of blurred vision that occurred after first ingestion of study drug through 48 hours after study drug intake."

CEC-confirmed visual endpoints were reported in 74 of 12,096 (0.612%) telithromycin-treated patients and in 5 of 11,883 (0.042%) amoxicillin-clavulanate-treated patients. Females were affected more commonly than males, and there was no significant age predominance. Telithromycin-associated blurred vision was most commonly described as mild or moderate in intensity, affecting both distance and near vision, with median onset one hour after drug administration, and lasting a median of two hours. All episodes resolved without sequelae. In 45% of reports, the blurring had a significant impact on patients' activities. In 35% of reports, telithromycin was discontinued because of the blurring.

4. Conclusions

In the two phase 1 studies intended to characterize the mechanism of telithromycin-associated blurred vision, detailed ophthalmologic examinations performed following drug administration demonstrated no consistent findings attributable to telithromycin, either in subjects reporting blurred vision or in subjects who were exposed but who did not develop blurring. In Study 3014, the confirmed safety endpoint of blurred vision was reported in 0.6% of telithromycin recipients and in 0.04% of amoxicillin-clavulanate recipients. Females were affected more commonly than males, and there was no significant age predominance. Telithromycin-associated blurred vision was most commonly described as mild or moderate in intensity, affecting both distance and near vision, with median onset one hour after drug administration, and lasting a median of two hours. All episodes resolved without sequelae. In 45% of reports, the blurring had a significant impact on patients' activities. In 35% of reports, telithromycin was discontinued because of the blurring. Labeling for this drug must provide adequate information about this adverse event for prescribers and patients.

Medical Officer Review
Visual Effects of Telithromycin
NDA 21-144

Applicant: Aventis Pharmaceuticals, Inc.
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Date of Submission: 7/24/02
Date Review Completed: 2/14/03

Drug Identification: Telithromycin (KETEK™)

1. Background

In the initial phase 1 studies of telithromycin, 40 of 1003 (4.0%) subjects reported blurred vision or other vision-related abnormalities. These events occurred in subjects receiving supratherapeutic doses of telithromycin. In the initial telithromycin NDA phase 3 safety database, blurred vision was reported as a treatment-emergent adverse event in 15 of 3265 (0.5%) telithromycin recipients vs. 1 of 1672 (0.1%) comparator recipients. There were 29 reports of blurred vision and possibly related visual adverse events (abnormal vision, eye disorder, and abnormality of accommodation) in telithromycin patients vs. 4 reports in comparator patients. These visual adverse event findings were unexpected and not well understood. In the approvable letter to the applicant, Aventis Pharmaceuticals, the FDA recommended that Aventis perform additional clinical studies of the effect of telithromycin on various measures of visual function. In addition, the Agency recommended that Aventis perform a large safety study in which particular attention was paid to adverse events of special interest, including visual adverse events.

In its response to the FDA approvable letter, Aventis has submitted reports from two phase 1 safety studies that evaluated the visual effects of high single doses of telithromycin. Aventis also performed a large, comparative, open-label trial of the safety and effectiveness of telithromycin in usual care settings. This study is described in detail in the review by George Rochester, Ph.D. The present review discusses the phase 1 studies and the subset of patients with visual adverse events in the large safety trial.

2. Phase 1 Studies

2.1. Study 1059: "Mechanism of blurred vision induced by HMR 3647 [telithromycin] at single supraclinical doses (2400 mg) versus therapeutic single dose (800 mg) in a younger and older population of healthy subjects"

2.1.1. Objective

The primary objective of this study was "to characterize the mechanism of action of blurred vision observed in previous phase 1 studies with HMR 3647 at a supraclinical dose in young and older subjects" (study report, p.23).

2.1.2. Study Design

This was a single-center, randomized, placebo-controlled, double-blind, single-dose, three-way crossover study with a one-week washout period between treatments.

2.1.3. Population

Two groups of healthy adult subjects were studied:

Group I: 15 subjects 18 to 40 years of age with normal uncorrected vision
Group II: 15 subjects 50 to 64 years of age with presbyopia

Approximately equal numbers of males and females were to be enrolled in each group.

2.1.4. Study Drug Administration

Each subject received three treatments: telithromycin 800 mg (two 400 mg tablets and four matching placebo tablets), telithromycin 2400 mg (six 400 mg tablets), and placebo (six matching tablets). The order of receipt was randomized, and treatments were administered as single doses with a one-week washout period.

2.1.5. Study Evaluations

Pharmacokinetic studies: Plasma concentrations and amounts of drug in tears were determined at baseline and at 1, 2, 3, 4, 6, 8, and 24 hours after study drug administration. Tear samples were collected with Schirmer strips.

Eye examinations:

At baseline and at 1, 2, 3, 4, 6, 8, and 24 hours after study drug administration:

- Far and near visual acuity for each eye
- Accommodation (near point and amplitude) using a Clark rule
- Pupil diameter
- Refraction
- Clinical evaluation of visual signs and symptoms (pain, discomfort, foreign body sensation, photophobia, blurred vision, stinging, burning, tearing)

At baseline and between 4 and 8 hours after study drug administration:

- Visual field with Amsler's grid
- Color vision
- Slit lamp examination (lids, cornea, lens, iris, fundus)
- Intraocular pressure using air puff tonometry method

Safety studies: Laboratory safety tests (hematology and blood chemistry including AST, ALT, and bilirubin), 12-lead ECG, blood pressure and heart rate measurements, and adverse event monitoring were performed before and after each study drug administration.

2.1.6. Statistical Analysis

Summary statistics were calculated for pharmacokinetic parameters and laboratory tests. Eye examinations and adverse events were recorded by treatment. These analyses are descriptive. Analysis of variance was performed on ECG parameters, and pairwise comparisons were performed between treatments.

Previous studies suggested that 30 to 40% of subjects would have blurred vision after receiving a 2400 mg dose of telithromycin. Aventis therefore estimated that a sample size of 30 subjects was needed to obtain at least 7 to 10 subjects with blurred vision.

2.1.7. Results

2.1.7.1. Demographics and Evaluability

Thirty subjects were enrolled, 15 in each group. Group I had 7 male and 8 female subjects; mean age was 26 years (range 18 to 37 years). Group II had 6 male and 9 female subjects; mean age was 56 years (range 49 to 63 years). All subjects completed the study.

2.1.7.2. Pharmacokinetics

Table 1 summarizes plasma pharmacokinetic parameters and amounts of telithomycin measured in tears. No tear samples were available for eight subjects in Group I because of "problems during shipment."

Table 1: Telithromycin plasma pharmacokinetics and amounts in tears

Parameter	Statistic	Group I (18-40 years)		Group II (50-64 years)	
		800 mg	2400 mg	800 mg	2400 mg
PLASMA		(n=15)	(n=15)	(n=15)	(n=15)
C_{max} (mg/L)	Mean (CV%) (Range)	1.42 (46)	3.89 (28)	1.71 (33)	4.21 (30)
t_{max} (h)	Median (Range)	3 (39)	4 (35)	2 (48)	3 (36)
C_{24h} (mg/L)	Mean (CV%) (Range)	0.02 (68) (<LOQ	0.16 (48)	0.03 (36)	0.22 (59) (<LOQ
TEARS		(n=7)	(n=7)	(n=15)	(n=15)
Maximum mean (ng/strip)	Mean (CV%) (Range)	108 (57)	341 (53)	55 (55)	201 (53)
Time (h)		3	4	2	8
Amount at 24h (ng/strip)	Mean (CV%) (Range)	6 (62)	38 (89)	5 (45)	36 (69)

C_{max}=maximum observed concentration; t_{max}=time of C_{max}; C_{24h}=concentration at 24h; CV=coefficient of variation; LOQ=limit of quantitation

Adapted from study report, pp.52, 54

MO comment: Plasma pharmacokinetic parameters were similar between groups. Measured amounts of telithromycin in tears were somewhat lower in Group II.

2.1.7.3. Eye Examinations

Four subjects (3 females, 1 male) in Group I and no subjects in Group II reported blurred vision. These reports are summarized in Table 2.

Table 2: Subjects with blurred vision

Subject	Age/ gender	Dose (mg)	Time post dose	Duration	Intensity	Description/symptoms	Eye exam	Other AE
2	18/F	2400	4 h	2 h	mild	blurred vision/far vision	No change	None
6	21/F	2400	6 h	1 h	mild	blurred vision/instability of far vision both eyes	No change	Nausea
9	25/F	2400	3 h	1 h	mild	blurred vision/difficulty focusing eyes, short latent period needed to focus for far vision	No change	Nausea
11	25/M	2400	3 h	30 min	mild	blurred vision/short latent period to focus for near and far vision	No change	Nausea, diarrhea

Adapted from study report, p.59

All cases occurred at the 2400 mg dose of telithromycin. Blurring developed 3 to 6 hours following drug administration, lasted 30 minutes to 2 hours, and was described as mild in intensity. Far vision was affected in all four subjects and near vision as well in one. The investigator reported that two subjects had a short latent period to focus, either for far

vision alone or for both far and near vision. Three subjects had concurrent nausea, and one also had diarrhea. There was no concurrent eye pain, discomfort, foreign body sensation, photophobia, stinging, burning, or tearing. During the episodes of blurred vision, there were no changes in visual acuity, refraction, pupillary diameter, color vision, visual fields, and slit lamp examinations. There were no decreases in amplitude of accommodation and no increases in intraocular pressure. These subjects reported no blurred vision and there were no changes observed in their eye examinations after they received either the 800 mg dose of telithromycin or placebo.

MO comment: The time of onset of blurring corresponds to the time of peak plasma concentration and amount of drug in tears. Other subjects with similar plasma concentrations or tear levels, however, did not report blurred vision.

No changes from baseline eye examinations were observed in any of the subjects in Groups I or II following receipt of study medication.

2.1.7.4. Safety

Treatment-emergent adverse events (TEAEs) are listed in Table 3. All events were characterized as mild or moderate in intensity and resolved without sequelae. There were no serious adverse events reported.

Table 3: Treatment-emergent adverse events

	Number of subjects (%)					
	Group I (n=15)			Group II (n=15)		
	Placebo	800 mg	2400 mg	Placebo	800 mg	2400 mg
Subjects with TEAEs	3 (20)	3 (20)	10 (67)	-	-	5 (33)
Event						
Diarrhea	-	-	4 (27)	-	-	4 (27)
Nausea	-	3 (20)	6 (40)	-	-	-
Blurred vision	-	-	4 (27)	-	-	-
Abdominal pain	-	-	2 (13)	-	-	-
Headache	2 (13)	-	1 (7)	-	-	-
Fatigue	2 (13)	1 (7)	1 (7)	-	-	-
Hypoaesthesia	-	1 (7)	-	-	-	-
Hot flushes	1 (7)	-	-	-	-	-
Somnolence	-	-	1 (7)	-	-	1 (7)

Adapted from study report, p.56

The most common TEAEs were diarrhea, nausea, and blurred vision. TEAEs occurred most frequently at the 2400 mg dose of telithromycin. TEAEs were reported more frequently in Group I subjects than in Group II subjects. In Group I, 6 of 7 men and 5 of 8 women had TEAEs. In Group II, 1 of 6 men and 4 of 9 women had TEAEs.

There were significant dose-dependent increases in heart rate and in corrected QT interval (QTc, Bazett's formula) for each group three hours after dosing with

telithromycin. In subjects receiving the 2400 mg dose, mean heart rate increased 16 and 9 beats per minute in Groups I and II, respectively, while mean QTc increased 20 msec and 13 msec, respectively.

2.1.8. Conclusions

Four of 15 subjects 18 to 40 years of age and 0 of 15 subjects 50 to 64 years of age reported blurred vision following a 2400 mg dose of telithromycin. Blurring developed 3 to 6 hours following drug administration, lasted 30 minutes to 2 hours, and was described as mild in intensity. Far vision was affected in all four subjects and near vision as well in one. There were no other associated eye symptoms, and no changes were observed from baseline eye examinations. The time of onset of blurring corresponded to the time of peak plasma concentration and amount of drug in tears. No subjects reported blurred vision following an 800 mg dose.

> **MO comment: This study provides a useful subjective description of the blurred vision that occurred in a small number of subjects administered a supratherapeutic dose of telithromycin. The eye examinations performed while subjects were symptomatic did not clarify the mechanism of this phenomenon. A larger study using more detailed examination techniques is necessary.**

2.2. Study 1064: "Assessment of ophthalmological safety of telithromycin at supraclinical dose (2400 mg) in healthy subjects"

> **MO comment: This study incorporated recommendations following FDA review and had several enhancements over Study 1059, including a larger sample size, dynamic measurement of accommodation and pupil size, automated visual field testing, and tests of contrast sensitivity function and tear film stability.**

2.2.1. Objective

The primary objective of this study was "to assess the risk for angle closure glaucoma by measuring intraocular pressure and anterior chamber angle, and the risk for retinal toxicity by performing visual field and color vision assessments" (study report, p.27). Secondary objectives were "to assess the ophthalmological safety of telithromycin further by performing a complete evaluation of the visual function with measurements of visual acuity, refraction and tear film stability, and by investigating accommodation using a dynamic approach" (study report, p.27).

2.2.2. Study Design

This was a single-center, randomized, placebo-controlled, double-blind, single-dose, two-way crossover study with a one-week washout period between treatments.

2.2.3. Population

Twenty-four healthy adult subjects were studied. At least 35% were to be between 50 and 64 years of age. All subjects were required to have normal uncorrected far vision; a correction for near vision was acceptable for the older subjects.

2.2.4. Study Drug Administration

Each subject received two treatments: telithromycin 2400 mg (six 400 mg tablets) and placebo (six matching tablets). The order of receipt was randomized, and treatments were administered as single doses with a one-week washout period.

2.2.5. Study Evaluations

Pharmacokinetic studies: Plasma concentrations were determined at baseline and at 1, 2, 3, 4, and 6 hours after study drug administration.

Eye examinations:

At screening: uncorrected and corrected visual acuity, fixation disparity test, refraction, intraocular pressure, color vision, slit lamp examination, fundus photography

At baseline, 3 hours, and 7 days after study drug administration:

- Far and near visual acuity for each eye
- Contrast sensitivity function for each eye
- Refraction
- Continuous recording of accommodation and pupil size using an autorefractor
- Slit lamp examination (lids, cornea, lens, iris, anterior chamber angle, fundus)
- Color vision
- Visual field threshold automated testing
- Tear film stability using a tearscope
- Intraocular pressure using air puff tonometry method
- Clinical evaluation of visual signs and symptoms (pain, discomfort, foreign body sensation, photophobia, blurred vision, stinging, burning, tearing)

At end of study: fundus photography

Safety studies: Laboratory safety tests (hematology, blood chemistry including liver function tests, and urinalysis), 12-lead ECG, blood pressure and heart rate measurements and adverse event monitoring were performed before and after each study drug administration.

2.2.6. Statistical Analysis

Summary statistics were calculated for pharmacokinetic parameters and laboratory tests. Eye examinations and adverse events were recorded by treatment. The sample size was chosen based on observed rates of blurred vision in previous studies.

2.2.7. Results

2.2.7.1. Demographics and Evaluability

Twenty-four subjects were enrolled; 18 were 18 to 49 years of age, and 6 were 50 to 64 years of age. Thirteen males and 11 females were enrolled. All subjects completed the study.

2.2.7.2. Pharmacokinetics

Telithromycin mean C_{max} was 5.11 mg/L (CV 29%; range ⟶ mg/L) and median t_{max} was 3 hours (range 1-4 hours).

MO comment: These values are consistent with those obtained with this dose in previous studies.

2.2.7.3. Visual Adverse Events and Eye Examinations

Table 4 is a listing of all eye-related TEAEs that occurred in this study.

Table 4: Eye-related treatment-emergent adverse events

	Number of subjects (%)	
	Placebo (N=24)	Telithromycin (N=24)
Subjects with eye disorders	5 (20.8)	14 (58.3)
Blurred vision	1 (4.2)	12 (50.0)
Dry eye	2 (8.3)	3 (12.5)
Ocular discomfort	-	2 (8.3)
Blepharospasm	-	1 (4.2)
Corneal epithelium disorder	-	1 (4.2)
Diplopia	-	1 (4.2)
Eye pain	1 (4.2)	1 (4.2)
Photophobia	-	1 (4.2)
Eye irritation	1 (4.2)	-

Adapted from study report, p.55

Twelve subjects (7 females, 5 males) reported blurred vision. These reports are summarized in Table 5.

Table 5: Subjects with blurred vision

Subject	Age/gender	Treatment	Time post dose	Duration	Intensity
1	55/M	Telithromycin	1h 10m	2h 50m	Moderate
2	20/F	Telithromycin	3h 20m	18h 29m	Moderate
5	21/M	Telithromycin	1h 18m	4h 27m	Mild
6	19/M	Telithromycin	5h	0h 53m	Mild
10	30/F	Placebo	3h	18h 55m	Mild
10	30/F	Telithromycin	2h 50m	3h 15m	Moderate
13	34/M	Telithromycin	3h 6m	1h 14m	Mild
15	40/F	Telithromycin	3h 7m	2h 43m	Mild
17	54/F	Telithromycin	3h 5m	2h 25m	Mild
18	22/M	Telithromycin	1h 25m	20h 20m	Mild
21	47/F	Telithromycin	2h	5h 30m	Moderate
23	27/F	Telithromycin	2h 55m	3h 55m	Mild
24	41/F	Telithromycin	2h 35m	2h 40m	Mild

Adapted from study report, p.56

All 12 subjects reported blurred vision following administration of telithromycin; one subject also reported blurred vision following administration of placebo. Blurring developed 1 to 5 hours after dosing (median 3 hours) and lasted for a median of 2h 50 min. Three subjects (two telithromycin, one placebo) had a duration of blurring of 18 to 20 hours; the exact duration is uncertain because these subjects reported blurring at bedtime and were questioned the following morning.

> **MO comment: In this study, as in Study 1059, the time of onset of blurring corresponds to the time of peak plasma concentration.**

Narrative detail about these episodes is limited. The blurring was most commonly described as difficulty focusing, particularly on distant objects. The intensity was described as mild for eight subjects and moderate for four. Several subjects had concurrent dizziness, nausea, and diarrhea. One subject reported photophobia, one reported ocular discomfort, and one had diplopia; there were otherwise no concurrent eye complaints.

The following eye examination findings were recorded for the subjects reporting blurred vision:

- One subject (Subject 2) had impairment of near visual acuity during the episode of blurred vision. Visual acuity was unchanged for the other subjects.
- Amplitude of accommodation was abnormal in two subjects (Subjects 2 and 18) and normal for the other subjects.
- Continuous recording of accommodation: Near-to-far reaction and/or response times were unchanged in four subjects and increased in four subjects (Subjects 1, 2, 10, and 15). Four subjects (Subjects 13, 17, 21, and 24) were unable to perform the test. Far-to-near reaction and response times were unchanged in five subjects. Far-to-near reaction times were increased in two subjects (Subjects 10 and 18), but response times were normal. Five subjects (Subjects 13, 15, 17, 21, and 24) could not perform the test.

MO comment: Several older patients with and without blurring were unable to perform this test, most likely because of age-related impairment of accommodation.

- The accommodation range was reduced in Subject 2 and increased in two older subjects (Subjects 21 and 24).
- Slit lamp examination was abnormal in Subject 5, who had a small corneal epithelial defect that was believed possibly due to rubbing his eye; this finding was reported as a TEAE. The remaining slit lamp examinations were normal.
- Tear film was unstable in three subjects (Subjects 2, 17, and 21).
- There were no changes in refraction, visual fields, color vision, contrast sensitivity function, intraocular pressure, anterior chamber angle, pupil diameter, or fundus photographs.

The following eye examination findings were recorded for the subjects who did not report blurred vision:

- Continuous recording of accommodation: In subjects receiving telithromycin, near-to-far reaction and/or response times were increased in two and unchanged in six; four subjects could not perform the test. Far-to-near reaction and response times were increased in three subjects and unchanged in six; three subjects could not perform the test. In subjects receiving placebo, near-to-far reaction and/or response times were increased in three and unchanged in 13; six subjects could not perform the test. Far-to-near reaction and response times were increased in three subjects and unchanged in 12; seven subjects could not perform the test.
- Tear film was unstable in three subjects (one following telithromycin and two following placebo).
- There were no changes in visual acuity, amplitude of accommodation, refraction, contrast sensitivity function, visual fields, pupil diameter, slit lamp examination, intraocular pressure, anterior chamber angle, color vision, or fundus photographs.

MO comment: There were no consistent examination findings attributable to telithromycin, either in those reporting blurred vision or in those exposed but without blurring.

2.2.7.4. Safety

TEAEs occurring in more than one subject are listed in Table 6. All events were characterized as mild or moderate in intensity and resolved without sequelae. There were no serious adverse events reported.

Table 6: Treatment-emergent adverse events occurring in more than one subject

	Number of subjects (%)			
	Placebo (N=24)		Telithromycin (N=24)	
Subjects with TEAEs	10	(41.7)	20	(83.3)
Eye disorders	5	(20.8)	14	(58.3)
Blurred vision	1	(4.2)	12	(50.0)
Dry eye	2	(8.3)	3	(12.5)
Ocular discomfort		-	2	(8.3)
Nervous system disorders	2	(8.3)	15	(62.3)
Dizziness (excluding vertigo)		-	13	(54.2)
Dysgeusia		-	5	(20.8)
Headache	1	(4.2)	4	(16.7)
Gastrointestinal disorders		-	13	(54.2)
Nausea		-	9	(37.5)
Diarrhea		-	8	(33.3)
Abdominal pain		-	3	(12.5)
Dyspepsia		-	2	(8.3)
General disorders		-	4	(16.7)
Lethargy		-	2	(8.3)
Musculoskeletal disorders		-	2	(8.3)
Myalgia		-	2	(8.3)

Adapted from study report, p.64

The most common TEAEs were dizziness, blurred vision, nausea, and diarrhea.

Mean heart rate increased by 10 beats per minute 3 to 6 hours following administration of 2400 mg of telithromycin. Mean QTc (Bazett's formula) increased 18 msec at 3 hours postdose. One subject had an increase in QTc of 62 msec.

2.2.8. Conclusions

Twelve of 24 healthy subjects reported blurred vision following a 2400 mg dose of telithromycin. This effect was reported in 5 of 13 males and in 7 of 11 females, and it occurred in both young and older subjects. Blurring developed 1 to 5 hours (median 3 hours) following drug administration and lasted for a median of 2h 50 min. It was most commonly described as difficulty focusing, particularly on distant objects, and was generally described as mild in intensity. Several subjects had concurrent dizziness, nausea, and diarrhea. The time of onset of blurring corresponded to the time of peak plasma concentration.

Eye examinations following drug administration demonstrated no consistent findings attributable to telithromycin, either in those reporting blurred vision or in those exposed but without blurring. There were no changes from baseline in visual fields, color vision, intraocular pressure, anterior chamber angle, or pupil diameter. One subject with blurring had impairment of near visual acuity, decrease in amplitude of accommodation,

and impaired near-to-far reaction and response times. Continuous recording of accommodation in all subjects revealed no consistent changes in reaction or response times following drug administration. Tear film stability was reduced in three subjects with blurring and in three without blurring (one following telithromycin, two following placebo). Slit lamp examination was abnormal in one subject with blurring who had a corneal defect believed possibly due to eye rubbing; all remaining slit lamp examinations were normal.

MO comment: This study corroborates the description of the blurred vision that occurred in four subjects who received a supratherapeutic dose of telithromycin in Study 1059. In these studies, the blurring was self-limited and generally mild. The more comprehensive eye examinations performed in Study 1064 still do not explain the mechanism of this phenomenon. While the absence of serious abnormalities on examination is reassuring, the overall sample size remains limited and allows detection only of a large drug effect.

3. Visual Adverse Events in Phase 3 Studies

3.1. Study 3014: "Randomized, Open-Label, Multicenter Trial of the Safety and Effectiveness of Oral Telithromycin (Ketek™) and Amoxicillin-Clavulanic Acid (Augmentin®) in Outpatients with Respiratory Tract Infections in a Usual Care Setting"

3.1.1. Study Design

This was a comparative, randomized (1:1 ratio), open-label, multicenter study with the primary objective of characterizing the safety of telithromycin when used for the outpatient treatment of respiratory tract infections. The primary safety outcome measure was the incidence of particular hepatic, cardiac, vasculitic, and visual adverse events that had been identified in the original NDA submission.

Patients with acute sinusitis (AS), acute exacerbation of chronic bronchitis (AECB), or community-acquired pneumonia (CAP) received either telithromycin 800 mg qd for 5 days (AS) or 7 to 10 days (AECB, CAP) or amoxicillin-clavulanate 875/125 mg bid for 7 to 10 days (all indications); doses were adjusted for renal impairment. Patients were instructed to notify investigators of any adverse events that occurred. Evaluations of safety and effectiveness were performed at posttherapy follow-up visits between days 17 and 22 (Visit 2) and between days 30 and 35 (Visit 3). At these visits, investigators determined if patients had serious adverse events (SAEs) or predefined "adverse events of special interest" (AESIs), which necessitated more detailed data collection and follow-up. For AESIs, an "Adverse Event of Interest" form was completed. These forms, along with case report forms and other pertinent data, were forwarded to independent Clinical Expert Committees (CECs) to determine whether the reported events met criteria for safety endpoints. CECs were blinded to treatment assignment and in most cases performed endpoint reviews at the end of the study. The applicant used the CEC endpoint determinations to calculate incidence rates for the AESIs.

The visual AESI was "blurred vision," which was not otherwise defined in the study protocol. The CEC for visual AESIs had a single member, [redacted] an ophthalmologist at [redacted] The confirmed safety endpoint definition used by Dr. [redacted] for blurred vision was "all drug-related episodes of blurred vision that occurred after first ingestion of study drug through 48 hours after study drug intake."

3.1.2. Results

3.1.2.1. Demographics and Evaluability

Total enrollment in this trial was 24,562 patients from 1,824 U.S. sites. The safety evaluable population was defined as "all subjects who took study medication and had investigator contact at any time after start of study medication." This population contained 24,137 patients, 12,159 treated with telithromycin and 11,978 treated with amoxicillin-clavulanate. The number of subjects with known adverse event status on Day 28 or later was used as the denominator for calculating the incidence of confirmed safety endpoints. This population contained 23,979 patients, 12,096 treated with telithromycin and 11,883 treated with amoxicillin-clavulanate.

In the safety evaluable population, 60.5% of patients were female and 85.8% were white. The mean age was 49.2 years (range 16-100 years; median 48.0 years).

3.1.2.2. Safety

3.1.2.2.1. Confirmed Visual Endpoints

The applicant reported CEC-confirmed visual endpoints in 74 of 12,096 (0.612%; 95% CI 0.481-0.767%) telithromycin-treated patients and in 5 of 11,883 (0.042%; 95% CI 0.014-0.098%) amoxicillin-clavulanate-treated patients.

> **MO comment: The reported rate for telithromycin-treated patients is nearly 15 times that reported for the amoxicillin-clavulanate-treated patients and is similar to the rate reported for blurred vision and other possibly related visual adverse events in the initial telithromycin phase 3 studies.**

Table 7 summarizes the reported visual adverse events for the patients with confirmed visual endpoints.

Table 7: Confirmed visual endpoints and associated adverse event terms

	Number of patients	
	Telithromycin	Amoxicillin-clavulanate
Total with confirmed visual endpoints	74	5
Vision blurred	62	4
Diplopia	4	1
Vision abnormal NOS	4	-
Visual disturbance NOS	3	-
Hallucination, visual	1	-

NOS=not otherwise specified

Adapted from study report, p.126

MO comment: The case report forms of all patients with visual AESIs were reviewed to check for agreement with CEC endpoint determinations and to ensure accurate transcription of information into the database. The database listings and adverse event tables were also searched for additional vision-related adverse events that could have been classified as AESIs and possibly as confirmed endpoints. Five additional adverse events were found that might represent the phenomenon of interest. Three patients had visual adverse events (visual distortion, visual disturbance, and diplopia) that were not reported as AESIs but should have been reported. One patient with blurred vision was determined by the CEC to have a confirmed endpoint, but this judgment was not correctly transcribed into the database. One patient with blurred vision was judged by the CEC not to have a confirmed endpoint because an ophthalmology report was not available; the CEC adjudication form, however, states, "I suspect drug-related." All five of these patients were treated with telithromycin. Inclusion of these cases as confirmed endpoints does not significantly affect the reported incidence of blurred vision in a population of over 12,000 patients. The applicant's endpoint determinations have therefore been accepted by this reviewer.

Table 8 describes the characteristics of the confirmed visual endpoints.

Table 8: Characteristics of confirmed visual endpoints

	Number of patients	
	Telithromycin (N=74)	Amoxicillin-clavulanate (N=5)
Symptoms		
Blurred vision	69	5
Distance only	10	-
Near only	13	-
Distance and near	46	4
Color abnormalities: color appears lighter	3	-
Light perception: increased brightness	7	-
Median onset after drug administration (h)	1	37
Median duration (h)	2	16
Intensity (mild/moderate/severe)	61/17/6	4/1/0
Significant impact on activities (%)	33 (45)	2 (40)
Discontinuation due to adverse event (%)	25 (34)	1 (20)
Serious adverse event	3	-

Adapted from study report, p.127

MO comment: The case report forms used to compile the information in this table were often incomplete and generally lacked detailed narrative comments, although space for comments was provided on the forms. The precise onset, duration, and frequency of events were often difficult to determine, especially when the investigators did not provide additional comments. In many cases, there was a significant delay between the occurrence of an adverse event and the time the event was reported. For example, treatment-emergent adverse events were often not reported until Visit 2, which was 17 to 22 days into the study. These delays limit the precision of patient recall.

In the telithromycin group, the most commonly described abnormality was blurred vision affecting both distance and near vision. The onset of blurred vision was following the first dose in 50% of cases (37/74) and following the second dose in an additional 23% of cases (17/74). The blurring was not generally reported to occur with each dose. The median reported time of onset was one hour after taking the drug, and the event lasted a median of two hours. The blurring was mild to moderate in most cases; six patients reported severe blurring. In 45% of cases (33/74), the blurring had a significant impact on the patients' activities; the most frequently reported specific problems were difficulty reading (7 patients), inability to work (5 patients), and inability to drive (5 patients). In 34% of cases (25/74), telithromycin was discontinued because of blurring. All patients recovered without sequelae.

Three reports were considered by investigators to represent serious adverse events. One patient had severe blurring that was incapacitating, causing him to miss work and be confined to bed for two days; this patient completed his five day course of therapy for acute sinusitis. Another patient had diarrhea, dehydration, hypotension, chest pain, shortness of breath, and mild blurring of vision that were considered to be medically important and that resulted in discontinuation of telithromycin. The third patient had mild blurring that was considered to be medically important; she completed her 10-day course of therapy for CAP, missed no time from work, and reported that the blurring had no significant effect on her activities.

The most common adverse events reported concurrently with blurred vision in telithromycin recipients were dizziness (14 patients), nausea (11 patients), and headache (10 patients). Several patients reported concurrent vomiting, dry mouth, abdominal pain, taste disturbance, fatigue, or diarrhea.

MO comment: The occurrence in some patients of blurred vision with dizziness, dry mouth, or taste disturbance is suggestive of an anticholinergic drug effect. Only one patient reported blurred vision and somnolence, however.

The telithromycin patients with confirmed endpoints were disproportionately female (62/74; 83.8%, compared with 60.9% of all telithromycin patients). The incidence of

confirmed visual endpoints was 0.84% in women (62/7404) and 0.25% (12/4755) in men, using the safety evaluable population figures as the denominator. There was no significant age predominance; the median age of patients with CEC-confirmed blurring was 48 years, the same as that of the safety evaluable population.

> **MO comment: The explanation for this gender difference is unclear. A female predominance was also noted in the original submission. Of interest, all seven visual AESIs in amoxicillin-clavulanate patients in Study 3014 were in females. Overall, TEAEs were more common in women in both treatment groups. There is no evidence from this study that blurring is more likely to occur in younger patients.**

The incidence of blurred vision was not increased in patients taking both telithromycin and a CYP3A4 inhibitor (2/353; 0.6%). One patient taking a strong CYP3A4 inhibitor and one taking a mild CYP3A4 inhibitor had blurred vision.

> **MO comment: In the integrated phase 3 studies, blurred vision was more likely to be reported as a TEAE in telithromycin patients who were taking CYP3A4 inhibitors (10/686; 1.5%) than in those who were not (10/3786; 0.3%).**

3.1.2.2.2. Visual AESIs

Visual AESIs were reported in 83 telithromycin patients and in seven amoxicillin-clavulanate patients. For nine of the telithromycin patients and two of the amoxicillin-clavulanate patients, the recorded events were reported by the applicant not to be confirmed endpoints. Most of these events occurred more than one week after completion of therapy, did not involve blurring (e.g., blepharospasm, "tunnel vision" attributed to a vasovagal event), were present pretherapy, or were manifestations of other conditions (e.g., migraine).

> **MO comment: For two of the nine telithromycin patients, the reported events should have been considered confirmed endpoints. These cases are discussed in the previous section.**

3.1.2.2.3. Other Treatment-Emergent Eye Disorders

Treatment-emergent eye disorders were reported in 101 (0.8%) telithromycin patients and in 15 (0.1%) amoxicillin-clavulanate patients. Confirmed endpoints and other visual endpoints are discussed above. Twenty-three telithromycin patients and 10 amoxicillin-clavulanate patients had treatment-emergent eye disorders that did not meet the definitions of confirmed visual endpoints or visual AESIs. Conditions occurring in more than one telithromycin patient included conjunctivitis or similar disorders (eight patients vs. four for amoxicillin-clavulanate), eye irritation (three vs. zero), and photophobia (three vs. zero). No other eye disorder was reported in more than one patient in either treatment group. There were no serious adverse events among these reports.

MO comment: The incidence of these other eye disorders was greater in telithromycin patients but low overall. Of note, one telithromycin patient was reported with the preferred term "blindness not otherwise specified." On the case report form, the investigator reported that the patient had "loss of vision" that was considered nonserious and of mild intensity. This patient completed his 10-day course of therapy for AECB. The reported preferred term is obviously incorrect.

3.1.3. Conclusions

In this study, the confirmed safety endpoint of blurred vision was reported in 0.6% of telithromycin recipients and in 0.04% of amoxicillin-clavulanate recipients. Females were affected more commonly than males, and there was no significant age predominance. Telithromycin-associated blurred vision was most commonly described as mild or moderate in intensity, affecting both distance and near vision, with median onset one hour after drug administration, and lasting a median of two hours. All episodes resolved without sequelae. In 45% of reports, the blurring had a significant impact on patients' activities. In 35% of reports, telithromycin was discontinued because of the blurring.

MO comment: This general description is consistent with that obtained in Studies 1059 and 1064. Although the phase 1 studies were small and used supratherapeutic single doses, they probably provide a more accurate characterization of this adverse event because of the detailed ophthalmologic examinations that were performed. Study 3014, with the large population studied, provides a description of the incidence and natural history of this event when therapeutic dosing is used.

3.2. All Integrated Phase 3 Studies

In the initial telithromycin NDA phase 3 safety database, blurred vision was reported as a treatment-emergent adverse event in 15 of 3265 (0.5%) telithromycin recipients vs. 1 of 1672 (0.1%) comparator recipients. In the recent phase 3 trials (Studies 3012, 3013, 3107, and 4003), blurred vision was reported in five patients receiving telithromycin and in two receiving comparators. In all integrated phase 3 studies, therefore, blurred vision was reported as a TEAE in 20 of 4472 (0.4%) telithromycin recipients vs. 3 of 2139 (0.1%) comparator recipients.

MO comment: The case report forms of the five newly-submitted telithromycin patients with blurring were reviewed. The reports were from three females and two males ranging in age from 25 to 54 years. The intensity was described as mild in four cases and moderate in the fifth. None of these events was considered to be serious. All patients recovered without sequelae, and all completed their study medications.

In all integrated phase 3 studies, there were 32 reports of blurred vision and other possibly related visual TEAEs (blurred vision, 20; visual disturbance, 5; vision abnormal, not otherwise specified, 2; visual acuity reduced, 2; accommodation disorder, 1; binocular eye movement disorder, 1; eye disorder, not otherwise specified, 1). The estimated incidence of blurred vision and other possibly related visual TEAEs is 0.7% (32/4472), assuming that each report represents a separate patient with the phenomenon of interest.

> **MO comment: This assumption is reasonable, since in the integrated phase 3 database, 55 treatment-emergent eye disorders were reported in 54 telithromycin patients. The resulting estimated incidence of 0.7% is similar to the estimate of 0.6% from Study 3014.**

The integrated phase 3 safety data are described in more detail in the review by Charles Cooper, M.D.

4. Visual Adverse Events of Special Interest from Postmarketing Reports

Two Periodic Safety Update Reports covering the periods 7/9/01 to 1/9/02 and 1/10/02 to 7/9/02 were reviewed. The applicant reported 159 events in the MedDRA System Organ Class "Eye Disorders." The most commonly reported events were blurred vision (67 cases), visual disturbance NOS (47 cases), accommodation disorder (10 cases), diplopia (10 cases), and vision abnormal NOS (7 cases). The remaining 18 reports were for events that occurred in one or two patients each. Most of the reports of visual disturbance were consistent with the reports of blurred vision from the clinical studies. The reported cases of diplopia were not confirmed by ophthalmologists and were often associated with blurred vision. It is likely that these reports also represent manifestations of the blurring phenomenon observed in the clinical studies.

> **MO comment: One spontaneous report from a physician was for a serious adverse event reported as "visual loss" and coded with the preferred term "blindness." The case report form states that on day 3 of treatment for a presumed mycoplasma illness, "the patient experienced visual disorder with visual loss." She reportly had a normal CT scan and visual field studies and recovered completely after discontinuing drug. No other information is available. The term "blindness" appears to have been misapplied in this case.**

The postmarketing safety data are described in more detail in the review by Charles Cooper, M.D.

5. Conclusions

In Study 3014, the confirmed safety endpoint of blurred vision was reported in 0.6% of telithromycin recipients. Females were affected more commonly than males, and there was no significant age predominance. Telithromycin-associated blurred vision was most

commonly described as mild or moderate in intensity, affecting both distance and near vision, with median onset one hour after drug administration, and lasting a median of two hours. All episodes resolved without sequelae. In 45% of reports, the blurring had a significant impact on patients' activities. In 35% of reports, telithromycin was discontinued because of the blurring. In the two phase 1 studies intended to characterize the mechanism of this phenomenon, detailed ophthalmologic examinations performed following drug administration demonstrated no consistent findings attributable to telithromycin, either in subjects reporting blurred vision or in subjects who were exposed but who did not develop blurring.

6. Labeling Issues

6.1. Proposed Label

In the applicant's initial proposed label, the **ADVERSE REACTIONS** section contained [redacted] including the following:

[redacted]

The **WARNINGS** and **PRECAUTIONS** sections contained nothing about visual adverse events.

Revised proposed labeling submitted 1/14/03 contains the following in the **PRECAUTIONS** section, under **Information for patients**:

> Patients should be advised that:
>
> - KETEK tablets can be taken with or without food.

[redacted]

The **ADVERSE REACTIONS** section includes the following:

[redacted]

6.2. Current European Label

The European Agency for the Evaluation of Medicinal Products (EMEA) approved package leaflet for patients taking telithromycin lists blurred vision as one of numerous "uncommon or rare side effects" occurring in 1 in 10,000 to less than 1 in 100 patients. A precautionary subsection entitled **Driving and using machines** advises that telithromycin "may reduce the capacity to carry out certain tasks, such as driving or operating machinery." The information for prescribers lists blurred vision as an "undesirable effect" occurring in 0.1 to 1% of patients. A subsection entitled **Effects on ability to drive and use machines** states:

> Leviaxx [telithromycin] may cause undesirable effects which may reduce the capacity for the completion of certain tasks. Patients should be informed of the potential for these undesirable effects and should be aware of how they react to this medication before driving or operating machinery.
>
> **MO comment: This language encompasses other adverse reactions such as dizziness and somnolence which also may impair the ability to drive or operate machinery and have been reported to occur with similar or increased frequency to the incidence of blurred vision in patients taking telithromycin. There is no text relating specifically to blurred vision.**

In response to concerns raised from postmarketing reports, German authorities have recommended strengthening the text in this section to state:

6.3. Other Products with Blurred Vision as an Adverse Reaction

The **ADVERSE REACTIONS** sections of the labels of the following orally-administered products report an incidence of blurred vision of greater than or equal to 3% of patients in one or more clinical studies: Artane (trihexyphenidyl HCl), Coreg (carvedilol), Depakene (valproic acid), Depakote (divalproex sodium), Ditropan (oxybutinin Cl), Effexor (venlafaxine HCl), Lamictal (lamotrigine), Limbitrol (amitriptyline HCl and chlordiazepoxide), Luvox (fluvoxamine), Mexitil (mexilitine HCl), Paxil (paroxetine HCl), Rhythmol (propafenone HCl), Serzone (nefazodone HCl), Soriatane (acitretin), Temodar (temozolomide), Tonocard (tocainide HCl), VFEND (voriconazole), Viagra (sildenafil citrate), Wellbutrin (bupropion HCl), and Xanax (alprazolam). Of these products, only Lamictal, Soriatane, VFEND, and Xanax contain

language about visual adverse reactions in the **WARNINGS** or **PRECAUTIONS** sections of their labels. The Lamictal label contains a precaution about an increased incidence of dizziness, diplopia, ataxia, and blurred vision when this drug is administered to patients who are also receiving carbamazepine as opposed to other enzyme-inducing antiepileptic drugs. The Soriatane label contains a warning listing blurred vision among numerous ophthalmologic effects of this drug. The warning states, "Any patient treated with Soriatane who is experiencing visual difficulties should discontinue the drug and undergo ophthalmologic evaluation." The Xanax label contains a table in the **WARNINGS** section that lists blurred vision as one of 23 discontinuation-emergent symptoms which occurred in over 5% of patients in a database of 641 patients.

The **ADVERSE REACTIONS** section of the VFEND label contains a table in which abnormal vision is listed as one of numerous treatment-emergent adverse events. There are also two paragraphs which discuss the visual disturbances, including blurred vision, that occurred in approximately 30% of patients in clinical trials. The **WARNINGS** section of this label states that the effect of voriconazole on visual function is not known if treatment continues beyond 28 days and recommends monitoring of visual function if treatment exceeds this duration. The **PRECAUTIONS** section of the label, under **Information for Patients**, states that patients should be advised:

- **that they should not drive at night while taking VFEND. VFEND may cause changes to vision, including blurring and/or photophobia.**
- **that they should avoid potentially hazardous tasks, such as driving or operating machinery if they perceive any change in vision.**

Among antimicrobial agents, the **ADVERSE REACTIONS** sections of the labels for Bicillin (benzathine penicillin G), Cipro (ciprofloxacin), dapsone, Floxin (ofloxacin), Minocin (minocycline), and Noroxin (norfloxacin) list blurred vision as one of numerous adverse reactions occurring in less than 3% of patients. The Minocin label contains a general precaution regarding the association of pseudotumor cerebri with the use of tetracyclines. Headache and blurred vision are listed as the usual clinical manifestations of this condition. The other product labels have no additional text referring to blurred vision.

> **MO comment: For most of these agents, a causal relationship between drug administration and the occurrence of blurred vision has not been established.**

6.4. Recommendation

The blurred vision associated with telithromycin administration is an uncommon adverse event that is generally mild to moderate in intensity and resolves without sequelae. Patients experiencing blurred vision may have significant impairment in their ability to perform certain activities, however. Telithromycin may be used widely in the outpatient setting, and physicians and patients must be aware of the risks as well as the potential benefits of this drug. In response to concerns raised from postmarketing reports, German authorities have recommended strengthening the European label to state that —

[redacted] At the January, 2003, Anti-Infective Drugs Advisory Committee meeting, several committee members also expressed concern about the postmarketing reports of visual adverse events and recommended strong cautionary language in the label. The applicant's proposed label should be revised to provide adequate information for prescribers and patients.

Thomas Smith, M.D.
Medical Officer, HFD-520

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

/s/

Thomas Smith
3/11/03 01:09:59 PM
MEDICAL OFFICER
Review of phase 1 visual effects studies and visual effects component of Study 3014
Please sign off.

David Ross
3/11/03 04:27:44 PM
MEDICAL OFFICER

Janice Soreth
3/20/03 05:40:46 PM
MEDICAL OFFICER

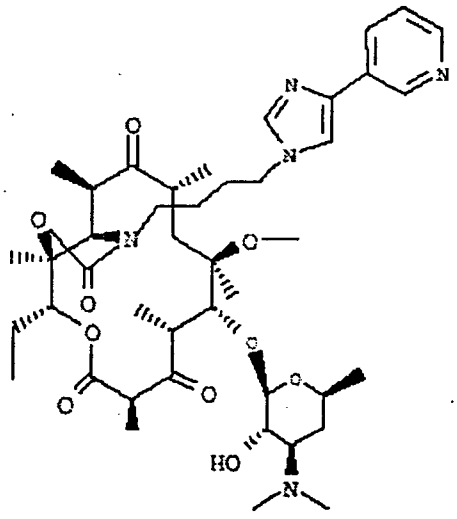
MEDICAL OFFICER REVIEW OF EFFICACY:
NDA 21-144 RESUBMISSION

Date of Resubmission: July 24, 2002
Date Review Assigned: October 17, 2002
Date Review Completed: January 21, 2003

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

Drug Information

Proprietary Name: Ketek™
Established Name: Telithromycin
Chemical Name: 11, 12-dideoxy-3-de[(2,6-dideoxy-3-C-methyl-3-0-methyl-alpha-L-ribo-hexo-pyranosyl)oxy]-6-0-methyl-3-oxo-12,11-[oxycarbonyl [(4-(4-(3-pyridinyl)-1H-imidazol-1-yl])butyl]imino)]-erythromycin
Drug Class: Ketolide
Formulation: 400-mg oral tablets
Chemical Structure:



Chemical Formula: $C_{43}H_{65}N_5O_{10}$
Molecular Weight: 812.03

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