CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-144

MEDICAL REVIEW(S)

MEDICAL OFFICER SAFETY REVIEW OF NDA 21-144: TELITHROMYCIN (KETEK™)

General Information

Date Submitted:	October 17, 2003
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Medical Officer	Charles Cooper, M.D.

Applicant: Aventis Pharmaceuticals Inc.
200 Crossing Blvd, PO Box 6890
Bridgewater, NJ 08807-0890

Contact Person: Steve Caffé
Head, U.S. Regulatory Affairs
(908) 231-5863

Drug: Proprietary Name: Ketek™
Generic Name: Telithromycin

Drug Class: Ketolide antibiotic

Formulation: 400 mg tablet

Route of administration: Oral

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Executive Summary

The applicant's submission dated October 17, 2003 provides additional safety information to allow for approval of telithromycin. This safety information includes post-marketing adverse event reports generated from an estimated — uses in countries where it is already approved. In addition, safety information was provided in which phase 3 visual adverse event data was re-analyzed. Review of all available safety data has allowed for a better assessment of telithromycin's remaining safety issues. Specifically, analysis of post-marketing data shows that the frequency and severity of hepatic and cardiac toxicity with telithromycin is similar to other macrolides. Severe life-threatening exacerbations of myasthenia gravis have been identified as a safety issue.

The visual adverse event syndrome associated with telithromycin has been better characterized. This syndrome was first identified in Phase 1 and 3 trials and involves the disturbance of accommodation. Visual adverse events can occur at any time during treatment, although most often occur within the first three doses. Duration of these events is usually from several hours to a few days and is most often mild to moderate. Disabling visual events were identified in post-marketing data. Visual adverse events were most common in females and people under 40 years of age. Rates of occurrence of visual adverse events in controlled phase 3 trials ranged from 1.1% in all subjects to 2.1% in females under 40 years of age.

Although the rate of telithromycin-associated visual adverse events is relatively low, this drug is expected to be given to a large number of patients thereby resulting in large absolute numbers of patients experiencing visual adverse events. In addition, because telithromycin is expected to be used most often in relatively mild infections, such as acute bacterial sinusitis and acute exacerbations of chronic bronchitis, patients are more likely to be engaged in activities of daily living, such as driving, while on therapy. These visual adverse events could result in some degree of impairment in the conduct of these activities. Therefore, specific measures should be taken to minimize the overall potential public health impact of telithromycin-associated visual adverse events. Such measures include prominent labeling, advertising that notes visual adverse events as part of fair market balance, as well as inclusion in the label of information that would be useful to both the prescribing clinicians and the patients.

Overall, the medical officer recommends approval of telithromycin. Substantial evidence of safety has been provided. The toxicities of telithromycin are similar to those of macrolides and other antibiotics. The visual adverse event syndrome associated with telithromycin has not been seen in other antibiotics. There is an additional risk that is conveyed by these visual adverse events, but this can be managed in clinical practice. Life threatening exacerbation of myasthenia gravis has been identified and clinicians should be warned of this potential effect.

In the post-marketing data, there were a small number of cases involving prolonged visual adverse events. In order to characterize the potential for long-term sequelae, the applicant should conduct careful follow up of visual events in post-marketing. An analysis of collected visual events should be provided as a phase 4 commitment.

Summary Basis of Finding

Introduction

This Summary of Safety provides an overview of the safety profile of telithromycin. Some of the information in this summary was obtained from the second review cycle and is intended to provide an overview of the tolerability and safety of telithromycin. Details of this information can be found in the medical officer safety review of the July 24, 2002 submission. Other information provided in this summary pertains to the review of post-marketing data and a phase 3 visual adverse event re-analysis submitted on October 17, 2003. Details of this information are contained in this review. The post-marketing data were collected in 36 countries where telithromycin has already been approved. The majority of prescriptions were dispensed in Germany and France [redacted] out of [redacted] where pharmacovigilance is thought to be very good. Other countries with more than [redacted] prescriptions dispensed included Italy, Spain, and Mexico.

Deaths / Serious Adverse Events / Adverse Events in Phase 3 Clinical Trials

The number of deaths on treatment and post-treatment for telithromycin and comparators were 10/1207 (0.83%) and 5/467 (1.1%) respectively. There were no deaths in telithromycin-treated or the comparator-treated patients which were attributed by the applicant to study drug. This was confirmed by a detailed Medical Officer review of all case report forms for those patients who died. Serious adverse events occurred with equal frequencies in the telithromycin-treated patients and comparator-treated patients. The majority of these serious adverse events were related to underlying co-morbidities or the infection for which the patient was being treated. Demographic factors and concomitant medications did not affect the rates of serious adverse events for telithromycin-treated and comparator-treated patients.

In all controlled Phase 3 trials, telithromycin-treated patients had higher rates of diarrhea (10.8% vs. 8.6%), nausea (7.9% vs. 4.6%) and vomiting (2.9% vs. 2.2%) than those receiving comparator drugs. Telithromycin-treated patients also had higher rates of dizziness (3.7% vs. 2.7%) than those receiving comparator drugs. These adverse events occurred in a higher proportion of telithromycin-treated females than males. The incidences of these adverse events in telithromycin-treated females compared to males were: diarrhea, 12.2% vs. 9.3%; nausea, 10.4% vs. 5.2%; vomiting, 4.1% vs. 1.7%; and dizziness, 4.4% vs. 2.9%.

The rates of discontinuation of study medication were slightly higher for telithromycin-treated patients than comparator-treated patients for certain gastrointestinal adverse events. The rates of discontinuation due to specific adverse events for telithromycin-treated patients vs. comparator-treated patients were: diarrhea 0.9% vs. 0.6%; vomiting 0.8% vs. 0.5%; and nausea 0.7% vs. 0.5%.

All deaths reported in the post-marketing database were reviewed in detail. Most of the deaths were confounded by underlying disease. There were no deaths which likely represented a safety signal.

Hepatic Toxicity

In all Phase 3 studies, the rates of hepatic adverse events and of treatment discontinuation because of a hepatic adverse event were 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 alanine aminotransferase (ALT) of 81 U/L (Normal Range (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 ALT and AST elevation and a repeat liver biopsy showed changes consistent with chronic hepatitis, probably autoimmune.

Analysis of liver function tests from the comparative Phase 3 CAP studies in patients who were normal at baseline showed a greater proportion of telithromycin-treated patients with low level elevations of AST and ALT (<5 x Upper Limit of Normal) relative to comparator. The AST and ALT elevations from patients in the CAP studies were present during the On-Therapy and Post-Therapy visits. This pattern was not seen in non-CAP patients.

There were a total of 90 reported telithromycin-associated hepatic adverse events in the post marketing database. These hepatic AE occurred in 43 different patients. All post-marketing reports of hepatic adverse events were evaluated. A majority of these cases had missing information making it difficult to assess causality and liver injury pattern. For those reports which did contain sufficient data, a cholestatic pattern of injury was most common. The pattern most resembled a hepatocanalicular injury which has been well described in patients exposed to erythromycins. There were reports of cytolytic injury, however, these were less common. There was only one reported death due to a hepatic adverse reaction, but this case was confounded by the presence of acute hepatitis A, possible Q fever, and high dose acetaminophen consumption. Although it is difficult to determine accurate incidence rates of adverse events based on post-marketing data, the number and severity of the telithromycin-related reports is similar to the erythromycins. Given the overall exposure of ——— prescriptions, it is reassuring that there was only one hepatic-related death which occurred in a highly confounded patient.

Based on review of the available data, telithromycin-associated hepatotoxicity appears to be similar in severity and pattern to drugs in the macrolide class.

Cardiac Toxicity

Telithromycin treatment was associated with a mean on-therapy increase of QTc (Bazett's formula) of 1.5 ms and a mean on-therapy increase of QTc (Fridericia's formula) of 3.8 ms. The proportion of outliers for absolute QTc values for telithromycin-treated patients was similar to that for patients pre-therapy. The number of patients pre-therapy with a QTc of $\geq$ 500 ms was 8/3098 (0.3%) vs. 4/2451 (0.2%) for patients on-therapy.

The incidence of serious and non-serious treatment emergent cardiac adverse events was low and similar between telithromycin-treated patients and comparator-treated patients.

There were a total of 101 cardiac adverse events in 86 different patients. The majority of these events were either symptoms, such as palpitations or tachycardia, occurring as part of a non-cardiac multi-symptom event; or cardiac events occurring in older patients with pre-existing cardiac disease. QT interval prolongation often results in cardiac events outside the setting of the type of medical monitoring necessary to identify them, and because these events may degenerate into non-distinct ventricular fibrillation, it is often difficult to identify drug-related QT toxicity in the post-marketing setting. Despite these limitations, review of the post-marketing data does not indicate any unusual cardiac safety signal for telithromycin.

Visual Toxicity

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 all controlled Phase 3 studies for telithromycin-treated patients was 1.1% vs. 0.28% for comparator-treated patients. Visual adverse events were more common in women than men (1.5% vs. 0.68%) in controlled studies and were more common in younger patients (mean age: 35.6 years, median age: 32 years). Women under age 40 years of age had a visual adverse event rate of 2.1%. Visual adverse events in telithromycin-treated patients most commonly began on treatment day 2, however the onset ranged from treatment day 1 to 13 and 35% of patients experienced onset of visual adverse events after day 2. The duration of visual adverse events in telithromycin-treated patients was most commonly 1-2 days with a range of 1-12 days. Of telithromycin-treated patients with visual adverse events, 13/30 (43.3%) experienced the event for > 3days. Approximately 39% of telithromycin-treated patients with visual adverse events in controlled clinical trials had a reported severity of moderate to severe.

In the post-marketing database, there were a total of 414 telithromycin-associated visual adverse events occurring in 316 patients. Adverse events likely to comprise the telithromycin-associated visual adverse event syndrome were the most common post-

marketing signal and comprised 33.7% (316/937) of all patients with a reported post-marketing adverse event. Review of these events indicates that telithromycin-associated visual impairment can result in significant disability/incapacity. The majority of these cases are temporary, lasting on the order of hours to a few days. Onset of visual adverse events in the post-marketing database was not predictable and occurred at any time during treatment, although most occurred after doses one, two, or three. In support of phase 3 data, the post-marketing data suggest that more events occurred in younger patients and females. There were a small number of poorly documented cases that suggest a possible longer term effect on vision. Additional data from carefully collected post-marketing reports would be needed to determine whether longer-term sequelae occur in some patients.

Myasthenia Gravis

Review of post-marketing data revealed a total of 13 patients with likely telithromycin-associated myasthenia exacerbation and 6 with possibly telithromcyin-associated myasthenia exacerbation. Six patients experienced life-threatening respiratory arrest and required intubation soon after exposure to telithromycin; one of these patients died. Other patients experienced muscle weakness, dysarthria, deglutition disorder, ptosis, dyspnea, dysphagia, and diplopia. In total, this experience represents a clear safety signal regarding the danger of telithromycin administration in patients with myasthenia gravis.

Summary

The most common adverse events related to telithromycin in Phase 3 studies were gastrointestinal (in controlled studies: diarrhea NOS 10.8%; and nausea 7.9%). There were no deaths reported by the sponsor as having been related to telithromycin treatment and the rates of possibly related serious adverse events was the same between telithromycin-treated patients and comparator-treated patients (0.3%). The types of possibly related serious adverse events that occurred in telithromycin-treated patients were similar to those of comparator-treated patients and were consistent with well described antibiotic-related adverse events such as pseudomembranous colitis.

From the available Phase 3 safety data, it can be concluded that telithromycin does cause an increase in the rate of visual adverse events, many of which are moderate to severe. This increase is highest in females and young patients (<40 years old). Post-marketing data indicates that telithromycin-associated visual adverse events have the potential to be temporarily incapacitating and are likely to result in inability to perform activities of daily living in some patients.

Based on the current available data, the cardiac adverse event profile and the degree of QT prolongation exhibited in telithromycin-treated patients appear to be similar to approved macrolides, such as clarithromycin.

Pre-clinical data suggests that telithromycin may be a significant hepatotoxin in humans. However, the available data from Phase 3 trials and post-marketing adverse event

reporting are consistent with other macrolide antibiotics, which are well known to cause hepatocanalicular toxicity. It is reassuring that in a post-marketing database of 3.7 million, there was only one death related to a hepatic adverse event; this hepatic event was confounded and telithromycin's role cannot be determined.

Post-marketing data suggest that telithromycin may cause severe life-threatening exacerbations of myasthenia gravis with at least one case of death resulting from such an exacerbation. Thus, such patients should be warned about this risk.

Medical Officer Safety Review of NDA 21144, Third Submission

Introduction

Information from pre-clinical, phase1, and phase 3 data raised several specific safety concerns with regard to telithromycin. A strong pre-clinical hepatic signal and a possible case of severe idiosyncratic hepatic reaction in the phase 3 database raised concerns about the potential hepatotoxicity of telithromycin. An attempt was made to address these concerns by the conduct of a large safety study, Study 3014. However, review of Study 3014 revealed serious data integrity problems which did not allow for a meaningful assessment of the hepatic safety concerns for which the study was designed. With no other way to evaluate the potential hepatotoxicity of telithromycin, an approvable letter was issued January 24, 2003 requesting the submission of post-marketing data (from outside the U.S) which would provide an opportunity to evaluate telithromycin's potential as a hepatotoxin.

Additional safety concerns which were not adequately addressed with the first two submissions were identified. In phase 3 data, an unusual and poorly understood visual adverse event syndrome was observed in association with telithromycin exposure. Because of the potential for a high degree of public exposure to this drug and because patients would likely be engaging in activities of daily living during treatment with telithromycin, the approvable letter of January 24, 2003 requested a detailed re-assessment of this visual toxicity in phase 3 data. The letter also requested an evaluation of the post-marketing data pertaining to visual adverse events. The intent of this request was to allow for a more thorough assessment and a better understanding of this particular telithromycin toxicity. A better understanding was required so that an accurate risk-benefit analysis could be performed and to allow for the inclusion in the label of useful information for clinicians.

Post-marketing data was also requested to allow for the analysis of cardiac adverse events. Telithromycin was identified in pre-clinical and phase 1 studies to prolong the QT interval in a dose dependant manner. In addition, telithromycin was found to be metabolized and inhibit the cytochrome P450 system. This combination of characteristics has resulted in increased rates of QT related adverse events in other drugs in the past. For this reason, a detailed assessment of the post-marketing data to look for evidence of QT related cardiac toxicity was determined to be necessary.

This document consists of the Medical Officer review of the safety information described above which was included in the October 17, 2003 NDA 21,144 submission. The majority of the review focuses on post-marketing safety. Additional review is included on the reanalysis of Phase 3 visual adverse events.

Post-Marketing Safety Data

Telithromycin is marketed in 36 countries around the world as of June 30, 2003: Argentina, Bahrain, Belgium, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, Egypt, El Salvador, Finland, France, Germany, Greece, Guatemala, Honduras, Ireland, Italy, Jamaica, Kuwait, Lebanon, Luxembourg, Malta, Mexico, Nicaragua, Norway, Paraguay, Peru, South Africa, Spain, Sweden, United Arab Emirates, United Kingdom, Venezuela, and Vietnam.

The total number of prescriptions sold of telithromycin in countries where it has been approved is approximately for the period of time from September 2001 through January 30, 2003.

Exposure data by country from post-marketing use of telithromycin is presented in **Table 1**.

Table 1. Post-marketing Exposure to Telithromycin, by Country

Country	Cumulative total
France	
Germany	
Italy	
Spain	
Mexico	
Brazil	
Other EU countries[a]	
Other LA countries[b]	
International Region[c]	
TOTAL GLOBAL EXPOSURE	

Source:

[a]Other EU countries include Belgium, Finland, and Greece.

[b]Other Latin American countries include Argentina, Chile, Colombia, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Peru, Paraguay, and Venezuela

[c]International region includes Lebanon and the French Overseas Territories (Martinique, Guadeloupe islands, French Guyana, Reunion island. Mayotte island, French Polynesia, and New Caledonia)

*Includes a correct for difference between sales to wholesalers and sales to pharmacies.

Table 2 shows the number of patients with post-marketing AE's reported by country as well as the rate of AE reports according to total prescriptions sold.

Table 2. Post-marketing AE's by Country to Telithromycin

Country*	Total Patients	Total AE's	Rate**
France	338	848	
Germany	284	798	
Brazil	111	271	
Italy	60	120	
Spain	40	93	
Belgium	26	41	†
Mexico	20	74	
Finland	14	22	†
Peru	12	18	†
Argentina	10	21	†
Total	937	2,345	

* Countries with 10 patients or more; ** AE's per prescriptions sold; † unable to provide rates for these countries because separate prescription data not provided by applicant

Medical Officer Comment: The reporting rate of adverse events per prescriptions varied between countries. Amongst countries with at least prescriptions sold, Germany had the highest rate while Italy had the lowest Because post-marketing data is collected in a passive manner, reported adverse event rates are usually lower than what is seen in clinical trials. Some of the potential factors affecting rates include the methodology of collecting passive post-marketing reports and national policies regarding the reporting of adverse event reports for newly marketed drugs. There also are potential cultural influences on the rate of reported post-marketing adverse events. Overall, the reporting rates of adverse events are similar.

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Spontaneously Reported Post-marketing Adverse Events

There were a total of 2,345 adverse events in 937 patients reported in the post-marketing period from September 2001 through June 30, 2003. Adverse events by MedDRA system organ class and by seriousness are presented in **Table 3**.

Table 3. Cumulative Reports of AE's From Post-marketing Spontaneous Reports, by SOC From September 2001 Through June 30, 2003

	Number of AEs reported as diagnosis or symptom (Number of patients*)		
MedDRA System Organ Class	All AEs	Serious AEs	Non-serious AEs
Eye disorders	415 (315)	101 (66)	314 (253)
Gastrointestinal disorders	402 (259)	125 (73)	277 (188)
Nervous system disorders	392 (272)	141 (94)	251 (183)
Skin and subcutaneous tissue disorders	255 (169)	100 (63)	155 (107)
General disorders and administration site conditions	158 (134)	60 (51)	98 (83)
Psychiatric disorders	119 (72)	41 (23)	78 (50)
Cardiac disorders	91 (72)	46 (33)	45 (39)
Investigations	91 (62)	48 (29)	43 (33)
Musculoskeletal and connective tissue disorders	81 (63)	27 (22)	54 (41)
Vascular disorders	66 (56)	32 (28)	34 (30)
Ear and labyrinth disorders	47 (42)	12 (9)	35 (33)
Hepatobiliary disorders	41 (26)	32 (18)	9 (8)
Infections and infestations	36 (35)	14 (13)	22 (22)
Renal and urinary disorders	25 (21)	17 (15)	8 (6)
Metabolism and nutrition disorders	20 (18)	14 (12)	6 (6)
Immune system disorders	19 (19)	11 (11)	8 (8)
Blood and lymphatic disorders	8 (8)	6 (6)	2 (2)
Injury, poisoning and procedural complications	7 (6)	4 (3)	3 (3)
Pregnancy, puerperium and perinatal conditions	4 (4)	3 (3)	1 (1)
Reproductive system and breast disorders	4 (4)	0 (0)	4 (4)
Social circumstances	1 (1)	1 (1)	0 (0)
Congenital, familial and genetic disorders	1 (1)	0 (0)	1 (1)
Social circumstances	1 (1)	1 (1)	0 (0)
Surgical and medical procedures	0 (0)	0 (0)	0 (0)
Neoplasms	0 (0)	0 (0)	0 (0)
Total number of AEs reported			2345
Total number of patients with at least 1 AE Reported			932

Source: APPENDIX H.3.2

Spontaneous Post-Marketing Reports of Death

There were spontaneous post-marketing reports of death in 14 patients who were reported to have a total of 35 adverse events reported. The following is a review of each reported death.

200211064EU
This is a report of a 69 year-old woman from [redacted] with a history of myasthenia gravis, diabetes mellitus, and respiratory insufficiency who died of "fatal cardiorespiratory failure" following exposure to telithromycin.

"Concomitant drugs included Mestinon (pyridostigmine bromide) for myasthenia, gliclazide for diabetes mellitus, famotidine for respiratory insufficiency and aerosol therapy with salbutamol and budesonide. On [redacted], the patient received telithromycin (2 tablets at 02:00pm) for respiratory infection. Two or three hours after telithromycin intake, the patient died of cardio-respiratory failure. The physician considered the death as probably related to a myasthenic crisis, and he considered the death as a coincidence with telithromycin administration."

Medical Officer Comment: This case was initially reported to an Aventis sales representative. It was reported to the sales representative by the physician that "the problem was due to an interaction between telithromycin and other drugs mainly metabolized by cytochrome P450." No explanation was given as to why the physician later reported telithromycin exposure and the ensuing death as a coincidence. It is the opinion of the reviewing medical officer that because of the temporal relationship between the adverse event and the drug exposure and the biologic plausibility of a drug related myasthenic exacerbation, that this adverse event should be viewed as being at least "possibly related" to the study drug exposure.

200211203DE
This is a report of an 80 year-old man from [redacted] with a history of diabetes mellitus, atrial fibrillation, global cardiac insufficiency, gammopathy with massive anasarca, hypertension, renal insufficiency, and adenoma of the prostate who died of "worsening of condition" and "acute cardiac pumping failure." This patient was treated for three days with telithromycin for a bronchial infection immediately prior to onset of the adverse event.
"Concomitant medication: homeopathic anti-tussive preparation, salt water nasal spray, bibrocathol, furosemide, enalapril/hydrochlorothiazide, human insulin and acetylsalicylic acid."
"The patient was hospitalised on [redacted] in a state of preexistent gammopathy with massive anasarka in preexistent heart failure with an acute marked cardiac decompensation. The patient was stabilised by diuretic, antibiotic and insulin therapy and discontinuation of bradycarding drugs. The cardiac pumping function was extensively impaired and the patient suffered from peripheral pulse deficit. The patient showed a clinical picture of global-cardiac decompensation with pronounced anasarca, pleural effusion, pulmonary congestion (radiologic picture of pulmonary edema). Pleural

effusion was relieved over two days of 2100ml fluid, forced diuretic therapy combined with respiratory exercises and inhalation resulted in a initial regression of dyspnea on the third day of hospitalisation. The patient improved considerably but his state was still critical. In the morning of [redacted] the patient developed an acute respiratory insufficiency with circulatory arrest, an immediate resuscitation was unsuccessful. The patient died in acute cardiocirculatory failure based on an (not confirmed) coronary heart disease with consecutive dysrhythmia and severely impaired cardiac pumping function in the course of the known multiple underlying diseases. Diagnoses: exitus letalis in acute cardiac pumping failure in the course of global cardiac insufficiency with cardiac decompensation; pronounced bradycardia with peripheral pulse deficit in the course of chronic atrial fibrillation and ventricular extrasystoles; arterial hypertension; diabetes mellitus with renal insufficiency."

Medical Officer Comment: This patient had significant confounding pre-existing medical conditions which could have been responsible for the fatal event. However, it is difficult to determine if telithromycin may have contributed to the adverse event because no specific description of ECG tracings is given. Presumably, such tracings were made since this patient's cardiac decline took place after four days while hospitalized. A QT interval is not mentioned and neither is the presence of absence of torsades.

200213089EU
"The physician reports on a patient whom he had treated with Ketek™ (telithromycin). The patient changed to another physician so that he has no further information except that the patient died. Treatment with Ketek™ from 17-DEC-2001 onwards for bronchopneumonia (end of treatment unknown) Concomitant medication (by colleague): roxithromycin, oxiropium, herbal expectorant. The physician does not know the name of the physician who cared for this patient in the further course."

Medical Officer Comment: There is not sufficient information in this MedWatch report to make any assessment of the report. No mention is made of any attempts to identify the unknown physician who cared for the patient.

200214003EU
This patient was a 42 year-old woman from [redacted] who died from fatal pulmonary thromboembolism and possible intestinal ischemia. No information is given about past medical history of concomitant medications.
"A 42 year-old female patient who received Ketek™ (telithromycin), 800 mg/d, PO, for 10 days (from November 15 to 25) for a respiratory infection, developed pulmonary thromboembolism, on [redacted] The reporting physician stated that the patient would also have experienced possible intestinal ischaemia. Fatal outcome (exact date of death not stated). The cause of death was given as being pulmonary embolism. It is unknown if an autopsy was performed. At the time of the event, patient was not taking any other concomitant drug. Exact chronology, surrounding conditions of the events, countermeasures taken, patient's medical history with possible risk factors were not specified at the time of this initial report. The reporting physician considered the events to be probably related to telithromycin."

Medical Officer Comment: Follow up did not provide additional useful information and further follow up is reported as pending. No conclusions can be reached about the potential relationship of this adverse event with telithromycin exposure. Prior history (i.e., recent trauma, surgery etc) or concomitant medications (such as oral contraceptives) or other predisposing factors such as activated protein C deficiency could significantly impact on the interpretation of this case. Unfortunately, such basic information is lacking making it difficult to draw conclusions.

200215044FR

This was a 75 year-old male patient with a past history of chronic bronchitis with chronic stable respiratory insufficiency who died of hepatic failure. The patient had no alcoholism or familial history of hepatitis. Concomitant medications included: paracetamol prn. His liver function tests (LFT's) were normal 6 months prior to event. On 11/27/02, the patient was treated with Ketek™ 800 mg q d x 5 d for AECB exacerbation. He was also treated with prednisolone, paracetamol 4 gr/day, and formoterol. On —, the patient experienced fatigue, jaundice and fever. Lab tests revealed ALT 2810, AST 1490, total bilirubin 133 (nl <10). Ultrasound (U/S) revealed "liver normal for size and for contour with homogenous echostructure. There was no dilatation of intra and extrahepatic biliary ducts..." During the night of admission, "the patient aggravated with coma, was transferred in ICU and intubated." On — lab tests revealed an ALT of 595 and AST of 255. The patient underwent exploratory laparotomy which did not confirm cholecystitis but did show hard and nodular liver. Post-operatively, the patient experienced hemorrhage and "multivisceral failure with anuria" and metabolic acidosis.
On — his total bilirubin increased to 282 (nl<10), and the patient died on —
No post-mortem was performed as family refused. Hepatitis B, C serology neg, Hep A IgM strongly positive. Patient also found to have positive acute serology for *C. burnetti*
Measurement of paracetamol two days after admission was low.

Medical Officer Comment: The potential role of telithromycin in this case is confounded by an acute hepatitis A infection and large doses of acetominophen. It is possible that the telithromycin did contribute to the hepatic toxicity. However, it is difficult to quantify what role, if any, it may have played.

200310149FR

This was a case of a male patient with ALS (age unspecified) who was treated with telithromycin for pneumonia and who died of respiratory failure. Concomitant medications included: riluzole, cefotaxime, and ofloxacin.
"Forty-eight hours after the start of treatment with telithromycin and 30 minutes after the intake, the patient experienced Quincke's oedema with tongue and lip oedema and aggravation of respiratory disorder. On the same day, treatment with telithromycin was discontinued. No corrective treatment was administered and the patient spontaneously recovered. No information on previous treatment with telithromycin and macrolides was provided. Three days after, the patient was hospitalized for aggravation of pneumonia and was treated with cefotaxime and ofloxacin. Three weeks after the hospitalization, the

patient died. Death was related to acute respiratory insufficiency due to ASL. There was no infectious shock. The physician did not suspect telithromycin, cefotaxime or ofloxacin for fatal acute respiratory insufficiency."

Medical Officer Comment: It appears that the initial event associated temporally with telithromycin exposure was probably related to an allergic reaction. However, because the event did include respiratory symptoms, other causes such as myasthenia gravis, could be considered. It is possible that this patient had or developed underlying myasthenia gravis which was not recognized. Myasthenia gravis has been observed in patients with ALS and is listed as a possible adverse event in the product label for riluzole, which the patient was taking during the time of the fatal respiratory decompensation.[1] It does not appear that myasthenia gravis was considered as a possible contributing cause to the patient's respiratory failure. Further assessment of this possibility is not possible because of the limited data. This patient is not included in the section of the review covering myasthenic exacerbation following telithromycin exposure.

200310215DE

This was a case of a 76 year-old male with a past history of pneumonia, stress ulcer, tachyarrhythmia, metastatic renal carcinoma (lung, skeleton), global cardiac insufficiency grade 4, anemia caused by tumor, pain, bronchial obstruction, obesity, high serum lipids, hypertension who died of sudden cardiac death. Concomitant medications included: hydromorphone hydrochloride, theophylline, clenbuterol hydrochloride/ ambroxol hydrochloride, pantoprazole sodium, dimenhydrinate, mistletoe, darbepoetin and metoclopramide.

This patient had advanced renal carcinoma with metastases in lungs and skeleton. Other than hypertension, he had no history of cardiac disorder including no history of syncope, no known coronary artery disease and available ECGs (several years old) reportedly showed no QT changes. In November 2002, the patient developed bronchopneumonia and received first a cephalosporin (unsuccessfully) and then Ketek. Prior to receiving Ketek and during this course of bronchopneumonia, he developed tachyarrhythmia (150 bpm) with cardiac decompensation. Ketek was started on 28-Nov-2002 for 8 days but was discontinued because of worsening emesis. The tachyarrhythmia subsided on — — however, cardiac insufficiency (global insufficiency Grade 4 with oedema and dyspnea, requiring at least 80 mg furosemide) persisted until death. On — the patient was prescribed Ketek for pneumonia with fever of 39.8 degrees Celsius and purulent sputum. The patient received 800 mg Ketek at about 4-5 p.m. and died at 6:45 p.m. The reporting physician considered possible causes of death to include cardiac dysrhythmia or pulmonary embolism but he stated that other causes could also be possible. The death certificate lists the cause of death as "sudden cardiac death." The patient was buried without autopsy. Further information is therefore not available. The physician considered arrhythmia as the cause of death and ticked both "possible" as well

[1] Restivo DA et al. ALS and myasthenia: an unusual association in a patient treated with riluzole. Muscle Nerve. 2000 Feb;23(2):294-5.

as "insufficient data" concerning causal relationship between this event and treatment with Ketek.

Medical Officer Comment: The temporal relationship between Ketek administration and the fatal event suggest a possible contributing role of Ketek. However, this patient had severe cardiac disease and was certainly at risk for such an event. Such confounding factors do not eliminate the possibility that Ketek-related toxicity was at least in part responsible for the fatal event, but defining the role that Ketek may have played is not possible based on the given information. A telemetry rhythm strip was not provided and no mention of the fatal cardiac rhythm was made in the MedWatch report.

200310925FR
This case was of a 46 year-old female with a past medical history of alcoholism and vein surgery NOS who died of pneumococcal sepsis. Concomitant medications were not reported.
The patient was started on treatment with telithromycin on 12-JAN-03 for bronchitis. She remained on this until — when, while reportedly in satisfactory condition, she experienced "cardio respiratory arrest with cyanosis." The patient was resuscitated and reported to have a sinus tachycardia at 150/min. On transfer/admission to the hospital, the patient was found to have sinus tachycardia with hypokalemia (k= 2.9 mmol/l) and a mixed acidosis. The chest x-ray showed diffuse bilateral alveolar interstitial opacities. Echocardiography showed deterioration of left ventricular function and dilated right cavities. No information on ECG was provided and no comment was made on the QT interval. On — treatment with telithromycin was discontinued. The following day, the patient developed fulminant septic shock due to *Streptococcus pneumoniae* (positive blood cultures) and died on — No autopsy was reported as being performed.

Medical Officer Comment: This patient's arrest with sinus tachycardia may have been the result of hypotension secondary to pneumococcal bactaremia/sepsis. It is also possible that the combination of hypokalemia and telithromycin resulted in a malignant cardiac rhythm, although the only rhythm reported was sinus tachycardia. It is concerning from an efficacy standpoint that this patient would develop such a severe infectious complication of *S. pneumoniae* on day — of treatment with telithromycin. No antibiotic susceptibilities were reported in the MedWatch report, so it is not known whether the infecting organism was resistant to telithromycin.

200311271FR
This case is of a 79 year-old female with a past history of respiratory and cardiac insufficiency, Alzheimers, and hypertension who was being treated with telithromycin for bronchitis and who died of a "fatal sudden syncope." Concomitant medications included: ramipril, furosemide, carbolevure, spironolactone, omeprazole, donepezil hydrochloride, bambuterol hydrochloride, and smectite. Acetylsalicylate lysine, diflucortalone, activated charcoal, dried yeast, and fenoterol hydrobromide, and ipratropium bromide were started on admission on the same day the patient died (— . It is not clear how much, if any, of these medications the patient actually received.

On — at 9:15 PM, the patient experienced sudden syncope with loss of consciousness, and urinary/fecal incontinence while she was sitting in her armchair. The patient did not develop dyspnea at this time. "At 9:30 PM, the physician found the patient in apparent death status with extreme bradycardia at 27 bpm, cardiovascular collapse, no pulse and no BP. Cardioscope showed bradycardia at 20 QRS/min. On the arrival of mobile emergency medical unit, the patient was intubated and adrenaline was administered. ECG was recorded. No prolonged QT was reported and the record was reportedly similar to the record observed on cardioscope. Despite resuscitation, the patient died on —— The physician will send the Company copy of this ECG and of a previous ECG recorded in last December. The physician did not suspect telithromycin."

Medical Officer Comment: The absence of a prolonged QT was not specifically reported and no ECG or specific interval measurements were available for review. This case is confounded by the presence of underlying cardiac disease and other comorbidities. It is possible that telithromycin played a contributing role in this fatal adverse event. However, the limited data provided make it difficult to assess telithromycin's potential role.

200311561DE
This case was of a 73 year old male with a past history of arterial hypertension, insulin dependent diabetes mellitus, chronic obstructive respiratory disease, pulmonary fibrosis, nicotine abuse, peripheral arterial occlusive disease, and hyperuricemia who died of a "perforated ventricular ulcer, liver cirrhosis, decompensated heart failure."

The patient was treated with Ketek 400mg/day from 25 until 27-APR-2004 for exacerbated chronic obstructive pulmonary disease. On — , the patient was hospitalized for dyspnea that had been progressing for 3 months. On admission the patient complained of severe pain in right upper abdomen and physical examination revealed a heart rate of 130/min, cyanosis, sweating, dyspnea, pain in right upper abdomen, and extremities were reported as "cool." Admission labs showed some mild LFT abnormalities and an x-ray of the abdomen (— revealed free intra-abdominal air below the right diaphragm, air-fluid levels, and signs of ileus and intestinal perforation. Abdominal sonography was performed and revealed: congested hepatic veins, possible intra-hepatic cholestasis, full gallbladder without signs of concretions, and enlarged left ventricle with high-grade restriction of pump function. A diagnosis of acute abdomen was made and the patient was referred to the surgery service on — where he immediately underwent laparotomy. A perforated gastric ulcer was found, a local excision was done, and the defect was closed uneventfully. The surgeon reported as a secondary finding the presence of coarse-nodular liver cirrhosis with markedly enlarged liver and spleen. Post-operatively, the patient's condition did not improve and cardiac function worsened. The patient died on — with the final diagnoses of a perforated ventricular ulcer, liver cirrhosis, and decompensated heart failure. No mention of telithromycin was made in the medical records and, apparently, no autopsy was performed.

Medical Officer Comment: Although it is not possible to completely rule out a contributing role of telithromycin in this case, it is unlikely that telithromycin was the cause of this patient's poor outcome.

200311717FR

This case is of an 82 year-old male with a past medical history of COPD, atrial fibrillation, moderate renal insufficiency, bilateral hip prostheses, and metastatic prostate adenocarcinoma whose cause of death was reported as unknown.
Concomitant medications included: pravastatin, furosemide, fluindione, terbutaline, ipratropium, bicalutamide, bambuterol, augmentin, ofloxacin, methylprednisolone, and acetylcysteine.
The patient had been hospitalized on [redacted] for bronchial superinfection, cardiac decompensation and diffuse pain reportedly due to metastasis of prostate cancer. On [redacted] treatment with bicalutamide PO 1U/d for prostate adenocarcinoma and bambuterol hydrochloride 20 mg/d was started. On [redacted], the patient developed fever and dyspnea, and blood culture found *Streptococcus*, although chest X-ray did not show pneumonia. Treatment with telithromycin PO, 800 mg/d, was started on 12-MAR-03 for chronic bronchitis superinfection.. On [redacted] the patient experienced chest pain. Lab tests revealed an elevated myoglobin (peaked at 1286 with normal range of 16 –76) and CPK (peaked at 396 with a normal range of less than 210). CKMB was normal and tropinin was only very slightly elevated at 0.7. Ventilation-perfusion pulmonary scintigraphy ruled out pulmonary embolism and bone scintigraphy revealed several vertebral metastases. On [redacted] treatments with telithromycin and with pravastatin were discontinued and treatment with amoxicillin clavulanate PO 3 g/d and ofloxacin PO was started. On [redacted], the patient developed vomiting reportedly due to amoxicillin clavulanate and on [redacted] both treatments were changed to the IV route. The patient improved "under antibiotherapy." On [redacted] methylprednisolone was started. Lab tests revealed normalizing serum myoglobin and CPK and according to the cardiologist, the patient recovered from rhabdomyolysis. On [redacted] the patient died during sleep. The physician considered the possible causes of death to include cerebral hemorrhage or cardiac rhythm disorder but there was no established cause and there was no autopsy. The physician did not suspect ofloxacin or telithromycin as potential causes of death. The physician did consider telithromycin as a possible cause for the moderate rhabdomyolysis.

Medical Officer Comment: There is no information to make a determination as to the cause of this patient's death and therefore, it is not possible to determine if telithromycin may have played a role. Since the patient had metastatic cancer and only received 1 or 2 days of therapy with telithromycin, and since the death occurred 3 days after stopping the telithromycin, it seems unlikely that telithromycin played a role in this patient's death.

200311846FR

This case is of a 90 year old male with a past history of gonarthrosis and left ankle fracture who developed new onset myasthenia gravis after exposure to telithromycin. He eventually died of a mesenteric infarction. Concomitant medications included: acetycysteine and rofecoxib.

The patient was treated with telithromycin for bronchitis from 23-OCT-02 to 25-OCT-02. However, he took twice the recommended dose (1600 mg/d instead of 800 mg/d). Two to three weeks after the telithromycin exposure, the patient experienced dysarthria, deglutition disorder, diplopia and ptosis. The patient was hospitalized from [redacted] in the ENT department for exploration of a deglutition disorder. Hypopharyngoscpy was normal and laryngoscopy found 2 nodules on vocal cords for which a biopsy was done. The patient had difficulty in moving his tongue and experienced cough with drinking fluids. On [redacted], after the patient developed dyspnea, antiacetylcholine receptor antibodies were measured and found to be elevated at 5.8 nmol/l (normal is less than 0.2 nmol/l). A neostigmine test was performed and found to be positive. The patient was treated with pyridostigmine bromide which resulted in improvement of patient's condition. On [redacted], the patient experienced worsening of anarthria including marked dysphagia and orthopnea during the night. He was hospitalized on the neurology service and found to have ptosis of the left eye on exam. On [redacted] EMG revealed block of conduction at the neuromuscular junction. Pyridostigmine bromide was replaced with ambenonium chloride PO 4U/d and on [redacted], treatment with veinoglobulins 30 g/d was started for 3 days. On [redacted] the patient experienced clinical signs of anticholinesterase drug overdose including hypersalivation, myosis, diarrhea, and hypertension that led to decrease daily dose. That day, after experiencing respiratory arrest (no cardiac arrest), the patient was intubated and transferred in ICU. According to the hospital reports, it was the conclusion of the neurologist the patient had experienced a myasthenic crisis. The patient recovered and was extubated on [redacted] Further evaluation included a chest CT scan which revealed a thymoma with superior vena cava syndrome due to mediastinal extension that led to administration of corticosteroids at high daily dose. On [redacted], the patient died form mesenteric infarction. No details of that event were included in the MedWatch form.

Medical Officer Comment: This report is interesting because the patient developed symptoms of myasthenia gravis a few weeks after exposure to the drug. There are drugs such as penicillamine and ciprofloxacin which have been associated with induction of myasthenia gravis. The mechanism is thought to involve binding of the drug to the acetylcholine receptor (AChR). After binding, the drug may become directly antigenic leading to the production of anti-receptor antibodies in response to this drug-receptor complex. Although this case represents only a single report, it does raise the possibility that telithromycin may not only be capable of causing an exacerbation of myasthenia gravis, but it may also possibly induce the disease of myasthenia gravis. The patient's death due to mesenteric infarction does not appear to be related to telithromycin exposure because of the lack of temporal relationship.

200311947FR
The patient was an 82 year old male with a past history of atrial fibrillation, stable angina, hypertension, and idiopathic pulmonary fibrosis who experienced sudden death some time (2-12 hours) after his second dose of telithromycin.

Concomitant medications included captopril, buflomedil, nicardipine, methyl-prednisolone (started [redacted] the day of death), and prednisone (started [redacted] one day before death).
The patient was started on therapy with telithromycin and steroids on 4/30/03 for treatment of chronic bronchitis. The following day ([redacted] at 10:30PM) the patient lost consciousness. A mobile emergency medical unit arrived and found the patient to be in cardiac arrest. The unit suspected the cause of death to be either acute arrhythmia or a massive pulmonary embolism. No autopsy was performed.

Medical Officer Comment: It is not clear how many doses of telithromycin this patient took. Also, there is no information available to assess the actual cause of death. Given the patient's age and underlying health conditions, it is not unreasonable to assume this patient's death is not related to the telithromycin. However, this assumption cannot be confirmed. It is also possible that his underlying heart disease could have predisposed him to telithromycin-associated arrhythmias (i.e., torsades).

200214256DE
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 methionine, 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 ventricle 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.

Medical Officer Comment: There is a 27 minute gap between two of the rhythm strips, 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. The patient did have underlying cardiac disease which is a confounder.

Spontaneous Post-Marketing Reports of Serious Adverse Events

A total of 894 serious adverse events (SAEs) were reported in 292 patients. There were 167 patients with 464 SAEs for whom "medically important" was the serious criterion cited. This was the most common criterion cited. The next most common was "requiring/prolonging hospitalization" in which 115 patients had 390 SAEs events (**Table 4**). Fourteen patients had 35 serious events that resulted in death (described in detail above).

Table 4. Post-marketing Spontaneous SAE Reports by Serious Event Criterion

SAE criterion	No. of patients [a]	No. of events (Diagnoses + Symptoms)
All SAEs	292	894[b]
Death	14[c]	35
Life-threatening	20	62
Required/prolonged hospitalization	115	390
Permanently or significantly disabling	22	53
Medically important	167	464

a Numbers in each column are not additive because a patient may have more than 1 SAE, and an SAE may have satisfied more than 1 serious event criterion

[b] There were 878 SAEs in the cumulative data through June 30, 2003, which was run on July 3, 2003. An additional 16 SAEs were received and/or updated between July 3, 2003, and July 19, 2003, which was the creation date for SAS transport file from which Table PV/cae_01t.lst was generated.

C Includes case 200311947FR that did not initially meet case selection parameters for the June monthly and cumulative tables and listings.

SAE's by System Organ Class (SOC)

Table 5. Cumulative reports of AE's from Post-marketing Spontaneous Reports, by SOC from September 2001 Through June 30, 2003

MedDRA system organ class	Number of AEs (Number of patients*) reported as diagnosis or symptom		
	Serious AEs	Nonserious AEs	Total (serious + nonserious)
Nervous system disorders	141 (94)	251 (183)	392 (272)
Gastrointestinal disorders	125 (73)	277 (188)	402 (259)
Eye disorders	101 (66)	314 (253)	415 (315)
Skin and subcutaneous tissue disorders	100 (63)	155 (107)	255 (169)
Gen disorders and administration site conditions	60 (51)	98 (83)	158 (134)
Investigations	48 (29)	43 (33)	91 (62)
Cardiac disorders	46 (33)	45 (39)	91 (72)
Respiratory thoracic and mediastinal disorders	43 (33)	19 (17)	62 (50)
Psychiatric disorders	41 (23)	78 (50)	119 (72)
Vascular disorders	32 (28)	34 (30)	66 (56)
Hepatobiliary disorders	32 (18)	9 (8)	41 (26)
Musculoskeletal and connective tissue disorders	27 (22)	54 (41)	81 (63)
Renal and urinary disorders	17 (15)	8 (6)	25 (21)
Infections and infestations	14 (13)	22 (22)	36 (35)
Metabolism and nutrition disorders	14 (12)	6 (6)	20 (18)
Ear and labyrinth disorders	12 (9)	35 (33)	47 (42)
Immune system disorders	11 (11)	8 (8)	19 (19)
Injury, poisoning and procedural complications	4 (3)	3 (3)	7 (6)
Blood and lymphatic disorders	6 (6)	2 (2)	8 (8)
Pregnancy, puerperium and perinatal conditions	3 (3)	1 (1)	4 (4)
Social circumstances	1 (1)	0 (0)	1 (1)
Reproductive system and breast disorders	0 (0)	4 (4)	4 (4)
Congenital, familial and genetic disorders	0 (0)	1 (1)	1 (1)
Neoplasms	0 (0)	0 (0)	0 (0)
Surgical and medical procedures	0 (0)	0 (0)	0 (0)
Total number of AEs reported			2345
Total no. of patients with at least 1 AE Reported			932

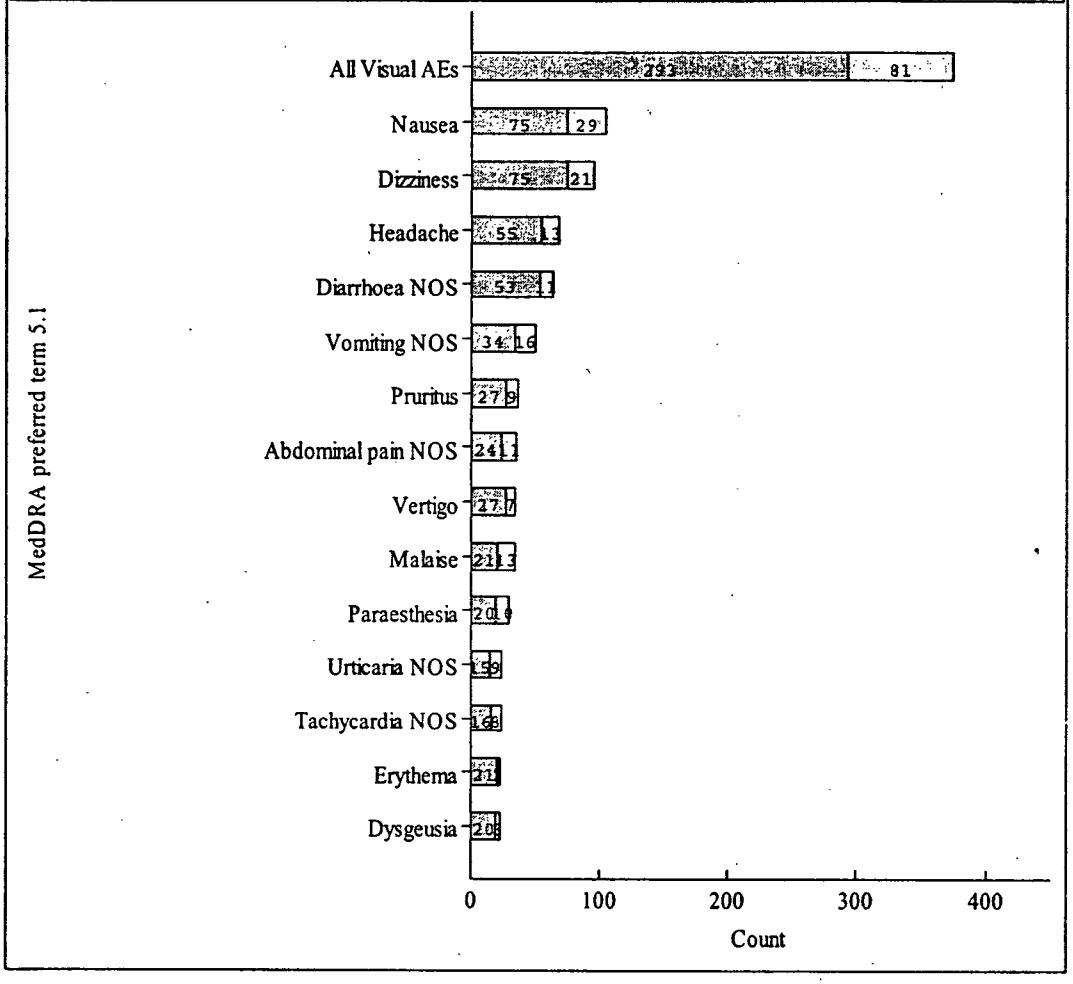
Source: APPENDIX H.3.2

A patient could have more than 1 event, so columns are not additive for number of patients.

* Number of patients with at least 1 AE reported for the SOC.

MO Comment: In the analysis contained in **Table 5** by System Organ Class submitted by the sponsor, eye disorders is third in frequency in terms of SAE's. However, if a separate analysis is done by MedDRA preferred term, in which all visual adverse events that are likely to belong to the same adverse event syndrome are pooled, a different picture emerges. Graph 1 shows this finding. The AE's in **Graph 1** are broken down by serious vs. non-serious. Patients may have had more than one adverse event.

Graph 1. Frequency of Post-marketing Preferred Terms with Visual Events



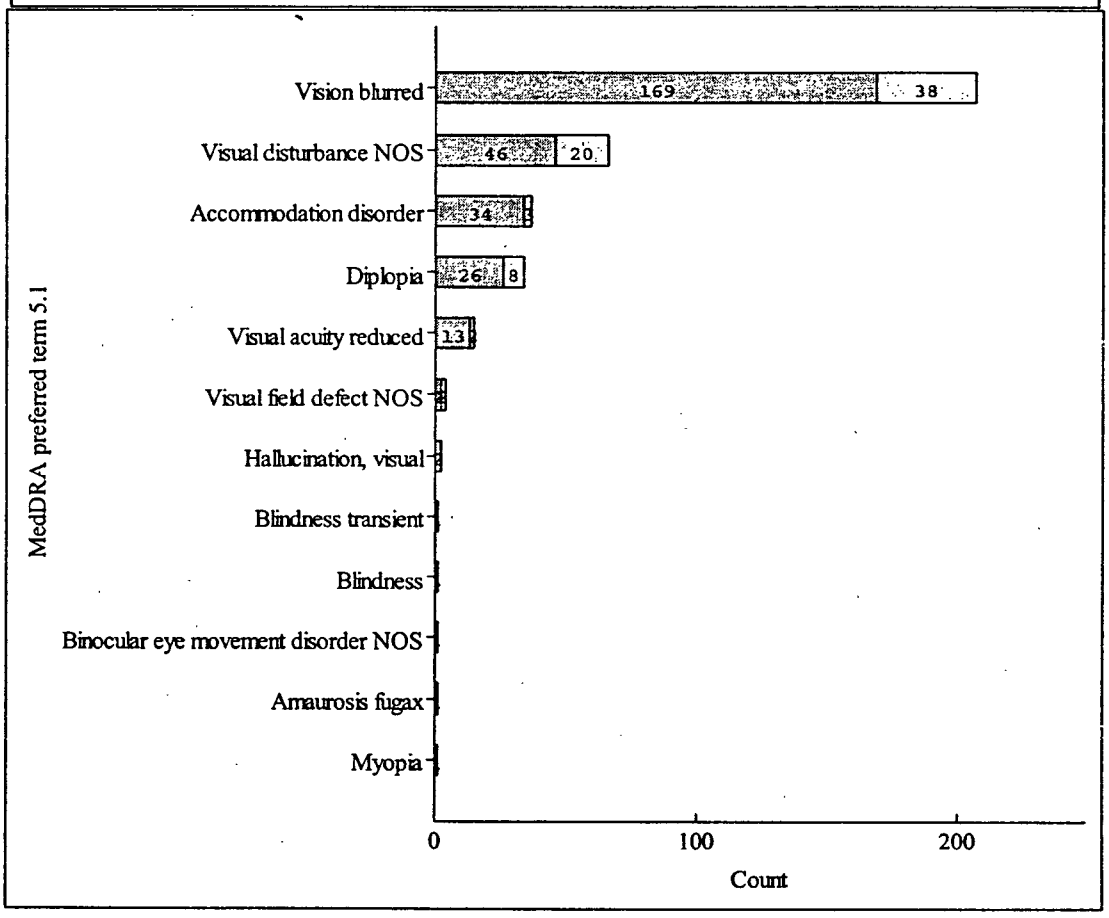
Visual Post-marketing Adverse Events

MO Comment: It is reasonable to combine visual adverse events because, most often, different preferred terms are used to report visual adverse events which are a part of the same adverse event syndrome. It is very common for different patients to report similar visual symptoms in different ways. In addition, the visual adverse event syndrome associated with telithromycin exposure may have a variety of manifestations. Therefore, it is a more accurate representation of the post-marketing visual adverse events to combine different visual AE preferred terms into a single grouping when comparing to other adverse events. The graph below does not include multiple reports of the same MedDRA preferred term for single patients. It does, however, include different MedDRA

preferred terms for single patients. Of all the patients with visual AE's, there were a total of 414 adverse events in 316 patients. This represents 17.7% of all reported AE's and 33.7% of all patients with a post-marketing adverse event.

Graph 2 depicts a breakdown of the preferred terms of all adverse events contained in the All Visual AEs category of Graph 1.

Graph 2. Individual Preferred Terms in All Visual Adverse Events Category

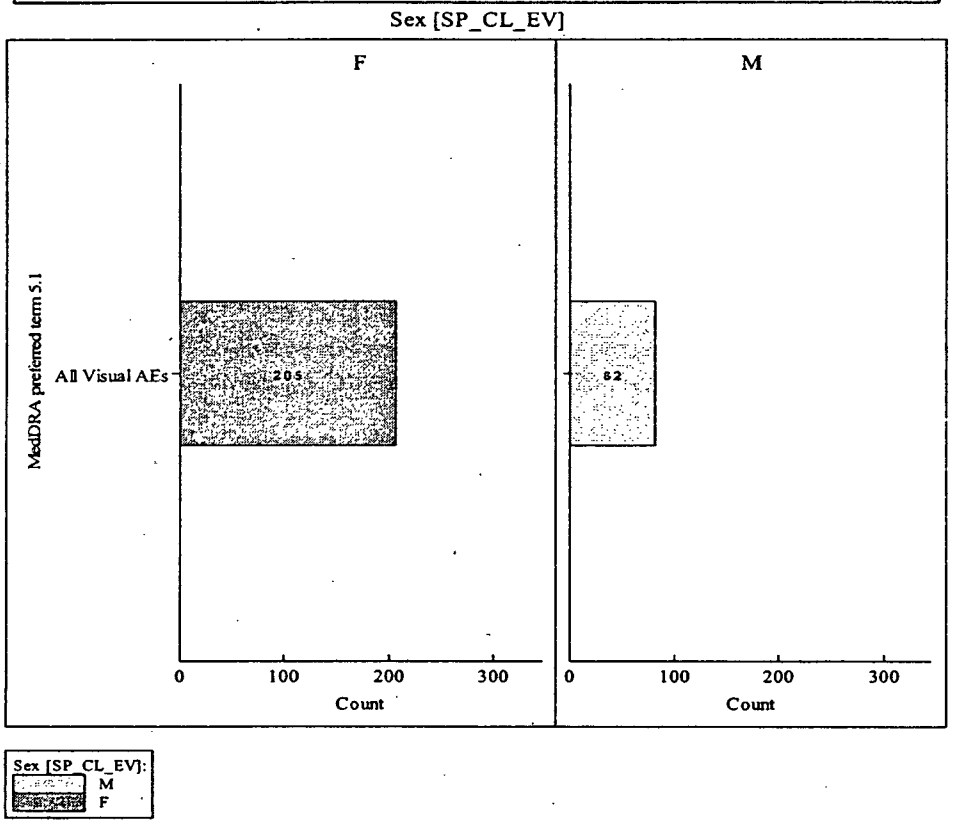


Medical Officer Comment: The twelve adverse event preferred terms contained in **Graph 2** are consistent with the visual adverse event syndrome thought to be caused by telithromycin exposure. The five most common preferred terms, vision blurred, visual disturbance NOS, accommodation disorder, diplopia, and visual acuity reduced account for 359 of 374 (or 96%) visual adverse event reports.

Graphs 3 and **4** below show visual adverse events by sex and by sex/serious criteria.

Medical Officer Comment: As can be seen in **Graph 3**, post-marketing reports of visual adverse events were more common in females than males. Females accounted for 72% of reports with males only accounting for 28% of reports (ratio of 2.5:1). This is almost exactly the same as what was seen in Phase 3 studies (23 females vs. 9 males; 72% in females, 28% in males). There were no reports for which the variable for gender was missing or unknown.

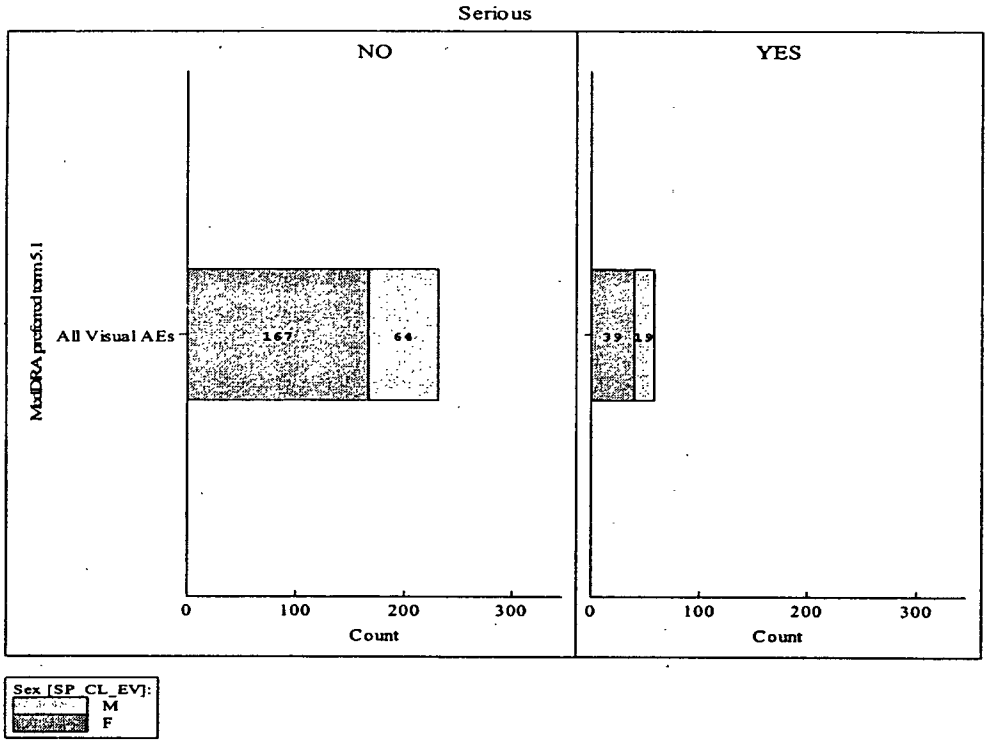
Graph 3. Visual Adverse Events by Gender



The medical officer's review of all serious visual adverse events revealed that, with a small number of notable, specific exceptions, the vast majority of visual adverse events were consistent with the visual adverse event syndrome associated with telithromycin exposure. Of note, there were three cases of diplopia that were most likely related to myasthenia gravis (200311337FR, 200311248FR, 200311846FR). In addition, there were two cases of visual hallucinations which were likely the result of high fever (200310513DE), in one case, and acute psychosis in the other (200210572DE).

Medical Officer Comment:
There are no specific universal criteria for determining which cases should be considered to be "serious" rather than not serious. In the setting of visual adverse events, the severity of visual alteration may not necessarily correspond with whether the adverse event is serious or not. For instance, even a mild visual adverse event might be considered to be serious if it occurs unexpectedly in a patient who is driving a car, piloting an airplane, conducting a surgical procedure, or driving a school bus. At the same time, a visual adverse event of much greater intensity may not be considered serious in a person who is confined to a bed in a nursing home or in a person who is undergoing chemotherapy and is confined to a hospital bed.

Graph 4. Visual Adverse events by Gender and Seriousness



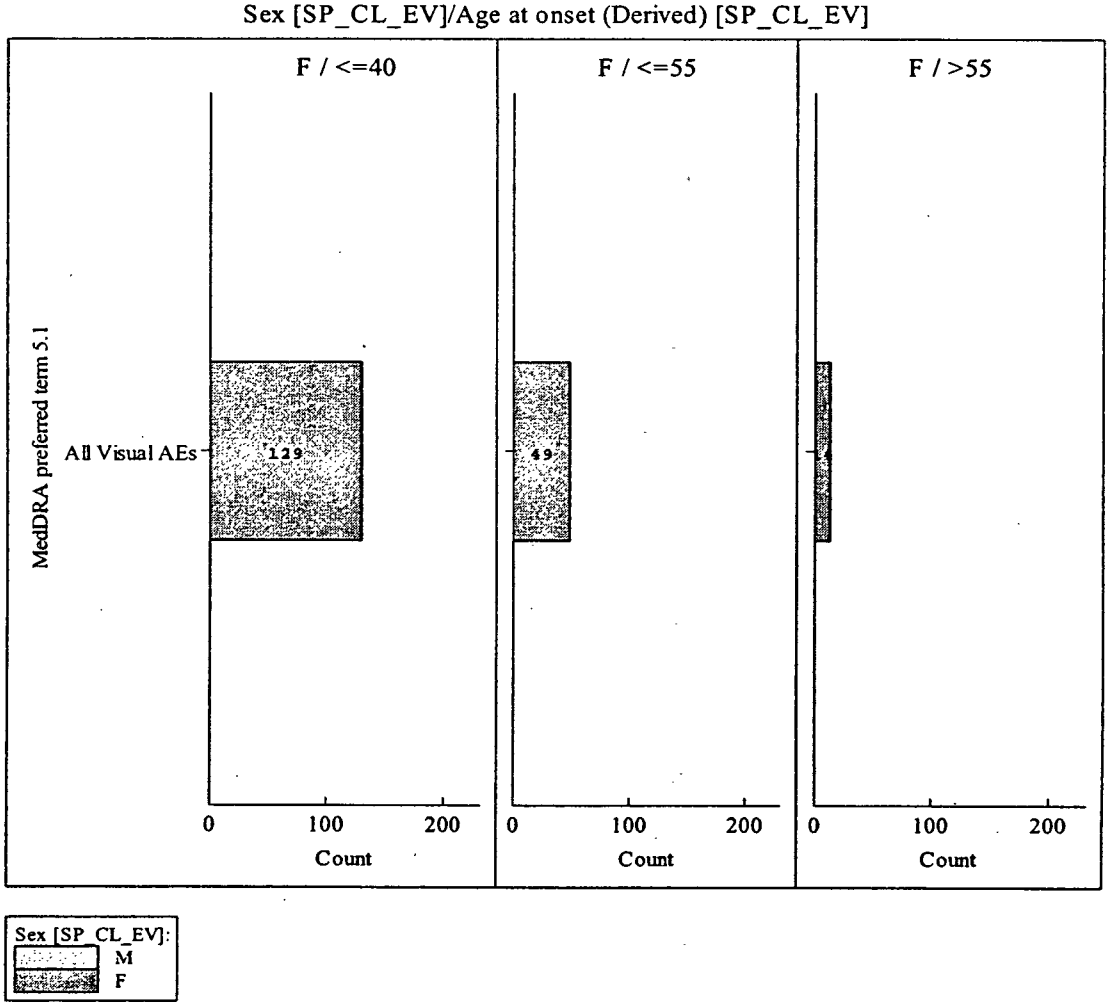
Medical Officer Comment: Graph 4 depicts serious visual adverse events by gender. The rates of serious visual adverse events were similar in males and females. Amongst all visual adverse events, the rate of serious visual adverse events for females was 19% while the rate for serious visual adverse events for males was 23%.

A review of MedWatch forms was conducted for those patients who had a serious visual adverse event. A large number of the descriptions of the visual events are consistent with the regulatory definition of serious, since they either resulted in incapacity or the potential for incapacity.

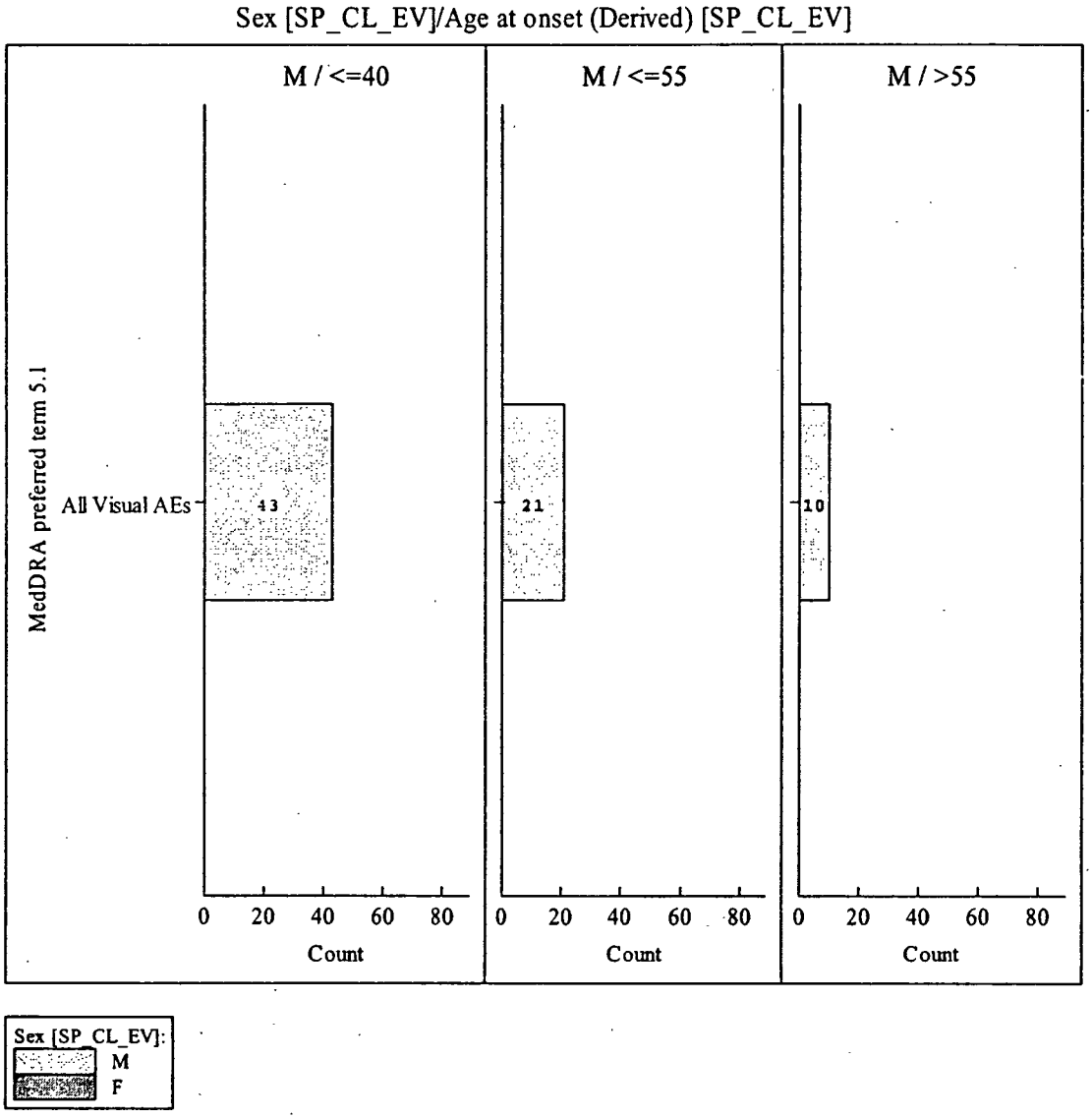
Analyses were also done in which the rates of serious visual adverse events were determined by age alone and by age and gender. These analyses revealed that the rates of serious visual adverse events by gender were not affected by the age of the patient.

Graphs 5 and **6** show the number of post-marketing reports of visual adverse event by age category and gender. There is a similar pattern between males and females of more reports from younger patients.

Graph 5. Visual Adverse Events by Age and Female Gender



Graph 6. Visual Adverse Events by Age and Male Gender



Visual Adverse Events by Outcome

Graph 7 shows visual adverse events by outcome. Of a total of 374 visual adverse events, 306 resolved. The outcome for 32 events is unknown, and for 33 events, the outcome was reported as ongoing. For 3 events occurring in 2 patients, the outcome was reported as having "sequelae."

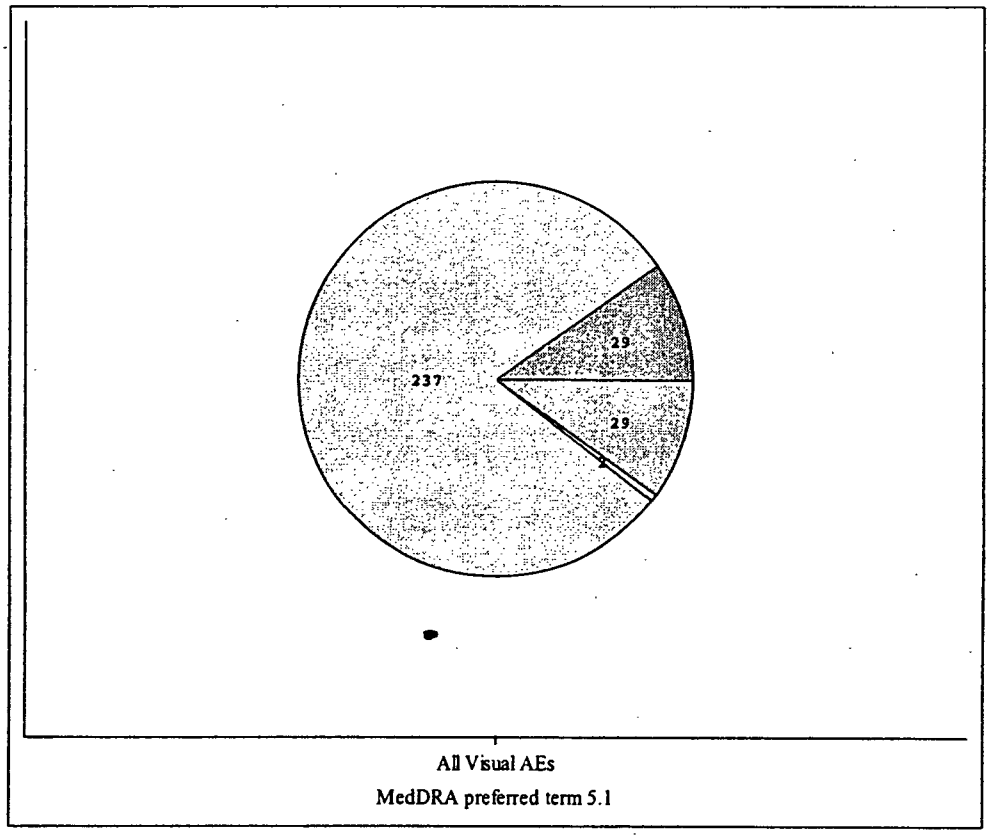
One of the patients (200311337FR) experienced diplopia as a result of myasthenia gravis.

One patient (200312220GDDC) was a 77 year-old male who experienced headache, diplopia, and blurred vision 2 hours after ingestion of 800 mg of telithromycin. The symptoms resolved mostly within 24 hours, but the ophthalmologist noted an alteration in the results of the refraction test. Results of the refraction test done before and after telithromycin exposure are found below:

Lab evaluations performed on —
Visual acuity: distance and near (right eye: 20/40/left eye: 20/20)
Fundoscopic exam (right eye: rare vitreous rods; normal optic nerve and macula/left eye: normal optic nerve and macula) Slit lamp exam (rare vitreous rods in the right eye)
Refraction test: 13/02/03 - Distance vision: right eye:+3.50/-2.25 130, left eye: +3.75/-3.25 50 ; 22/03/03 – Distance Vision: right eye: +4.75/-3.50 125 ; left eye: +3.75/-3.25 50

For 33 events in 29 patients, the outcome was reported as "ongoing." Review of these adverse events was conducted and summary information is provided for specific cases of interest.

Graph 7. Visual Adverse Events by Outcome



Cases of Interest/Symptoms ongoing

200212600GDDC
This report was submitted by a physician and is of a 54 year-old male who was treated with 5 days of telithromycin for acute sinusitis. No concomitant medications or medical history was provided. One day after beginning therapy (— , the patient developed blurred vision and diplopia. The patient continued therapy, however, after completion of telithromycin treatment, the visual symptoms did not resolve. The patient was seen by an ophthalmologist who did not find any abnormalities. The report states that the patient then planned on seeing a neurologist. No further information was provided. It is not clear from the report how long after cessation of therapy that the symptoms persisted. This adverse event was reported to the manufacturer on Feb 27, 2003. No follow up report is included and there is no indication that further information was sought.

200214844DE
This report was submitted by the patient who was a 29 year-old female with a history of tonsillitis, tooth infection, thrombosis, and borderline protein C deficiency. Concomitant medications included two days of phenoxymethylpenicillin potassium and phenprocoumon. She was treated with four days of telithromycin for tonsillitis and during the treatment course, she complained of a few hours of visual disturbance and paresthesias of the face after each intake of telithromycin. After the final dose of telithromycin, the symptoms resolved, however, these symptoms recurred approximately 3-4 weeks after completion of telithromycin therapy. The patient saw a neurologist. A CT scan and EEG were normal and the neurologist suspected that telithromycin was the cause of the symptoms. The patient assumes that the complaints were the result of an inflamed tooth.

200310596FR
This report was submitted by a physician and is of a 39 year old male who was treated for sinusitis with telithromycin. No concomitant medications, other than prednisolone, or past medical history were provided. An hour after the second intake of telithromycin on — , the patient complained of blurred vision of both far and near vision. No information was provided as to whether the telithromycin therapy was continued or discontinued. This adverse event was reported to the manufacturer on Feb 19, 2003 and had not yet recovered as of the time of the report.

200310075FR
This report, submitted by the French Health Authority, is of a 40 year-old female with a history of hypermetropia. The patient was treated with telithromycin for unknown reasons. She was also started on several other medications including: carbocisteine, paracetamol and Oropivalone, chlormethine hydrochloride, trientine, bacitracin zinc, pentosan polysulfate, and tixocortol pivalate. The day after starting telithromycin, the patient experienced worsening of hypermetropia, nausea, headache, and accommodation disorder. The telithromycin was not discontinued and the patient was treated for a total of 6 days. As of the time of the report (four weeks after cessation of telithromycin) the

patient had not yet recovered. The report does not indicate if all symptoms persisted but does state that "new ocular correction has been necessary."

200213915FR
This report was submitted by a physician and is of a 35 year-old male who lives in Guyana and has no relevant past medical history. The patient was started on therapy with telithromycin for treatment of sinusitis/otitis while visiting ___ The patient experienced blurred vision a few hours after first intake of telithromycin. The symptoms increased on days 2 and 3 of therapy and telithromycin was discontinued on day 3. Ophthalmologic exam was reported as normal, although symptoms persisted. The patient left to return to Guyana 12 days after cessation of telithromycin at which time slight blurred vision continued. The report states that the adverse event was ongoing at the time of the report (22 days after cessation of therapy) and repeat ophthalmic exam was planned upon return to his home country.

200310400DE
This report is of a 59 year-old male who was treated with telithromycin for 5 days for bronchitis. The patient has a history of COPD with frequent exacerbations of chronic bronchitis, amblyopia, "2 years ago musculogenic double images", hypertension, hypercholesterolemia, vestibular neuronitis in 2002, cerebral apoplexy, and partial resection of lung. On day 4 (of 5) of telithromycin treatment, the patient developed myalgia, arthralgia, fever, and blurred vision. Two weeks after completion of therapy with telithromycin, the muscular disturbance had nearly resolved, but the patient still complained of partial visual disturbance which did not resolve after cessation of telithromycin. The patient was examined by an ophthalmologist one week after cessation of telithromycin therapy. On the basis of decreased visual acuity, the ophthalmologist diagnosed the patient clinically as having nerve cell damage. The patient's visual acuity was found to be decreased from right 1.0 and left 0.5 eight months earlier to right 0.5 and left 0.3 one week after telithromycin cessation. The ophthalmologist felt that decrease in visual acuity was the result of irreversible toxic damage whose relationship to telithromycin exposure was probable. Further evaluation 16 days after cessation of telithromycin, including visual evoked potentials and clinical exam, did not reveal signs of neurogenic etiology of the visual disorder.

200310587FR
This report comes from the consumer, a 42 year-old female who was treated with telithromycin for bronchitis. Concomitant medications included: guaifenesin, chlorphenamine maleate, pholcodine, hexapneumine syrup, prednisolone, cetrimonium bromide, phenylephrine, and naphazoline. The patient experienced blurred vision two hours after intake of the first dose of telithromycin. The blurred vision improved briefly but then recurred and was ongoing at the time of the report, approximately 4 weeks later. Further detail was not provided.

Cases of Interest/ Severe symptoms

Many of the reported cases include descriptions which indicate that telithromycin-related visual disorders can be quite severe. Included below are some of these cases.

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 Ketek as "highly probable." Serious: Yes."

Mfr report# 200310224DE AE: "Blurred Vision"
Source: spontaneous report by physician via sales representative Patient: male, age unknown. The patient developed blurred vision under treatment with Ketek™ (telithromycin). The patient could not drive his car anymore. He was referred to an ophthalmologist for evaluation.
No further information was provided

Mfr report# 200315078GDDC AE: "Blurred Vision"
A 39 year-old male was treated with Ketek™ for bronchitis. The patient has no significant medical history and received no concomitant medications. On — at 07:30 hrs, he took his daily dose of telithromycin. One hour later, while driving, he began to have blurred vision and dizziness. The symptoms worsened over the next two hours. The patient was unable to read or work on his computer. He also complained of difficulty walking due to dizziness. He did not report diplopia. Five hours after the last dose of telithromycin, the patient still experiences mild symptoms.
Causality assessment: Highly probable

Mfr report # 200221623GDDC AE: Visual Disorder, Visual Loss *
"17 year old 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."

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 increasing 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."

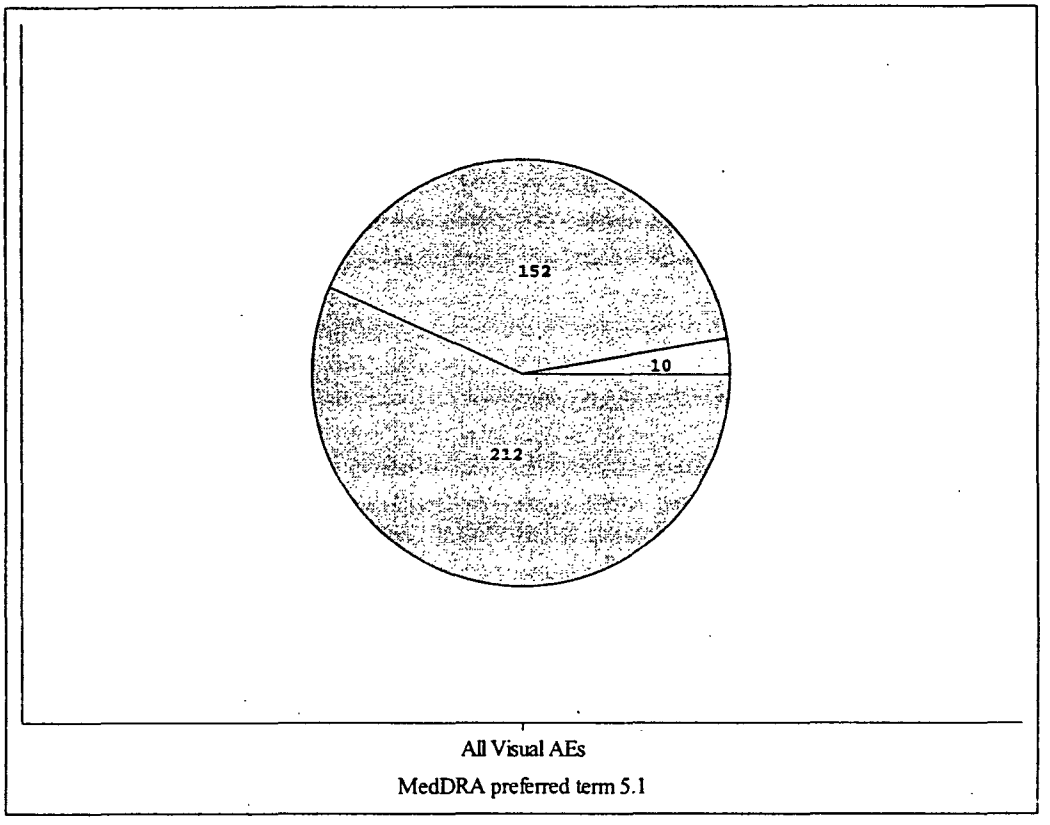
Mfr. Report #200220212GDDC AE: "Visual Lost"
Narrative: Initial Report: This spontaneous report from Brazil involves a 39 year old female patient who received therapy with Ketek 800 mg daily from 10/25/02-10/26/02 for the treatment of sinusitis. There was no mention of relevant history or concomitant 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" No additional follow up was provided for this patient.

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 mycoplasma 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.

Countermeasures

Graph 8 shows recorded countermeasures which occurred as a result of a visual adverse event. For a majority of events, no information was reported regarding any countermeasure. Among those patients who did have some countermeasure as a result of a visual adverse event, almost all were withdrawn from therapy. Only 10 patients were reported as having no change in therapy despite experiencing a visual adverse event.

Graph 8. Visual Adverse Events by Countermeasure



Concomitant Symptoms

There were 67 of 314 patients with visual adverse events who had concomitant headache and nausea. Visual complaints in the setting of headache and nausea are consistent with a migraine-like syndrome.

Medical Officer Comment:
Disturbance of accommodation is thought to be the primary mechanism for telithromycin-related visual adverse events. Review of concomitant visual phenomena which occur in the setting of migraine headaches failed to identify disturbances in accommodation as being associated with migraine headaches.

Medical Officer Summary:
Adverse events likely to comprise the telithromycin-associated adverse event syndrome were the most common post-marketing signal and comprised 33.7% (316/937) of all patients with a reported post-marketing adverse event. The severity of cases and relatively high rate of cases involving discontinuation of medication may be in part the result of a reporting bias, since serious cases are more likely to be reported in the passive post-marketing system. The post-marketing data is useful in that it provides a range of severity for this adverse event. It is clear from numerous visual adverse events associated with telithromycin exposure that telithromycin-associated visual impairment can result in significant disability/incapacity. The majority of these cases are temporary lasting on the order of hours to a few days. However, there are a small number of poorly documented cases that suggest a longer term effect on vision. It is reasonable to consider this as possible because of the novelty of this visual adverse event and the fact that its mechanism is not completely understood. Efforts should be made to monitor for such cases in the future and to attempt to collect more detailed data.

Hepatic Post-marketing Spontaneous Adverse Events

Introduction
There are many limitations of post-marketing adverse event reporting that apply when attempting to assess the potential hepatotoxicity of a particular drug. Capture of events in a passive-reporting post-marketing surveillance system is inefficient. A review article found that between 3% and 11% of hospital admissions could be attributed to adverse drug reactions.[2] However, another study suggests that as few as only 1% of all serious drug-related events are actually reported to the FDA.[3] A recent study reported that in France, fewer than 6 percent of hepatic adverse drug reactions are ever reported.[4]

Further complicating assessment of post-marketing reports of hepatic adverse reactions is the finding that many such reports lack enough basic information to evaluate the possibility of a drug reaction. Also, many such post-marketing reports are likely to be unrelated to the incriminated drug as was found in a study in which, using international consensus criteria, only 47.1% of reported post-marketing hepatic adverse events were determined to be related to the drug in question.[5]

In addition, the very nature of idiosyncratic drug-induced hepatic adverse events is such that they are characterized by a variable delay, or latency period, which may range from

[2] Beard K. Adverse reactions as a cause of hospital admissions in the aged. Drugs Aging. 1992;2:356-367
[3] Scott HD, Rosenbaum SE, Waters WJ, et al. Rhode Island physicians' recognition and reporting of adverse drug reactions. R I Med J. 1987;70:311-316
[4] Sgro C, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology 2002; 36:451-5
[5] Aithal GP, et al. BMJ 1999;319:1541-1541, 11 December.

5-90 days after the initial ingestion of the drug. This may result in difficulty for the treating physician in assessing possible causality of a drug.

It is quite possible that the cases reviewed here represent a very small percentage of the overall number of telithromycin-associated post-marketing hepatic adverse events. And, when considering that a significant proportion of the limited post-marketing hepatic adverse events in this database either lack sufficient basic information or may even be unrelated to telithromycin exposure, it is difficult to make definite determinations of causality, incidence, and severity of reported hepatoxic reactions.

However, past experience has shown with other drugs (such as bromfenac, troglitazone, and trovafloxacin) that despite this system's deficiencies, severe drug-related post-marketing hepatic adverse events are likely to be identified particularly when drug exposure is large and hepatic events occurring in otherwise healthy individuals are severe. The post-marketing hepatic adverse events reviewed here were generated from an estimated usage of — prescriptions in several countries. The majority of these prescriptions : —, were dispensed in France and Germany.

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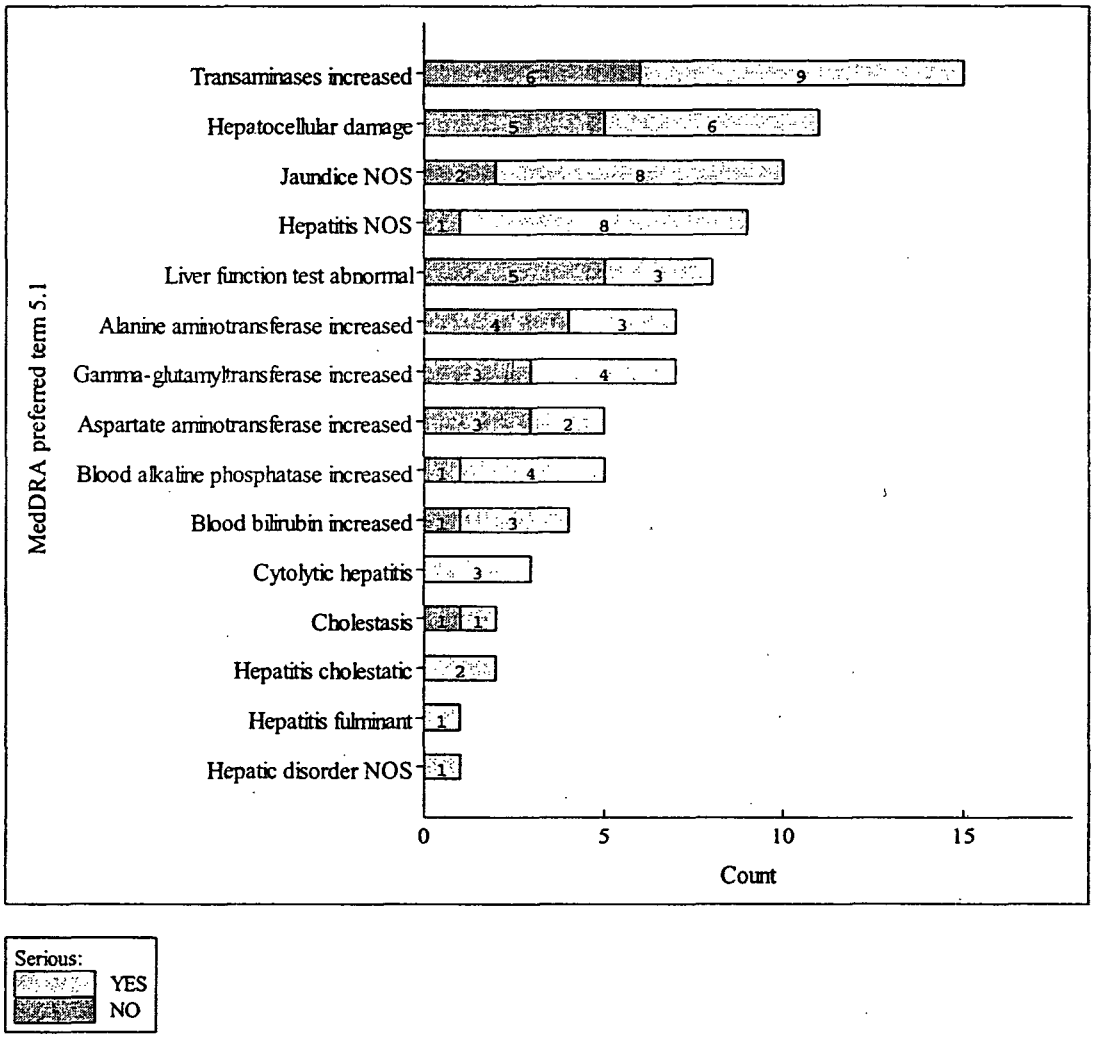
Adverse Events

There were a total of 90 hepatic adverse events reported from 43 different patients. The MedWatch forms for all hepatic adverse events were reviewed individually. **Graph 9** provides a breakdown of the numbers of each type of hepatic adverse event as well as a breakdown of the numbers of serious hepatic adverse events vs. non-serious hepatic adverse events.

Graph 9. Preferred Terms for All Hepatic Adverse Events

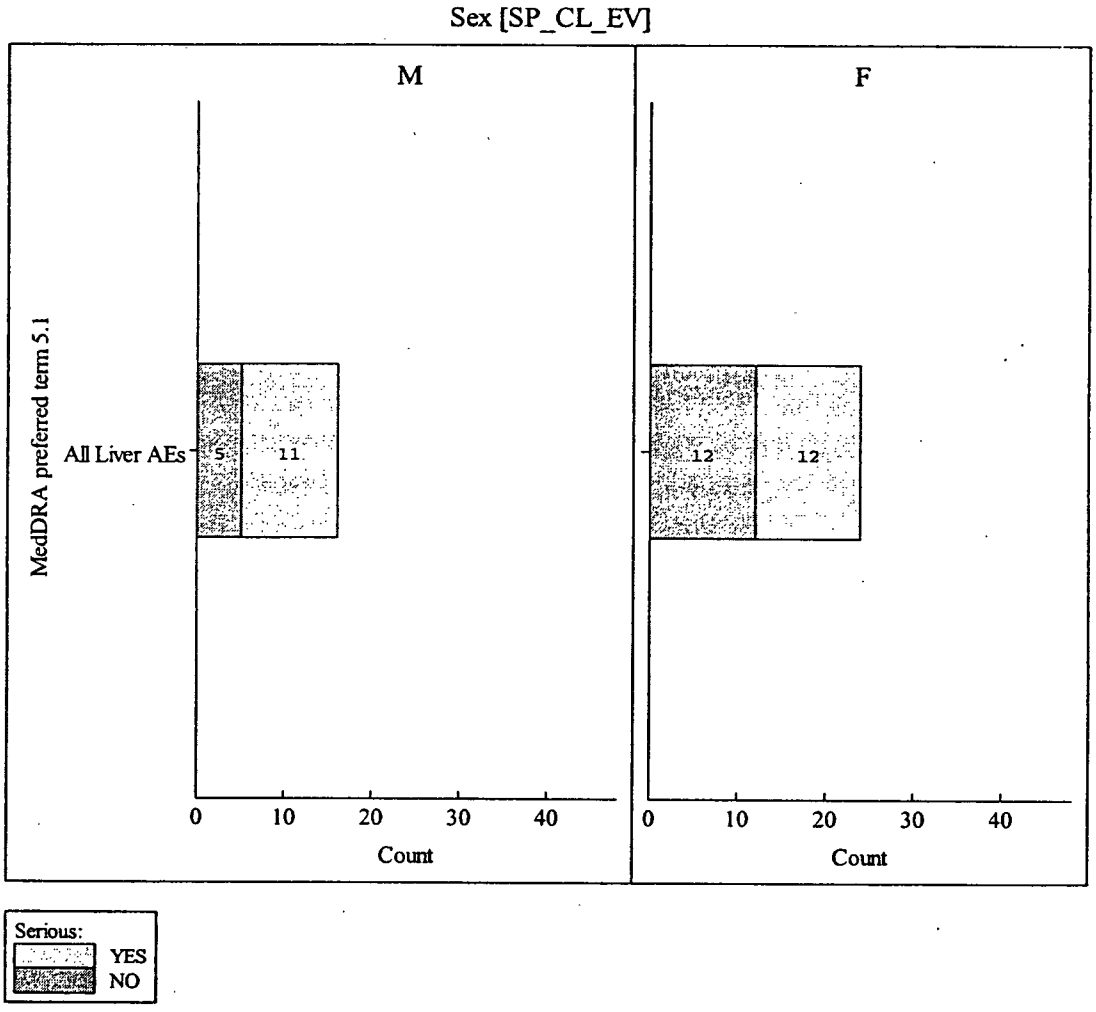


An analysis was done comparing the number of reported hepatic adverse events by gender (shown in **Graph 10**). There were more female patients with hepatic adverse events than male patients (24 vs. 16). This is consistent with published reports in which idiosyncratic drug reactions were found to occur more frequently in females than males.[6]

[6] Ostapowicz G, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med 2002; 137:947-54

The hepatic AE was reported to be serious in a larger proportion of males than females, but it is difficult to draw conclusions on the basis of such small numbers. The determination of whether an adverse event was serious in the post-marketing setting is generally made by the reporter without regard to specific criteria. This may result in some degree of inconsistency between cases.

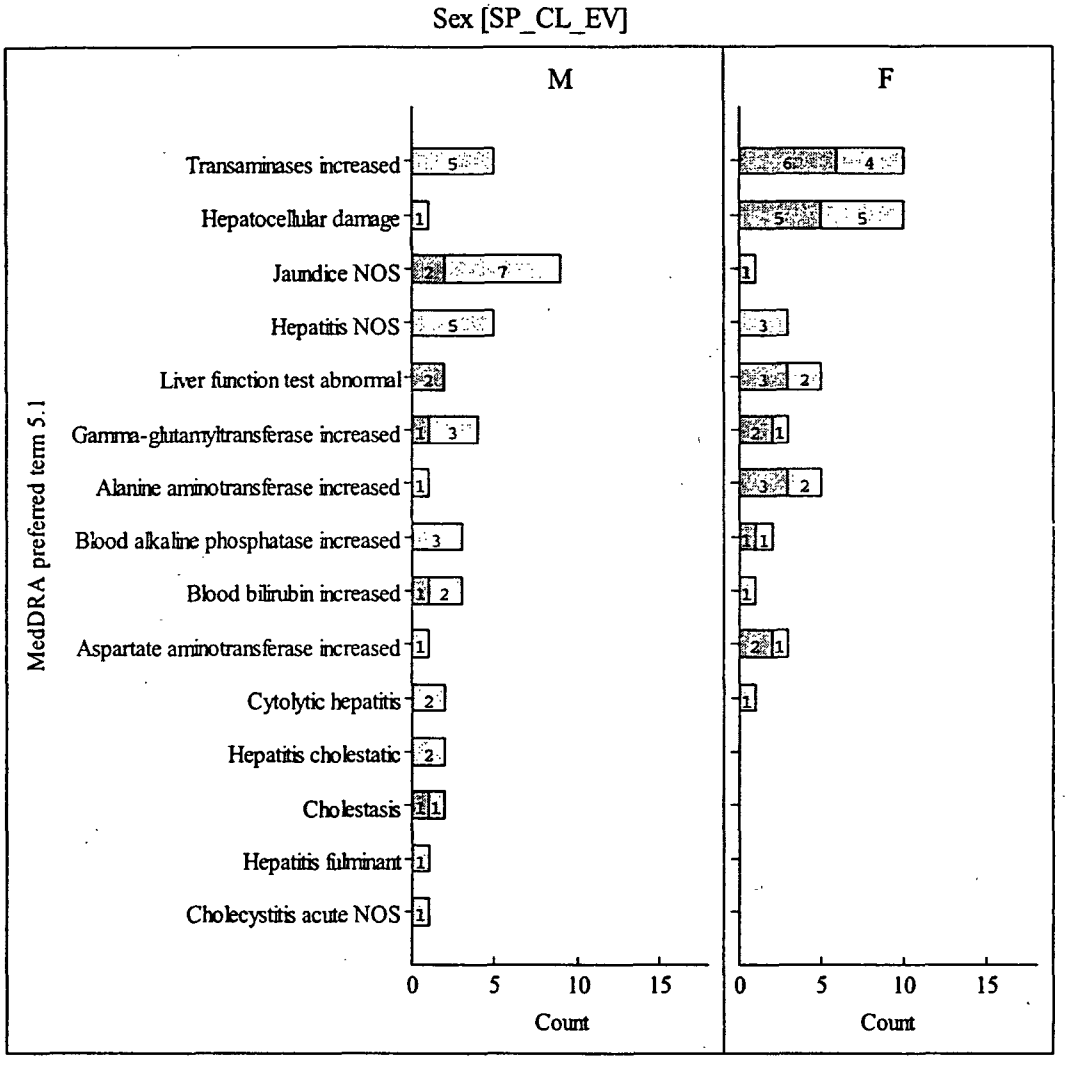
Graph 10. Hepatic Adverse Events by Gender and Seriousness



A further analysis was done comparing specific types of hepatic adverse events by gender (see **Graph 11**). The distribution of reports amongst the different types of hepatic adverse events appears to be relatively similar, given the small number of patients. However, there does appear to be a possible trend towards more reports consistent with a cholestatic pattern of liver injury in males vs. a cytolytic (hepatocellular) pattern in females. When specific laboratory criteria defining cholestatic and hepatocellular liver injury were applied to the patients, this trend persisted (see section below for details of analysis).

However, because of missing lab data, a majority of patients could not be characterized, making it difficult to draw firm conclusions.

Graph 11. Hepatic Adverse Events by Preferred Term and Gender



An additional analysis was done in which hepatic adverse events were assessed by age and by age/gender. There did not appear to be a difference in the incidence of hepatic adverse events by age or by age/gender. However, because of the small number of overall hepatic adverse events, there were not enough patients in each age category to conclude definitively that there is no age effect on the incidence of hepatic adverse events.

Liver Injury Pattern

It is possible for a drug to cause more than one pattern of liver injury (such as with nimeluside, diclofenac, and amoxicillin/clavulanate). However, drugs which cause

hepatotoxicity often have a single signature pattern of hepatic injury. Therefore, it is often useful to characterize a series of hepatic drug reactions to look for a distinct pattern. In an attempt to identify a specific pattern of injury, all hepatic adverse events were reviewed individually. Liver histology was determined to be unhelpful in this effort, since only 3 patients underwent liver biopsy. Categorization of the cases as "cholestatic", "cytolytic" , or "mixed" was made on the basis of the proposed criteria of an International Consensus Meeting.[7] Cytolytic type was defined as an alanine aminotransferase/ alkaline phosphatase (ALT/ALP) ratio ≥ 5, cholestatic type as ALT/ALP ratio ≤ 2 and mixed type as $2 <$ ALT/ALP ratio > 5. Summaries of specific cases of interest are presented and additional categories are included for those reports in which not enough information was provided to allow for categorization as well as those reports that are highly confounded.

More than half of the reports (24 of 43) contained insufficient data (lacking either ALT or alkaline phosphatase measurements, or both) to make a determination as to the liver injury pattern. Given this large number of patients with missing data, it is difficult to determine if any pattern of liver injury exists according to this method. It is also difficult to assess potential gender differences between liver injury patterns.

Table 6 shows the breakdown of these patients according to gender and injury pattern. Overall, there were a larger number of cases with a cholestatic pattern of liver injury. There were also more female patients with a cytolytic pattern of liver injury. However, because 24 patients could not be characterized, it is difficult to draw definite conclusions.

Table 6. Hepatic Injury Pattern of Telithromycin-treated Patients from Post-marketing Reports

	Cytolytic (hepatocellular)	Cholestatic	Mixed	Unclear
Male	1*	6**	0	8†
Female	4	6	2	11
Unknown	0	0	0	5

* Case 200215044FR Confounded case in which patient, in addition to telithromycin exposure, had concomitant acute hepatitis A, Q fever, and high dose acetominophen ingestion

** Case 200121010 Confounded case in which a 20 year-old male was diagnosed with acute EBV infection

† Case 200214071 Confounded case in which 26 year-old male was diagnosed with acute CMV infection

[7] Benichou C. Criteria of drug induced hepatic disorders. Report of an international consensus meeting. J Hepatol 1990;11:272-276

Medical Officer Comment:
The majority of patients whose pattern of liver injury could be categorized had a cholestatic pattern rather than cytolytic (12 vs. 5). Given the large number of patients whose liver pattern could not be categorized, it is difficult to determine conclusively if a predominant pattern of liver injury exists in this group of patients. Patients with a cytolytic pattern of hepatic injury who have increased bilirubin measurements are thought to have a fatality rate of as high as 10%.[8] Of the patients with a cytolytic pattern of injury, there were two who had both an ALT >3 times the upper limit of normal and a bilirubin >1.5 times the upper limit of normal. One of these patients (200215044FR) was highly confounded with multiple other possible explanations as to the cause of his liver injury. The other patient was a 33 year-old female (200213635DE) who eventually recovered and whose case is described in the Cases of Interest section. Although a cholestatic pattern of injury appears to be more common, this case is relatively non-confounded and it is important to recognize that there are drugs, including amoxicillin-clavulanate which can cause more than one pattern of injury.

Causality Assessment

A commonly used methodology for determining causality was proposed in 1990 by a working group of hepatology specialists convened by the Council for International Organizations of Medical Sciences (CIOMS). This group developed and implemented a method for evaluating drug hepatotoxicity. Most large case series reviews use this method or some variation of this method for determining which patients to include in the reviews. The CIOMS method for determining causality involves a scoring system designed to assess six major axes including: chronologic criterion, risk factors, concomitant therapy, exclusion of non-drug related causes, bibliographic data, and rechallenge.

Four major case series reviews[9,10,11,12] as well as the FDA white paper[13] reveal causality assessments based mainly around principles set forth in the CIOMS method. Of these publications, the minimum required information for assessing causality[9] included at least report of hepatitis A,B, and C serologies, hepatobiliary ultrasonography (to rule out biliary etiologies), as well as any pertinent investigations which were indicated for each patient (not specified). Another study[10] employed more detailed methods for assessing causality. That study excluded all patients under 15 years old, pregnant women, patients

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[8] Zimmerman HJ. Drug-induced liver disease. Clinics in liver disease. 2000 Feb; 4(1):73-96
[9] Sgro C, et al. Incidence of drug-induced hepatic injuries: a French population-based study. Hepatology 2002; 36:451-5
[10] Ibanez L, Perez E, Vidal X, Laporte JR; Grup d'Estudi Multicenteric d'Hepatotoxicitat Aguda de Barcelona (GEMHAB). Surveillance of acute serious liver disease unrelated to infectious, obstructive, or metabolic diseases: epidemiological and clinical features, and exposure to drugs.
J Hepatol. 2002 Nov;37(5):592-600.
[11] Ostapowicz G et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002 Dec 17;137(12):947-54.
[12] Friis H, Andreasen I'B: Drug-incluced hepatic injury: An analysis of 1,100 cases reported to the Danish Committee on Adverse Drug Reactions between 1978 and 1987. J Intern Med 232:133-138, 1992
[13] http://www.fda.gov/cder/livertox/postmarket.pdf

with serologically proven hepatitis, AIDS/HIV positive patients, IV drug users, those with malignant neoplasms, congestive heart failure, alcoholic liver disease, any process causing obstruction (U/S of liver and biliary tract or ERCP had to be performed on all patients), cholestatic metabolic diseases, organ transplantation, hemophilia, drug overdosage, or mushroom poisoning. The FDA White Paper suggests additional factors to help determine causality including: occupational toxic agent, acupuncture, recent travel to Asia or Africa, blood product transfusion, recent hypotension, and auto-immune serologies.

Review of the 43 patients with post-marketing hepatic adverse reactions revealed that a majority of them did not contain the minimum necessary information (U/S and hepatitis serologies) to allow for any assessment of causality. Of the 43 three patients, only 14 had information regarding results of an imaging study (ultrasound or CT scan) and hepatitis serologies (for hepatitis A, B, and C). Of those 14 patients, only 5 reports included any additional data commonly used for causality assessment as described above.

Medical Officer Comment:
The quality of the collected data is such that only a minority of reports can be evaluated in a meaningful way with regard to telithromycin causality. The lack of this information does not preclude the possibility that telithromycin contributed in some way to the hepatic adverse events for which causality data is lacking. However, because of the lack of sufficient amounts of causality data, the probability of making an accurate causality assessment is poor for most of the cases.

Case Severity

One possible way of defining severity was proposed in the FDA White Paper on Drug-Induced Hepatotoxicity[13]. The FDA White Paper on Drug Induced Hepatotoxicity was the result of a joint PhRMA/FDA /AASLD workshop which was held in November 2000. In this paper, severity was measured by the degree of laboratory abnormalities, (e.g., larger abnormalities of transaminases $\geq$ 10 times Upper Limit of Normal) which may be accompanied by abnormalities of excretory function (hyperbilirubinemia or jaundice) and by effects on synthetic function (prolongation of prothrombin time and reduction of Factor V to less than 50%).

Review of the 43 patients with post-marketing hepatic adverse events reveals a total of seven patients (4 male, 3 female) with hepatic adverse reactions which would be categorized as severe using these criteria. There were 12 cases in which no ALT was reported, and therefore, severity could not be determined. Of the seven patients with severe hepatic reactions, three had a cytolytic pattern of liver injury, two had a cholestatic pattern of injury, one had a mixed pattern of injury, and one had an unclear pattern of injury. One of the three patients with a cytolytic pattern of injury was highly confounded by the presence of acute hepatitis A infection, possible Q fever, and large dose ingestion of acetaminophen. Of the seven, five had ultrasounds reported as being done and six had hepatitis serologies reported. There were only three cases in which additional causality data were reported.

Medical Officer Comment: It is not clear what the basis of this severity measure is. It is reasonable to assume that increased transaminase levels are consistent with increased severity of disease. However, it is not known whether the particular classification of severity recommended in the FDA white paper can be accurately predictive of specific outcomes. In general, the degree to which data was reported for patients with a severe hepatic adverse event was better than for those without a severe event. However, the majority of patients with a severe hepatic event still lacked detailed causality data.

Resolution of Hepatic Adverse Events

The majority of cases did not provide follow-up lab values to demonstrate improvement or degree of improvement. Review of all cases showed that the majority (24/43) of patients had hepatic adverse events which were reported as either resolved or improving. There were 6 patients in whom the hepatic adverse event was reported as ongoing and 12 patients in whom the outcome was not reported. There was one fatality (200215044FR), however, this case was highly confounded in that the patient had concurrent acute hepatitis A infection, high dose acetominophen ingestion, and possible Q fever.

Hepatic Adverse Events of Interest

Cholestatic

200310305DE
This case was a 50 year-old woman with no relevant past medical history, no ethanol or drug abuse, allergies, or continuous previous medication. She was treated with telithromycin from 10/14/02-10/31/02 for pneumonia. On [redacted], the patient presented with 3 days of RUQ abdominal pain, asthenia, and tiredness. She was hospitalized that day and lab data revealed ALT 366, AST 111, ALP 437, LDH 242, bilirubin 1.78, WBC 16.2 with no differential given. U/S revealed ascites and liver biopsy revealed "drug toxic liver cell damage (liver parenchyma with extensive not very fresh) centrilobular parenchymal necrosis, collapse sclerosis and pronounced eosinophilia)." Symptoms improved after a few days but lab values improved only slowly. Lab values at time of discharge [redacted] were: LDH 242, AST 97, ALT 401, GGT 78, AP 179, bilirubin 1.59, CRP<8, WBC 9.1. Hepatitis serologies were negative including A, B, C, EBV, and CMV. Outcome was reported as "recovered with sequelae." No autoimmune work up was reported. No further follow up information was provided.

Medical Officer Comment: This case did have sufficient amounts of causality data as well as a biopsy. The elevated alkaline phosphatase and bilirubin increase are consistent with a cholestatic pattern of liver injury. This case is significant because the high ALT and the liver biopsy results demonstrate a pattern of liver injury consistent with hepatocanalicular jaundice. This type of drug-induced cholestatic jaundice is seen with erythromycins and is more likely than other forms of cholestatic liver injury, such as canalicular (or bland cholestasis) to result in parenchymal damage which was seen on this patient's biopsy. One of the potential serious complications of hepatocanalicular jaundice is chronic intrahepatic cholestasis which is a primary biliary cirrhosis (PBC)-like

syndrome and is an important cause of the vanishing bile duct syndrome. Erythromycin has been reported to cause this syndrome. In this case, the patient was reported as having "recovered with sequelae" however, there is no mention of what the sequelae were other than ongoing liver function test abnormalities. It is possible that this patient may eventually go on to develop a PBC-like syndrome, however, without detailed follow-up, it is not possible to know.

200214257FR
This report from a physician was about a 39 year-old male patient. There was no pertinent past medical history, including no ethanol abuse and no concomitant medications. He was treated with ketek from 9/13/02— for bronchitis. On the final day of treatment, he experienced asthenia, icterus, and dark urine. Evaluation revealed abnormal liver function tests. ALT peaked at 969 on — and ALP increased to 555. GGT was abnormal as well. Liver U/S was normal. Serologies for hepatitis ABC were negative. It is unclear if bilirubin was measured. Liver biopsy was not performed. Anti-smooth muscle antibody (Ab), anti MKM1 Ab, ANA, CMV, and Herpes virus serologies were negative. There was no eosinophilia. ALT normalized by — . GGT and ALP remained elevated at 190 and 132 but were trending downward.

Medical Officer Comment: This case had some causality data including U/S and hepatitis serologies. It is also consistent with hepatocanalicular jaundice, although no bilirubin measurement was reported. The patient's ALT normalized and ALP was improving, but no long term follow-up was reported.

200311338FR
A 28 year-old female started on ketek for an upper respiratory tract infection. She discontinued ketek after three days because she did not feel well. Immediately prior to treatment with ketek, she was treated with amoxicillin for 4-7 days. Concomitant medications included ibuprofen, paracetamol and betamethasone. Two to three weeks after the start of ketek treatment, she experienced fatigue and headache. Blood tests included an increased ALT to 298, AST 129, and GGT 77. Eosinophils were normal and bilirubin was 5.2 with conjugated bilirubin of 1.2. One week later, her transaminases hadn't changed much and ALP increased to 535 (nl<290). Hepatitis ABC serologies were negative and U/S was normal. No further information was provided and the event was ongoing at the time of the report.

Medical Officer Comment: Although this patient was being treated with concomitant acetaminophen, the pattern of cholestatic liver injury is not consistent with the direct hepatotoxicity that is seen with acetaminophen. This patient showed no improvement after one week and no follow up to assess for potential chronic intrahepatic cholestasis as can be seen after a drug-induced injury.

200214202DE
The patient was a 70 year-old male, with a history of COPD, DM, s/p Bilroth surgery (no history of liver disease or alcoholism). He was admitted — with flu symptoms, productive cough, and hemoptysis. Ketek treatment stopped on — and he was

discharged on prednisolone. He was re-admitted with "Cholestatic hepatosis, likely drug-induced by telithromycin." Labs: ALP 735, ALT 132, bilirubin 4.33. U/S: "liver homogenous, size normal, ductus hepchol 2 mm (enlarged), gall bladder with suspected polyp, pancreas normal, aorta 18mm, spleen size normal, kidneys normal." A Liver biopsy performed showed "marked cholestatic hepatopathy with mononuclear inflammatory infiltration in the periportal triangle with singular cell necrosis and surrounding granulocytic reaction. Comment: morphol picture compatible with a cholestatic drug--toxic hepatitis such as can occur after antibiotics." The MedWatch report contains the following statement: "no antibiotic between The patient had received moxifloxacin in late November of 2001. The report also includes the words "amoxicillin clavulanic acid" however, there is no information as to when or if the patient ever took this medication. Aventis has stated that the patient did take this medication some time prior to the event, however, this assertion is not confirmed in the existing post-marketing data. Obstruction, viral hepatitis, autoimmune hepatitis, sclerosing cholangitis, primary biliary cirrhosis, alpha-1 antitrypsin-deficiency and Wilson disease were excluded. "Suspected drug-induced hepatitis: the patient had received telithromycin a few days prior to admission." The report states that the liver function test abnormalities resolved.

Medical Officer Comment: This patient also had a liver injury consistent with a drug-induced cholestasis as is indicated by the biopsy. In this report, the liver function tests were reported as having normalized.

200211440DE

This report is of a 61 year-old male with recurrent sinusitis/tonsillitis who was s/p endocarditis and was treated with ketek for tonsillopharyngitis. Concomitant medication included acetyldigoxin and long-term antibiotic prophylaxis with amoxicillin/ cephalexin. At some point the patient developed a recurrence of fever and was admitted to the hospital for suspected recurrence of endocarditis. This diagnosis was not confirmed and only abnormal liver functions tests were found. The admitting physician suspected a liver reaction caused by ketek. A liver biopsy showed "focal fatty (mixed drop size of vacuoles) degeneration of hepatic tissue with moderate intrahepatic cholestasis as well as mild inflammatory mesenchymal activity (lymphocytes). No signs of malignancy or specificity. No typical histologic aspect of chronic viral hepatitis, the findings could indicate a nutritive-toxic genesis." The biopsy results are consistent with a drug induced injury which is what the admitting physician suspected. There presumably is a plausible temporal relationship between the liver injury and ketek exposure, however, the reporting physician reported that the overall course of event does not indicate a drug-induced injury. No laboratory data was provided.

Medical Officer Comment: This patient had no causality data reported, except some information on concomitant medications. He did have a liver biopsy which is consistent with a drug-induced hepatocanalicular liver injury.

Cytolytic

200213635DE
A 33 year-old female with a history of pyeloplasty of the left kidney in 1996 was treated with ketek from 3/10/02-3/14/02 for maxillary sinusitis and feverish bronchitis. Concomitant medications included OCP. On [redacted] he patient developed nausea, vomiting and right upper quadrant pain. Evaluation revealed increase in LFT's. Liver U/S was normal, and she was not hospitalized. LFT's returned to normal after 5 weeks. Her peak ALT was 823 on [redacted]. ALP remained normal but the first total bilirubin on [redacted] was elevated at 33 (normal is <21). There was a mild eosinophilia of 7% on [redacted] and no further eosinophil count was done. Serologic exam for viral hepatitis was negative. The physician assessed the causal relationship of ketek as "probable". The patient's laboratories returned to normal after 5 weeks.

Medical Officer Comment: This case was a relatively unconfounded case in that U/S, hepatitis serologies, and additional causality data were reported and were negative. Concomitant medications included only oral contraceptives. Although oral contraceptive medications can cause hepatic injury, they most often do so in a cholestatic canalicular pattern which was not consistent with this patient's laboratory parameters. In addition, this patient had a peripheral eosinophilia which is suggestive of a drug-induced hepatic event.

Mixed

200213996DE
This 58 year-old female with history of headache was treated with 10 days of ketek for tonsillitis. Concomitant medications included atorvastatin (stopped 10 days prior to the start of ketek), caffeine with propyphenazone, and a previous recent course of ceftibuten. One day after starting ketek, the patient experienced symptoms which developed gradually. These symptoms included fatigue, nausea, constipation, and headache. Four days after stopping therapy with ketek, the patient was hospitalized with a liver reaction and progressive increases in liver enzymes. The patient had no history of liver disease and no suspicion for other etiology (i.e., hypotension/sepsis, decompensated heart failure, malignancy, or gallstones). The patient was hospitalized on [redacted] and liver enzymes peaked on [redacted] with the following results: ALT 1207, AST 999, LDH 405, GGT 178, and ALP 405. Bilirubin (normal range 0.1-1.0) was only slightly elevated at 1.3. Serologies including Hepatitis A, B, C, and EBV were negative and U/S, EGD, and biopsy were unremarkable. On [redacted], the patients LFTs were slightly improved (ALT 969, AST 750, LDH 333). There was actually a slight increase in ALP 302 and bilirubin 1.4. It is unclear what "biopsy" refers to: liver vs. stomach from EGD. There was no suspicion for gallstones. Whether she had contact with liver patients is not known. Liver function tests were reported as improving but final outcome was not contained in the report.

Medical Officer Comment:
This patient's case had a good amount of causality data reported. She experienced a severe increase in transaminases, however, her bilirubin was only slightly elevated. Given the amount of hepatocellular damage that occurred in this patient, it is likely that the mentioned biopsy was taken during the EGD procedure and not from a liver biopsy.

Unclear

200213626EU
A 46 year-old male from Belgium with a history of hypertension was treated with Ketek for bronchitis and chlamydial pneumonia. The patient developed urticaria and allergic hepatitis and therapy with ketek was stopped on the fourth day of treatment. Treatment with Xyzall (levocetirizine) was started. Reportedly, the patient recovered on the day the Ketek was discontinued. The report includes no lab results or indication of whether the urticaria and the hepatitis resolved at the same time. The events (allergic hepatitis and urticaria generalized) were considered by the physician as highly probably related to telithromycin.

Medical Officer Comment:
This case is an example of a potentially important case of what was reported as "allergic hepatitis." However, unfortunately, there is a lack of causality data and there are no lab results reported. It is not possible to assess what this case means in relation to possible telithromycin toxicity.

200311437FR
This report is of a 69 year-old female with a history of colon tumor, NIDDM, and penicillin allergy, who was treated with ketek for bronchitis. Concomitant medications included gliclazide and metformin. On the third day of treatment, the patient experienced hepatic cytolysis with nausea and sudden anorexia with ALT increased at 19 times normal, AST at 6 times normal and reportedly moderate cholestasis with GGT 2 times normal. The patient also presented with diabetes imbalance. On [redacted] treatment with telithromycin was discontinued. Serologies for hepatitis A, B, C were negative and ANA, LKM and smooth muscle antibodies were also negative. The patient's condition improved with marked decrease of hepatic cytolysis 3 weeks after the discontinuation of treatment with telithromycin and the patient recovered except for digestive symptoms after 1 month. Liver U/S scan was not reported. The patient completely recovered at the time of the report. No further information was provided.

Medical Officer Comment:
This is a case of a hepatitis with significant elevations of transaminases. However, U/S, alkaline phosphatase, and bilirubin results were not reported. This patient was also on concomitant medications such as metformin which could have contributed to the hepatic reaction. Although telithromycin may have contributed to this hepatic reaction, it is less clear than in other cases. Also, a clear picture of the pattern of liver injury is absent because of the lack of important information.

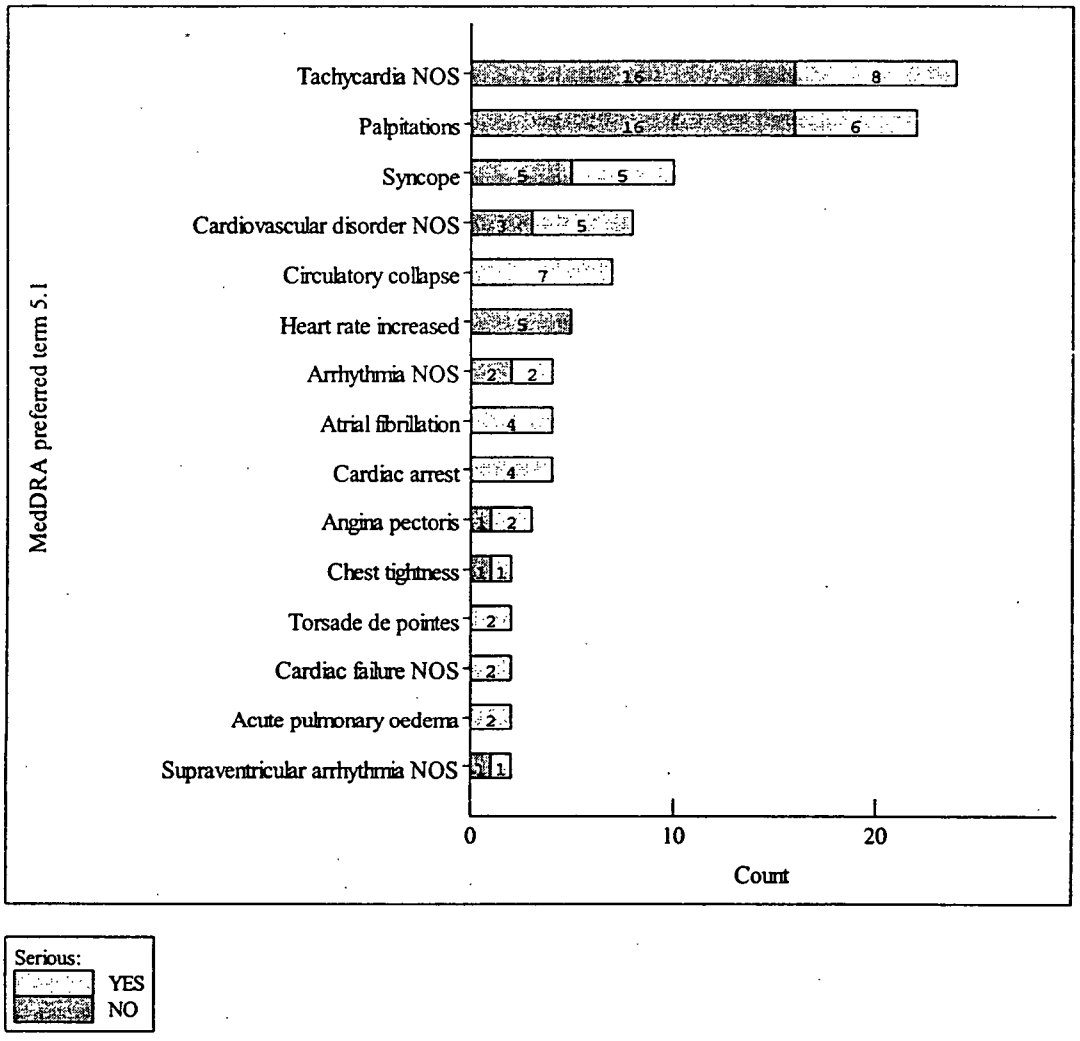
Medical Officer Summary:
It is difficult to draw firm conclusions about the incidence, severity, and potential sequelae of telithromycin induced liver toxicity based on the available data. As is common with post-marketing data, there are large amounts of missing data which make determinations of injury pattern and causality challenging. For those cases in which sufficient data were available, a cholestatic pattern of injury appears to be most common. The pattern most resembles a hepatocanalicular cholestatic injury which has been well described in patients exposed to erythromycins. Among patients who were exposed to telithromycin and who subsequently experienced a hepatic adverse event, there were no deaths except for one highly confounded case of a 75 year old with acute hepatitis A, possible Q fever, and high dose acetaminophen consumption. Cholestatic drug-induced liver injury is thought to be overall less likely to result in a fatal hepatic adverse event (1%) than cytolytic hepatic adverse events.[8] However, amongst patients with cholestatic acute serious liver disease, the prognosis may not significantly differ from that of the hepatocellular (cytolytic) pattern.[14] For this reason, it is important to carefully evaluate patients with reported cholestatic hepatic adverse events. Of those patients with severe hepatic adverse events, there were two with a cholestatic pattern of liver injury. Both of these patients survived. Although it is difficult to determine accurate incidence rates of adverse events based on post-marketing data, the number and severity of the telithromycin-related reports is similar to the erythromycins. Given the overall exposure of —— prescriptions, it is reassuring that there was only one hepatic-related death which occurred in a highly confounded patient and was unlikely to be related to telithromycin. The currently available data do not allow for an assessment of possible long-term complications resulting from telithromycin-related cholestatic hepatic adverse events which might include chronic intrahepatic cholestasis. Also unclear at this time are the possible consequences of re-challenge in patients with a prior episode of telithromycin-related hepatic adverse events or whether exposure to other erythromycin-like antibiotics would constitute such a re-challenge. As additional data is collected from European, US, and other post-marketing systems, hopefully a better characterization of potential sequelae of telithromycin-related hepatic adverse events will emerge.

[14] Ibanez L. Clin Liver Dis. 2002 May;6(2):381-97

Cardiac Post-marketing Spontaneous Adverse Events

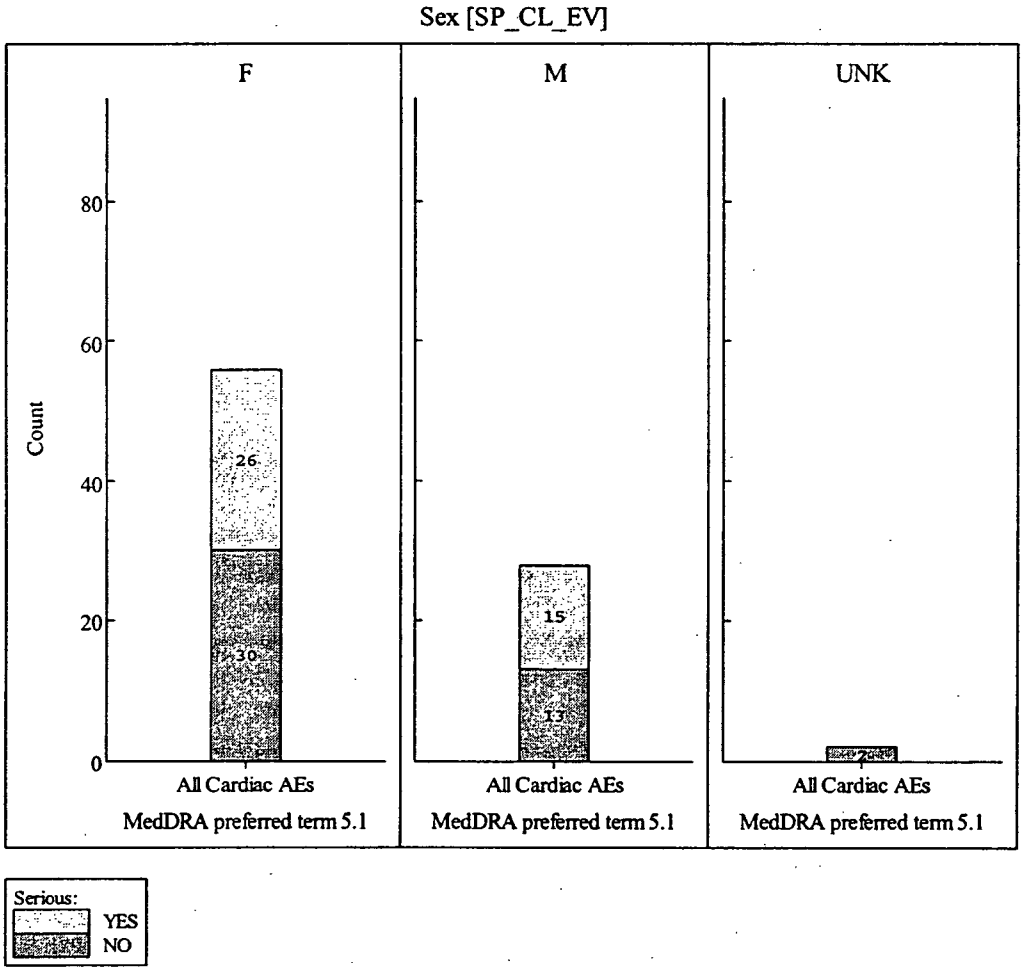
Phase 3 data did not indicate that the QT effects of telithromycin were substantially different than similar drugs in the macrolide class. However, because telithromycin is known to cause an increase in QT interval, a careful review of post-marketing data was performed. There were a total of 101 cardiac adverse events in 86 different patients. In 41 out of the 86 patients, the cardiac adverse events were considered serious. **Graph 12** shows a breakdown of all the different cardiac adverse events by MedDRA preferred term.

Graph 12. All Cardiac Adverse Events by Preferred Term



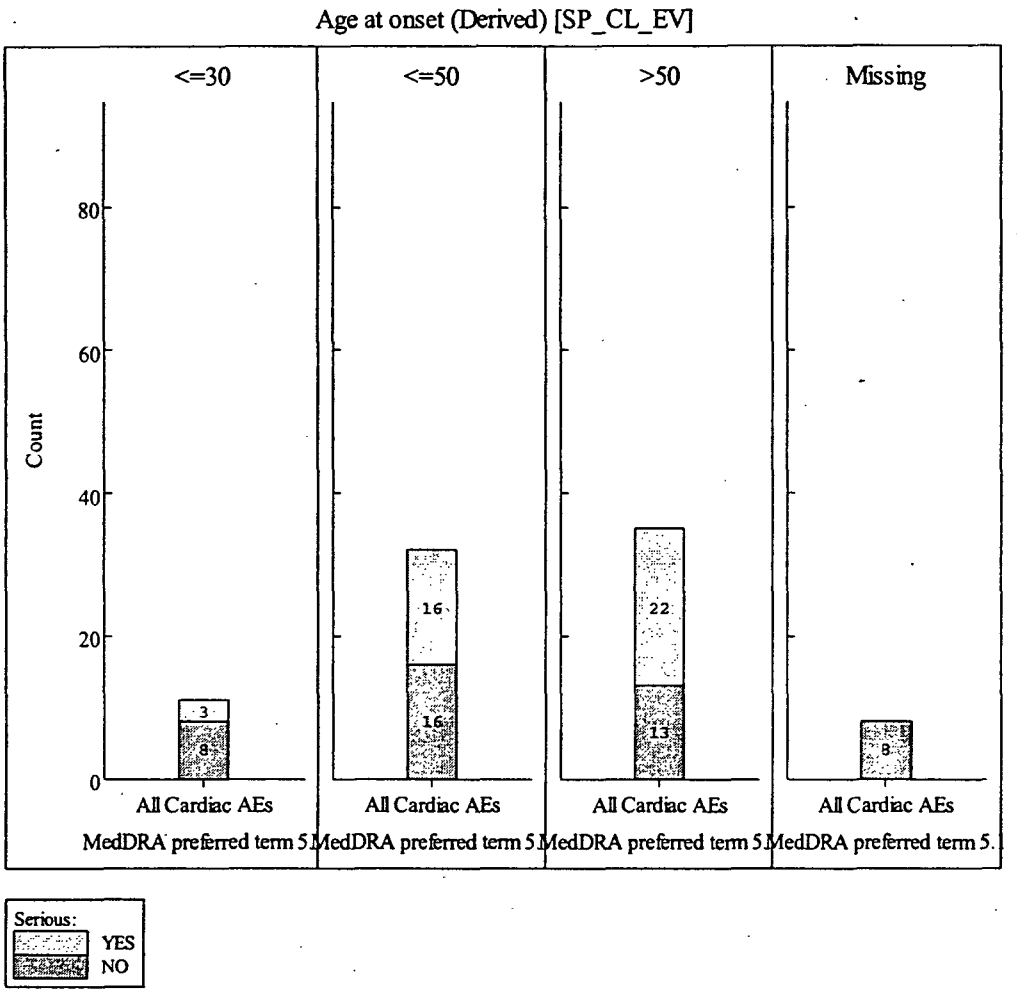
The majority of patients with a cardiac adverse event were females (56 vs. 28) as seen in **Graph 13**. There were similar proportions of serious cardiac adverse events between males and females (53.6% vs. 46.6%).

Graph 13. Cardiac Adverse Events by Gender



Of patients with a cardiac adverse event, there were more patients in higher age groups. Also, the proportion of serious adverse events increased with increasing age as is shown in **Graph 14**.

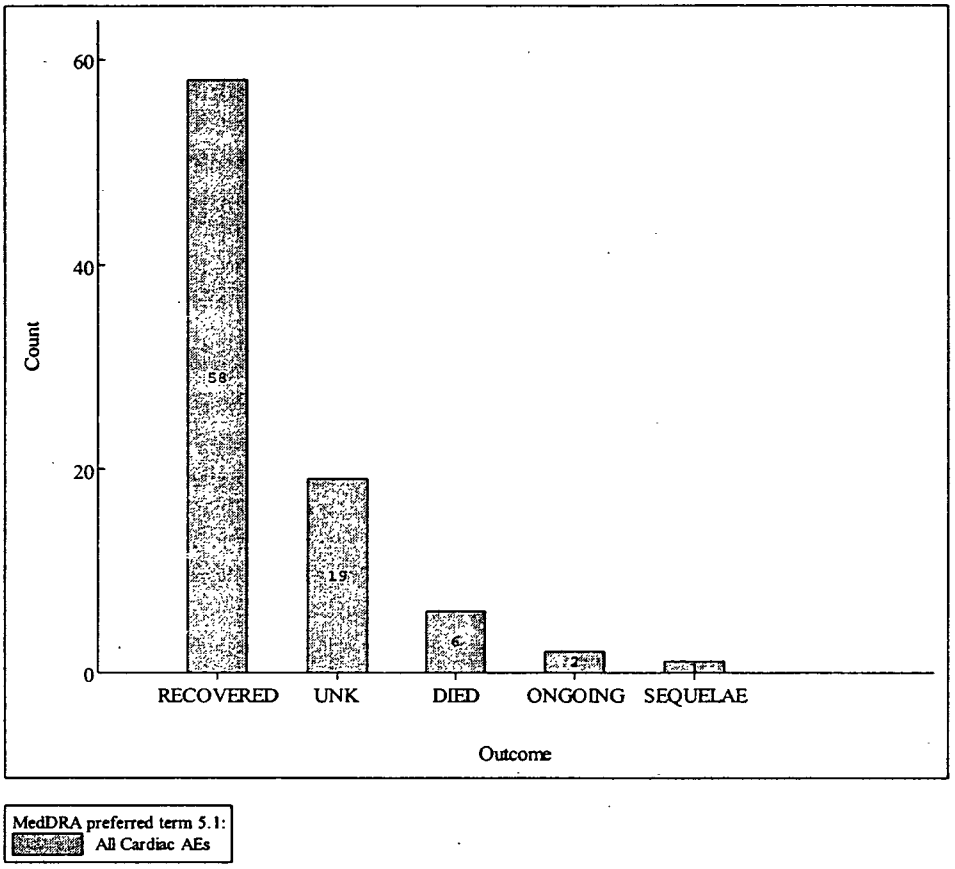
Graph 14. Cardiac Adverse Events by Age and Seriousness



Medical Officer Comment:
This trend of increasing cardiac adverse events with increasing age and increasing rates of serious cardiac adverse events with increasing age is consistent with the natural history of cardiac disease in humans. It doesn't, however, answer the question of whether patients with pre-existing cardiac disease have an increased rate of cardiac adverse events when exposed to telithromycin. Although post-marketing data is not capable of answering this question, available Phase 3 data are not suggestive of a telithromycin-associated increase in cardiac adverse events.

The outcome of all patients who had a cardiac adverse event is shown in **Graph 15.**

Graph 15. Cardiac Adverse Events by Outcome



There were six deaths. These six patients are reviewed in detail in the Deaths section and include the following patients: 200211064EU, 200211203DE, 200214256DE, 200310215DE, 200311271FR, 200311947FR.

Medical Officer Summary:
All serious cardiac adverse events were reviewed in detail. The majority of these events were either cardiac events occurring in older patients with pre-existing cardiac disease or symptoms, such as palpitations or tachycardia, occurring as part of a mainly non-cardiac multi-symptom event. Because of the way the data were submitted, it was not possible to do an analysis of cardiac events according to concomitant medications.

Review of these post-marketing data does not indicate any unusual cardiac safety signal for Ketek™. Because QT interval prolongation often results in cardiac events outside the setting of the type of medical monitoring necessary to identify them, and because these events frequently degenerate into non-distinct ventricular fibrillation, it is often difficult to identify drug –related QT toxicity in the post-marketing setting. Therefore, the absence

of a cardiac signal in this current data does not preclude the identification of such a signal based on future post-marketing data or literature reports. Given that this drug is known to prolong the QT interval (albeit slightly) and because this drug interacts with other drugs as an inhibitor of cytochrome P450 3A4, there should be ongoing efforts to monitor for QT related cardiac toxicity.

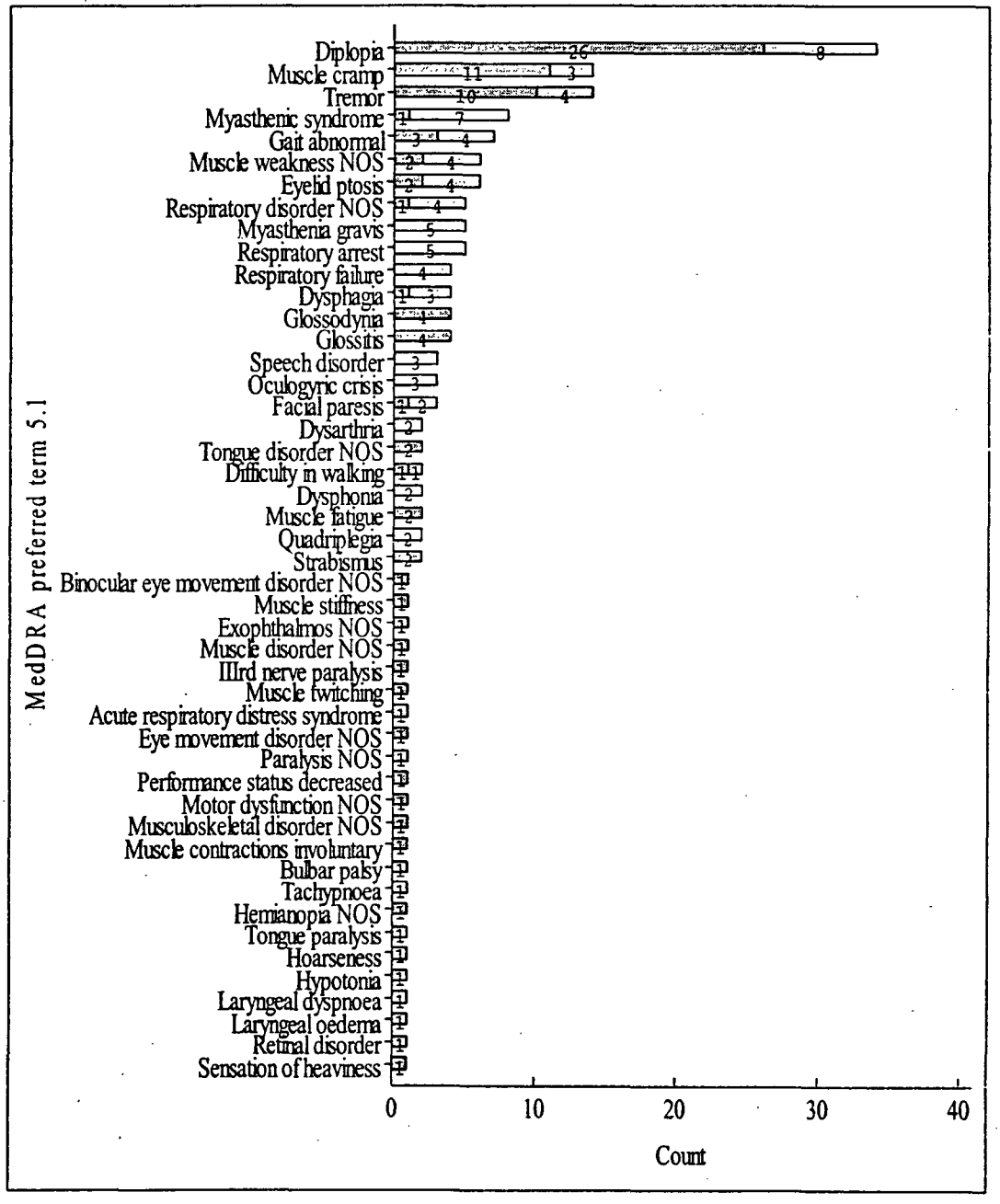
Myasthenia Gravis/Nervous System Events

Antibiotics have been identified in the past as potential causes of myasthenia gravis exacerbations. There are also drugs, such as ciprofloxacin and penicillamine, which have been implicated in the induction of myasthenia gravis. Penicillamine may be directly antigenic after binding to ACh receptors; anti-receptor antibodies are produced in response to this drug-receptor complex. No published reports have associated penicillamine with clinical worsening of existing myasthenia gravis; the mechanism of injury is believed to arise from immunologic effects rather than events at the neuromuscular synapse.

No safety signal for telithromycin-associated myasthenia gravis complications was detected in the Phase 3 safety database, however, after approval of the drug outside the U.S., several reports of myasthenic exacerbation with a temporal relationship to telithromycin exposure have been reported.

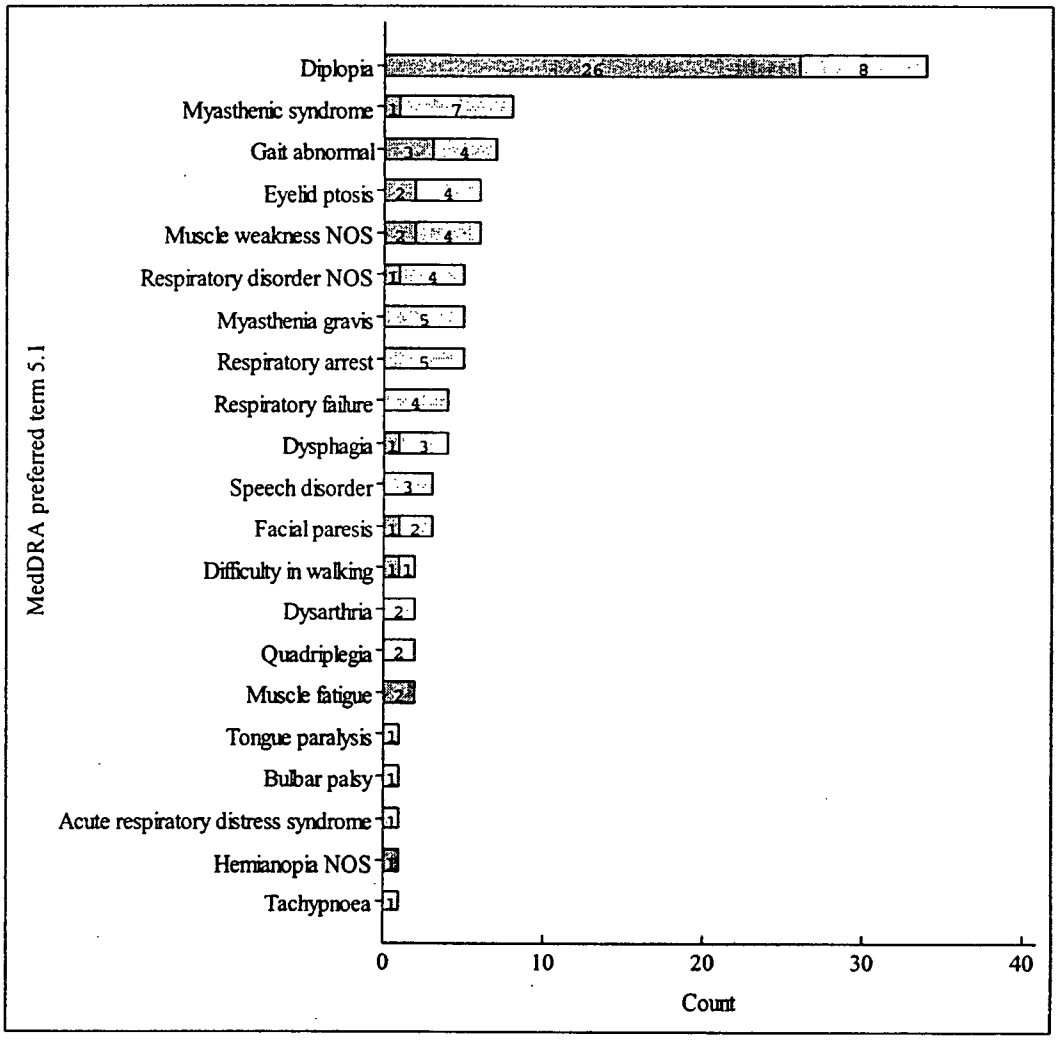
For this review, all MedDRA preferred terms which could possibly be related to myasthenia gravis were reviewed. The full list is contained in **Graph 16**.

Graph 16. All Adverse Events Reviewed for Possible Myasthenia Gravis



The MedWatch forms of all identified preferred terms were reviewed and preferred terms from MedWatch forms which were unlikely to be related to myasthenia gravis were eliminated, leaving the preferred terms in **Graph 17.**

Graph 17. All Adverse Events Likely or Possibly Related to Myasthenia



All MedWatch forms containing one or more of these preferred terms were reviewed in detail. Potential and likely cases of myasthenia gravis were identified. Likely cases were defined as patients with a history of myasthenia gravis who experienced sudden onset of one or more of typical myasthenic symptoms with a temporal relationship to telithromycin-exposure. Typical symptoms included: Muscle weakness/fatigue, dysphagia, dyspnea or respiratory failure/arrest, dysarthria, deglutition disorder, ptosis,

and diplopia. Possible cases include those patients without a diagnosis of myasthenia gravis, but who experienced one more typical symptoms of myasthenia with a temporal relationship to telithromycin exposure.

Of all cases reviewed, there were 13 cases likely to represent myasthenic exacerbations and 6 cases possibly represent myasthenic exacerbations. For 26 cases, they are either unlikely to represent myasthenia or a determination was not possible due to lack of data (**Table 7**). There were no cases in which telithromycin exposure was associated with onset of new myasthenia gravis symptoms at a later time as might be seen with drugs causing induction of the disease.

Medical Officer Comment:
Given that telithromycin is used in short courses, any induction of myasthenia gravis may result in diagnosis at a time far removed from telithromycin exposure. Such a finding of myasthenia induction might be more easily identified in chronic-use drugs such as penicillamine. At this time, there is no evidence that indicates that telithromycin is capable of inducing myasthenia gravis.

Table 7. Likelihood that Symptoms are Related to a Myasthenic Exacerbation for all Reviewed Reports

Unlikely/Unable to Determine	Possibly MG Exacerbation	Likely to be MG Exacerbation
26	6	13

Cases Likely to be Telithromycin-associated Myasthenia Gravis exacerbation

There were a total of 13 cases of patients with a history or new diagnosis of myasthenia gravis who experienced exacerbation of myasthenic symptoms after exposure to telithromycin. All but one of these patients had a history of myasthenia gravis and experienced a worsening of their symptoms after exposure to telithromycin. One patient was diagnosed with myasthenia gravis as a result of the occurrence of symptoms after telithromycin exposure.

Of the 13 cases likely to be telithromycin-associated myasthenic exacerbations, 7 involved significant respiratory symptoms. Six of these patients had respiratory arrest/failure requiring intubation and one had an exacerbation of dyspnea and other myasthenic symptoms which required hospitalization. One patient (200211064EU) who experienced acute respiratory failure 2-3 hours after telithromycin ingestion died.

Potential Cases of Telithromycin-associated Myasthenia Gravis Exacerbation

There were a total of 6 patients who experienced acute onset of myasthenic symptoms after ingestion of telithromycin. However, these patients did not have a previous