M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

RCM#: 2006-793

DATE: November 9, 2006

TO: Advisors and Consultants Staff

FROM: Division of Drug Risk Evaluation
Office of Surveillance and Epidemiology

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

SUBJECT: Safety Synopsis for December 14-15, 2006 Ketek Advisory Committee

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EXECUTIVE SUMMARY

Potential toxicities with regard to cardiac, hepatic, visual, and vascular safety were identified in clinical trials with telithromycin. At various intervals after telithromycin's U.S. approval in April 2004, the Office of Surveillance and Epidemiology's Division of Drug Risk Evaluation (DDRE) has reviewed postmarketing adverse events with telithromycin including hepatoxicity, exacerbation of myasthenia gravis, visual disorders, and loss of consciousness[1,2,3,4] (See appendices).

Telithromycin is approved for acute bacterial sinusitis (ABS), acute exacerbation of chronic bronchitis (AECB) and community acquired pneumonia (CAP). Since this advisory committee has been convened to reassess the benefit/risk calculus of this product, it is important to note recent public discussion regarding acute bacterial sinusitis (ABS) and acute exacerbation of

[1] Memorandum dated June 14, 2005. From Ronald Wassel, Joseph Tonning, Jonathan Levine, Ana Szarfman to Janice Soreth. One-year post approval evaluation of the safety of telithromycin.
[2] Memorandum dated May16, 2006. From Ronald Wassel and Allen Brinker to Janice Soreth. An evaluation of hepatic adverse events associated with telithromycin.
[3] Memorandum dated October 10, 2006. From Melissa. M. Truffa and Allen Brinker to Janice Soreth. Exacerbation of myasthenia gravis.
[4] Memorandum dated October 10, 2006. From Ronald Wassel to Janice Soreth. Update of visual adverse events and loss of consciousness reported with telithromycin from March 1, 2005 through July 7, 2006.

chronic bronchitis (AECB). The limitations of non-inferiority trials to reliably provide substantial evidence of efficacy for self-resolving diseases such as ABS[5,6] and AECB[7,8] were a topic of these deliberations. It is noteworthy that a new drug application for gemifloxacin was withdrawn for ABS indication following the September 12, 2006 FDA advisory meeting[6]. Telithromycin-related risk for a number of clinically significant adverse events has recently been identified from post-marketing data. With uncertainty surrounding the degree of benefit extrapolated from previously performed non-inferiority trials, concern has been raised over the tilt of the benefit/risk balance for telithromycin. This is especially the case for the ABS and AECB indications, which are often self-resolving conditions.

Hepatic adverse events

In controlled phase III clinical trials hepatic dysfunction including increased transaminases and increased liver enzymes (e.g., ALT, AST) were usually asymptomatic and reversible. Hepatitis, with or without jaundice, occurred in 0.07% of patients treated with Ketek and was reversible.

A May 16, 2006 evaluation by DDRE of spontaneous adverse event reports associated with telithromycin received through April 2006 identified a total of 110 unduplicated domestic reports of liver events. DDRE classified **12** of these as cases of telithromycin-associated acute liver failure (ALF) and **23** as cases of telithromycin-associated acute serious liver injury (ASLI). Selected case reports of telithromycin-associated ALF were clinically remarkable.

Notably, amongst the 12 cases of telithromycin-associated ALF identified as of May 16, 2006 the median latency (as time to onset of liver injury) among these cases was 4 days - although one case experienced symptoms shortly after only one (1) dose. Following symptom onset, these cases were marked by a profound degree of hepatic injury. Among cases which provided pertinent laboratory data, the medium reported peak bilirubin level was 18.3 mg/dl; the median reported peak ALT level was 2,489 IU/L. Death was reported as an outcome for four (4) cases and another case underwent orthotopic liver transplant. Three (3) of the other cases were evaluated for orthotopic liver transplant but recovered. In an analysis of the information provided in these cases as well as others with less severe liver injury a number appear to have few confounding factors and occurred in individuals who were generally healthy. Although dermatologic and hematological derangements were not prominently reported (or not prominent enough to be reported), the rapid tempo and severity of injuries and the reported presence of eosinophilia in four cases of ASLI suggest an acute immuno-allergic process.

It is notable that with repeated measurements over time, the telithromycin-associated ALF reporting rate has increased. Through December 2005 and based on 5 cases and 4,084,000 dispensed Rx, the observed prescription-based U.S. reporting rates for telithromycin-associated

[5] FDA Anti-infective Advisory Committee Meeting , October 29, 2003 (http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3997T2.htm)
[6] FDA Anti-infective Advisory Committee Meeting, September 12, 2006 (http://www.fda.gov/ohrms/dockets/ac/cder06.html#AntiInfective)
[7] Infectious Diseases Society of America (IDSA) / PhRma / FDA Working Group Meeting, November 2002 (http://www.fda.gov/cder/present/idsaphrma/default.htm)
[8] FDA/IDSA/International Society of Anti-Infective Pharmacology Working Group Meeting, April 2004 (http://cdernet.cder.fda.gov/ode4/FDA_IDSA_ISAP_Presentations.html)

hepatic failure was 12 per 10 million Rx. This increased to 23 per 10 million Rx through April 06 based on 12 cases and 5,198,000 Rx. This reporting rate remains unchanged (at 23 per 10 million Rx) through September 2006 with a total of 13 cases and 5,650,000 Rx. This rate is 3 to 4-times that of moxifloxacin and gatifloxacin, which had ALF reporting rates of 6.6 and 6 per 10 million Rx, respectively, and also 10-times that of levofloxacin. In addition, the most recent telithromycin-associated ALF reporting rate is higher than those measured for azithromycin and clarithromycin. Reporting rates should not be interpreted as incidence rates although they have been used to support regulatory action in the past in conjunction with other data. In addition to possible differences in actual risk, the observed differences in reporting rates could also be influenced by 1) secular reporting trends and 2) different (longer) study windows.

Based on an analysis of only spontaneous adverse event (AE) reporting data at the time of the May 16, 2006 consult, it was difficult to definitively determine whether the risk for telithromycin associated ALF and ASLI is qualitatively higher than certain other currently marketed antibiotics that have been associated with idiosyncratic liver injury. Nonetheless, the rising trend of reporting rates associated with telithromycin is of concern.

An increased reporting rate for acute liver failure with telithromycin when used for the treatment of acute bacterial exacerbation of chronic bronchitis and acute bacterial sinusitis was of particular concern. Because of differences between patient populations, benefit risk considerations related to treatment and secular trends in spontaneous reporting there is no specific reporting rate threshold that would uniformly prompt automatic cessation of marketing for all drugs. With this background, previous post-marketing spontaneous report data of liver injury strongly influenced the decision to terminate out-patient prescribing of another antimicrobial agent, the fluoroquinolone trovofloxacin, a product with both oral and IV formulations. In the case of trovofloxacin, an ALF reporting rate of 58 per 10 million prescriptions was observed. Despite concerns for stimulated reporting, DDRE recommended that if the telithromycin associated reporting rate of ALF rises to this level, regulatory action other than labeling changes, such as restricted use for only patients who have failed other antibiotic treatments, or possible market withdrawal, should be considered.

Because of the concerns regarding telithromycin's hepatotoxic potential DDRE had recommended the following actions: 1) continued regular monitoring for additional cases and re-evaluation of reporting rates; 2) labeling of events to include a bolded or boxed **WARNING** that contains a description of the clinical characteristics of severe life-threatening telithromycin-associated liver injury and liver failure; and 3) communication of appropriate patient selection for telithromycin use to physicians and patients.

In response to the concern surrounding cases of telithromycin-induced liver injury the sponsor changed the Ketek® labeling (June 2006) to include the following:

Warnings

Hepatoxicity

Acute hepatic failure and severe liver injury, in some cases fatal, have been reported in patients treated with KETEK. These hepatic reactions included fulminant hepatitis and hepatic necrosis leading to liver transplant, and were observed during or immediately after

treatment. In some of these cases, liver injury progressed rapidly and occurred after administration of a few doses of KETEK (see **ADVERSE REACTIONS).**

Physicians and patients should monitor for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness, or hepatomegaly. Patients with signs or symptoms of hepatitis must be advised to discontinue KETEK and immediately seek medical evaluation, which should include liver function tests. (See ADVERSE REACTIONS, PRECAUTIONS, Information to Patients.) If clinical hepatitis or transaminase evaluations combined with other systemic symptoms occur, KETEK should be permanently discontinued.

KETEK must not be re-administered to patients with a previous history of hepatitis and/or jaundice associated with the use of KETEK tablets, or any macrolides antibiotic. (See **CONTRAINDICATIONS.)**

Exacerbation of myasthenia gravis

An October 2006 review was conducted by DDRE to document exacerbation of myasthenia gravis (MG) in association with telithromycin, prompted in part by four spontaneously reported fatal cases, despite warnings in the product label. The labeling with regard to exacerbation of myasthenia gravis was recently changed as of June 2006 to include reports of fatal cases. In addition to other changes, the following text was advanced from the body of text within the WARNINGS section of the label to the first, or introductory, sentence under a new, discrete section called, "Exacerbation of myasthenia gravis."

"Telithromycin should not be used in patients with myasthenia gravis unless no other therapeutic alternatives are available"

Labeling changes were advanced with a Dear Healthcare Professional letter in addition and other communication avenues, including the FDA's MedWatch program.

At the time of the October 2006 DDRE review, telithromycin was associated with 15 cases of exacerbation of myasthenia gravis. Although telithromycin is the most recently marketed of selected antibiotics, it is currently associated with more cases of exacerbation of myasthenia gravis than all eight comparator agents combined (n=7). Furthermore, at least 6 cases of telithromycin associated MG have resulted in intubation. A formal quantitative (i.e. reporting rates) analysis was not conducted. These data nonetheless suggest that exacerbation of MG may be more frequent with telithromycin than similar antibiotics.

To further address concerns which prompted the June 2006 measures other strategies should also be considered 1) a Medication Guide, 2) to facilitate the Medication Guide unit-of-use packaging with printing specific to myasthenia gravis, and/or 3) the addition of the statement "Telithromycin should not be used in patients with myasthenia gravis" to CONTRAINDICATIONS section of the label.

Visual Disorders/Loss of Consciousness

Visual adverse events including blurred vision, diplopia, or difficulty focusing were identified in controlled phase III clinical trials. Telithromycin may cause these visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation. Most events were mild to moderate; however, severe cases have been reported causing some patients to discontinue therapy due to these events. Visual adverse events were reported as occurring after any dose during treatment, but most visual adverse events (65%) occurred following the first or second dose. Current labeling indicates that patients should be cautioned about the potential effects of these visual disturbances on driving a vehicle, operating machinery or engaging in other potentially hazardous activities.

A one-year post-approval safety review of telithromycin (June 2005) concluded that visual adverse event in the postmarketing cases were consistent with those seen prior to approval in worldwide experience as described in the approved labeling from June 2005. However, loss of consciousness was considered inadequately labeled. It appeared that the loss of consciousness is related to a vagal syndrome as nine cases noted concomitant bradycardia or conditions possibly related to increased vagal tone. As there is a high number of reports of loss of consciousness that can potentially lead to serious consequences such as road traffic accidents while driving (as seen in the cases received for that event), DDRE agreed with the Medical Officer's recommendation to include a statement about loss of consciousness in the **PRECAUTIONS** section. It was also recommended that consideration should be given to conducting clinical studies to elucidate the scope of these effects and the pathophysiology behind them (e.g., anti-cholinergic, cardiac conduction, and circulatory effects).

In response to these recommendations the sponsor changed the Ketek® labeling (November 2005) to include the following under **PRECAUTIONS**: *There have been postmarketing adverse event reports of syncope usually associated with vagal syndrome.* Loss of consciousness was also added to the statement in the Ketek® label cautioning patients about these adverse effects on driving a vehicle or operating machinery.

In summary, **PRECAUTIONS** in the current labeling contains the following:

KETEK may cause visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation. Visual disturbances included blurred vision, difficulty focusing, and diplopia. Most events were mild to moderate; however, severe cases have been reported. Patients should be cautioned about the potential effects of these visual disturbances on driving a vehicle, operating machinery or engaging in other potentially hazardous activities.

In view of concern surrounding safety events in clinical trials and in postmarketing reports, the potential seriousness of these effects (i.e. road traffic accidents) to patients receiving telithromycin, and a potential data mining signal, an October 2006 review was undertaken by DDRE to assess the cases of visual adverse events and loss of consciousness reported with telithromycin since March 2005. During the 16 months this review encompassed (3/1/05 to 7/7/06), an additional 276 reports of visual adverse events and 85 reports of disturbances in consciousness were retrieved, supplementing 114 reports of visual events and 52 reports of

disturbances in consciousness identified in the previous review, (4/1/04 to 3/11/05) (all of these figures are crude counts). In identifying cases that were judged serious by outcome, a total of 89 unduplicated cases were found for vision disorders and 61 unduplicated cases were found for disturbances in consciousness. Of these, 71 cases of visual events and 23 cases of disturbances in consciousness were considered possibly related to telithromycin. None of the cases resulted in the death of the patient, and three cases occurred while the patient was driving (one of blurred vision and two of loss of consciousness), one of which resulted in an accident killing a pedestrian.

Clinical characteristics of the 23 cases involving loss of consciousness include:

14 domestic and 9 foreign cases
9 females and 12 males (2 unknown)

•age- range from 18 to 78 years (n=16)
median 46 years; mean 46.9 years

•onset-
within 2 hours (n=7)
first day of therapy (n=5)
days 3 to 5 of therapy (n=4)
one day after completion of therapy (n=1)

•outcomes-
8 patients were hospitalized (7) or presented to the emergency room (1)
2 cases occurred while the patient was driving (in one case no accident occurred; in the other case an accident occurred in which a pedestrian was killed and the patient was injured)
1 case resulted in a disability as the patient fell and sustained a vertebral compression
12 cases were reported as other serious medical events

A common explanation for the events, such as a vagal reaction, could not be discerned. One case reported hypoglycemia temporally associated during telithromycin treatment (12 unduplicated cases of hypoglycemia searched with telithromycin are in AERS; a causal effect is not clear), and one case reported the loss of consciousness with torsade de pointes.

In view of the potential seriousness of these events with other identified serious adverse events (hepatic, exacerbation of myasthenia gravis), DDRE has recommended that the sponsor develop a plan to inform and educate prescribers regarding these risks. Also, consideration should be given for the development of a Medication Guide (MedGuide) to be provided to patients when telithromycin is dispensed.

APPENDICES

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OFFICE OF DRUG SAFETY

PID# D050035

DATE: June 14, 2005

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TO: Janice Soreth, M.D., Director
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SUBJECT: Consult:
An evaluation of the safety profile of telithromycin, a ketolide antibiotic approved April 2004. Of particular concern are the following adverse events: visual, car accidents, liver events, and syncope/loss of consciousness.

1.0 EXECUTIVE SUMMARY

A request was received from HFD-520 to evaluate reports in the Adverse Event Reporting System (AERS) of visual disturbances, automobile accidents, liver events, and syncope/loss of consciousness associated with telithromycin since its approval in April 2004. AERS was searched on 3/11/2005, which retrieved 46 cases of visual adverse events, 39 cases of loss of consciousness or possible loss of consciousness, 28 cases of hepatic adverse events and 4 cases of a road traffic accident (with a total of 421 for all adverse event reports for telithromycin).

Visual adverse events—these cases are consistent with those seen prior to approval in worldwide experience and as described in the current labeling. Therefore, there are no recommendations for a major change in labeling for these events.

Hepatic adverse events—these cases are consistent with those seen prior to approval in worldwide experience and as described in the current labeling. Therefore, there are no recommendations for a major change in labeling for these events; however, we recommend including a statement in the **PRECAUTIONS** section, following the current statement about hepatic dysfunction, that the hepatic dysfunction may be severe (as is currently stated in the **Post-Marketing Adverse Event Reports** section of the **Adverse Reactions** section).

Loss of consciousness—loss of consciousness is not adequately described in the labeling, but the sponsor proposes to add a statement under Nervous System in the **Post-Marketing Adverse Event Reports** section of the **Adverse Reactions** section noting rare reports of syncope usually associated with vagal syndrome. It appears that the loss of consciousness is related to a vagal syndrome as nine cases noted concomitant bradycardia or conditions possibly related to increased vagal tone. As there is a high number of reports of loss of consciousness that can potentially lead to serious consequences such as road traffic accidents while driving (as seen in the cases received for that event), we agree with the Medical Officer's recommendation to include a statement about loss of consciousness in the **PRECAUTIONS** section. Consideration should be given to conducting clinical studies to elucidate the scope of these effects and the pathophysiology behind them (e.g., anti-cholinergic, cardiac conduction, and circulatory effects).

Road traffic accidents—these cases are a consequence of loss of consciousness or visual abnormalities associated with telithromycin. Patient information in the labeling and conveyed to the patient at the time a prescription is filled should emphasize the appropriate cautions concerning the use of telithromycin while driving a vehicle, operating machinery or engaging in other potentially hazardous activities.

A data mining analysis was also performed to contextualize the potential toxicity of telithromycin (Ketek®), specifically with regard to visual adverse events, automobile accidents, hepatic adverse events, and syncope/loss of consciousness. The algorithm used for this analysis was the Multi-item Gamma Poisson Shrinker (MGPS) which calculates scores of drug-event associations from drug safety databases. Two databases were analyzed for this consult: FDA's

Adverse Events Reporting System (AERS) and the World Health Organization's Uppsala Monitoring Centre (WHO-UMC) database.

From the AERS data, telithromycin displayed the following signals (EB05 ≥ 2 by decreasing EB05) for "loss of consciousness," "vision blurred," "malaise," and "drug interaction" (Figure 1, Table 3). In the WHO-UMS database, telithromycin displayed signals (EB05 ≥ 2 by decreasing EB05) for "accommodation abnormal," "vision abnormal," "dizziness," and "parosmia" (Figure 2, Table 4).[9]

2.0 INTRODUCTION

Telithromycin (Ketek®, NDA# 21-144) is the first of a new class of antimicrobials called ketolides that was approved in April 2004 for the oral treatment of acute bacterial sinusitis, acute exacerbation of chronic bronchitis and community–acquired pneumonia.

Visual adverse events, most often blurred vision, have represented the most commonly reported post-marketing events for telithromycin since approval in Europe and South America (July 2001). As stated in the Medical Officer's NDA review, these events comprised approximately one-third of all patients with a reported post-marketing adverse event. Although the pathophysiology of the visual adverse events is poorly understood, data from Phase 1 studies, Phase 3 studies, and post-marketing adverse event reports (foreign database) are consistent with a disorder of accommodation as the primary disturbance.

Other adverse events of particular interest at the time of approval included QTc prolongation, exacerbations of myasthenia gravis, and hepatic dysfunction. Reports of loss of consciousness and automobile accidents associated with the use of telithromycin that have been submitted to the agency since approval have generated concern, which, with the sponsor's ongoing development plans for use of the drug in children and adolescents, have prompted this review.

A request was received from HFD-520 to evaluate reports in the Adverse Event Reporting System (AERS) of visual disturbances, automobile accidents, liver events, and syncope/loss of consciousness associated with telithromycin since its approval in April 2004.

3.0 CURRENT LABELING

Labeling as it pertains to the adverse events of interest:

In the **PRECAUTIONS, General** section:

[9] Scores for these data mining associations do not necessarily indicate causality or significance of risk. Because the data analyzed were from spontaneously submitted adverse event reports to the AERS and WHO-UMC databases, the exact degree of potential associations for these events cannot be elicited from this analysis alone. Further thorough individual case review and pharmacoepidemiological studies are also recommended.

KETEK may cause visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation. Visual disturbances included blurred vision, difficulty focusing, and diplopia. Most events were mild to moderate; however, severe cases have been reported. Patients should be cautioned about the potential effects of these visual disturbances on driving a vehicle, operating machinery or engaging in other potentially hazardous activities. (See ADVERSE REACTIONS, CLINICAL STUDIES.)

Hepatic dysfunction, including increased liver enzymes and hepatitis, with or without jaundice, has been reported with the use of KETEK. These events were generally reversible.

Caution should be used in patients with a previous history of hepatitis/jaundice associated with the use of KETEK. (See ADVERSE REACTIONS, Liver and biliary system.)

In the **PRECAUTIONS, Information for patients** section:

KETEK may cause problems with vision particularly when looking quickly between objects close by and objects far away. These events include blurred vision, difficulty focusing, and objects looking doubled. Most events were mild to moderate; however, severe cases have been reported. Problems with vision were reported as having occurred after any dose during treatment, but most occurred following the first or second dose. These problems lasted several hours and in some patients came back with the next dose. (See PRECAUTIONS, General and ADVERSE REACTIONS.)

If visual difficulties occur:

- patients should avoid driving a motor vehicle, operating heavy machinery, or engaging in otherwise hazardous activities.
- avoiding quick changes in viewing between objects in the distance and objects nearby may help to decrease the effects of these visual difficulties.
- patients should contact their physician if these visual difficulties interfere with their daily activities.

Patients should also be advised:

- that KETEK has the potential to produce changes in the electrocardiogram (QTc interval prolongation) and that they should report any fainting occurring during drug treatment.
- to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as uncorrected hypokalemia, or clinically significant bradycardia.

In the **ADVERSE REACTIONS** section:

Liver and biliary system: abnormal liver function tests: increased transaminases, increased liver enzymes (e.g., ALT, AST) were usually asymptomatic and reversible. ALT elevations above 3 times the upper limit of normal were observed in 1.6%, and 1.7% of patients treated with KETEK and comparators, respectively. Hepatitis, with or without jaundice, occurred in 0.07% of patients treated with KETEK, and was reversible. (See PRECAUTIONS, General.)

Special senses: Visual adverse events most often included blurred vision, diplopia, or difficulty focusing. Most events were mild to moderate; however, severe cases have been reported. Some patients discontinued therapy due to these adverse events. Visual adverse events were reported as having occurred after any dose during treatment, but most visual adverse events (65%) occurred following the first or second dose. Visual events lasted several hours and recurred upon subsequent dosing in some patients. For patients who continued treatment, some resolved on therapy while others continued to have symptoms until they completed the full course of treatment. (See PRECAUTIONS, General and PRECAUTIONS, Information for patients.)

Other possibly related clinically-relevant events occurring in <0.2% of patients treated with KETEK from the controlled Phase III studies included: anxiety, bradycardia, eczema, elevated blood bilirubin, erythema multiforme, flushing, hypotension, increased blood alkaline phosphatase, increased eosinophil count, paresthesia, pruritus, urticaria.

Post-Marketing Adverse Event Reports:
In addition to adverse events reported from clinical trials, the following events have been reported from worldwide post-marketing experience with KETEK.
Liver and biliary system: Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with telithromycin. This hepatic dysfunction may be severe and is usually reversible.
Nervous system: rare reports of syncope usually associated with vagal syndrome.

4.0 SEARCH TYPE AND DATE

AERS was searched on 3/11/2005.

5.0 SEARCH CRITERIA

Telithromycin was searched under four different adverse event fields.

- *Visual adverse events*

  MedDRA term: Vision Disorders (HLGT)

Note: This MedDRA term was chosen to capture a wide array of visual adverse events as different preferred terms may be 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. However, the limitation in searching over a wide group of visual adverse events is that it does not account for related pathology among the different events.

The HLGT Vision Disorders is one of the highest level group terms within the Eye Disorders SOC. This group contains the HLTs related to amblyopia, blindness, color blindness, partial vision loss (under which the PT Vision blurred appears), refractive and accommodative disorders, visual color distortion, visual disorders NEC (which includes such terms as diplopia, halo vision, optic nerve disorder, and visual disturbance), visual field disorders, and visual pathway disorders.

- *Loss of consciousness*

  MedDRA term: Disturbances in consciousness NEC (HLT)

  Note: The HLT Disturbances in consciousness NEC contains several PTs including Consciousness fluctuating, Depressed level of consciousness, Loss of consciousness, Syncope, and Syncope vasovagal.

- *Hepatic adverse events*

  MedDRA terms: Hepatic and hepatobiliary disorders (HLGT)
  Hepatobiliary investigations (HLGT)
  Liver transplant (PT)

  Note: The HLGT Hepatobiliary investigations was included to capture any cases coded with any hepatobiliary histopathology and imaging procedures, or liver function tests. The PT Liver transplant was included to capture any cases of liver transplants that may not have been coded as hepatic failure. This PT is under the Surgical and Medical Procedures SOC and would not be captured under the hepatic disorders group.

- *Automobile accidents*

  MedDRA term: Road traffic accident (PT)

6.0 SEARCH RESULTS

As of 3/11/2005 there were a total of 421 adverse event reports for telithromycin in AERS.

6.1 *Visual adverse events*

There were a total of 50 unduplicated cases in AERS as of 3/11/2005. Four of these cases were excluded as not associated with telithromycin (no temporal relation, a case of benign intracranial hypertension in a young female with a negative dechallenge).

Demographics (N=46)

Age (N=36)	Range—13 to 88 years; Median—39.5 years; Mean—40.3 years
Gender (N=44)	Female—34; Male—10
Source	Domestic—27; Foreign—19

The cases of visual adverse events were consistent with those reported in the original NDA and as described in the current product labeling (blurred vision, difficulty focusing, diplopia), therefore, no further analysis was performed.

6.2 *Loss of consciousness*

There were a total of 55 unduplicated cases in AERS as of 3/11/2005. Sixteen cases were excluded as not associated with telithromycin (primarily because of a poor temporal relationship or manifestations of sepsis). Of the 39 remaining cases, 31 involved an actual loss of consciousness, while 8 were included as possible because they described events such as "almost passed out," "vagal malaise," "feeling of sinking," or "consciousness disturbed."

Demographics (N=39)

Age (N=37)	Range—23 to 97 years; Median—70 years; Mean—67.2 years
Gender	Female—22; Male—17
Source	Domestic—9; Foreign—30 (Japan—18; France—10)
Dose (N=32)	600 mg daily—18; 800 mg daily—14
Onset (N=34)	Range—Day 1 to Day 8; Median—Between Day 1 and Day 2; Mean—2.1 days (17 instances occurred on Day 1)
Outcome (N=37)	Recovered—19; Hospitalized—11; Death—4; Road traffic accident—3

Representative case

ISR # 4443354-2; Case # 4204851; Mfr. Control # 200416329US (USA)—A 62–year–old female, who is a pediatrician, initiated telithromycin 800 mg once daily on 8/20/04 for bronchitis. Relevant medical history includes hypertension and lupus, for which she is taking diltiazem and hydrochloroquine. On 8/23/04, while working, the patient experienced three syncopal episodes of sudden onset witnessed by the office staff. An electrocardiogram was performed within five minutes of the episodes revealing bradycardia with a heart rate in the 40s. The patient was taken to the hospital for observation and recovered on an unspecified date. The patient does not have a history of heart failure, ventricular arrhythmia or loss of consciousness. The patient had not been diagnosed with an acute myocardial infarction within one week of the event. The patient

has no personal history of bradycardia, although the patient's mother was reported to have a history of bradycardia.

An additional nine domestic cases of loss of consciousness are summarized in Table 1.

Table 1. SUMMARY OF ADDITIONAL DOMESTIC CASES OF LOSS OF CONSCIOUSNESS

	MFR #	Age	Sex	Outcome	Dose	Time to onset	Event	Concomitant medications	Medical history	Comments
1	200419054US	?	F	Hospitalized	?	?	Passed out	None reported	None reported	
2	200417864US	?	F	Recovered	?	1st day	Passed out every time she stood up	None reported	None reported	
3	200419105US	23	M	?	?	?	Passed out	Cetirizine	None reported	Reported to have a Wenckebach arrhythmia
4	200417638US	34	F	Emergency room; Recovered	800 mg daily	4th day	Blurred vision, tremors, weakness, dizziness, nausea, headache, became nearly unconscious	Levothyroxine Fluoxetine Ortho Tri-Cyclen	Hypothyroidism Depression Hypoglycemia	Patient indicated she was pregnant at time of event
5	200510470US	45	F	Emergency room; Recovered	800 mg daily	1st day	Visual disturbance; not able to stay awake and fell asleep for 4 days; would pass out; mental status changes	Diltiazem Furosemide Potassium Clonazepam Zolpidem Loperamide Acetaminophen	Mitral valve prolapse Insomnia Restless leg syndrome Hypertension	
6	200419892US	48	M	Hospitalized	800 mg daily	40 minutes after 1st dose	Sudden shortness of breath with loss of consciousness	Mestinon Valsartan Diazepam Singulair Serevent Paroxetine Prednisone Aspirin	Myasthenia gravis	Experienced respiratory arrest requiring ventilator support
7	CTU 240012 Direct	51	F	?	"2 pills per day"	3rd day	Almost passed out	None reported	None reported	
8	200419142US	77	M	Hospitalized	?	3rd day	Suddenly lost consciousness	Rosuvastatin Chlorpheniramine Finasteride	None reported	Noted to have quadrigeminy by paramedics; no evidence of ischemia and normal LV function

6.3 *Hepatic adverse events*

There were a total of 39 unduplicated cases of hepatic adverse events in AERS as of 3/11/2005. Eleven cases were excluded as not associated with telithromycin (other drug therapy as a more likely cause, obstructive jaundice, viral etiology, sepsis with multi-organ failure, temporal relationship undetermined). Of the 28 remaining cases, 13 described a hepatic event (hepatitis [9], cholestatic jaundice [1], hepatocellular necrosis [1], hepatic failure/shutdown [2]), while 15 described increases in liver function tests.

Demographics (N=28)

Age (N=26)	Range—17 to 85 years; Median—49.5 years; Mean—50.0 years
Gender	Female—15; Male—13
Source	Domestic—10; Foreign—18 (Japan—12)
Dose (N=20)	300 mg daily—1; 400 mg daily—3; 600 mg daily—9; 800 mg daily—7 Three reports noted duration of therapy of 15 days, 22 days and 5 weeks
Onset (N=18)	During therapy: Range—Day 1 to Day 5; Median—Day 2; Mean—2.6 days (5 instances occurred on Day 2) After therapy completed: Range—3 days to 5 weeks; Median—1 week; Mean—10.4 days
Outcome (N=22)	Hospitalized—16 (of which 10 were noted to have recovered); Recovered (no hospitalization)—3; Death—3 (2 unrelated)

The cases of hepatic dysfunction were consistent with those described in the current product labeling (increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, which may be severe and is usually reversible).

In the three cases in which the patient died, two were the result of other causes (endocarditis with a brain abscess; infection and dehydration leading to circulatory failure). The case in which hepatic failure led to death is described below.

> ISR # 4579921-5; Case # 5744493; Direct report # CTU 240274 (USA)—A 26–year–old Hispanic male developed hepatic and renal failure and died about 3 days after presenting to the ER with symptoms of nausea, vomiting and fatigue. It was known he had taken Ketek 400 mg BID for about 5 days previous to admission, but the exact dates are unknown. He was found to have elevated bilirubin, LFTs and creatinine (bili 12, AST and ALT in the 2000 to 3000 range, alk phos 242, creatinine about 3). He was admitted to the ICU and started to vomit blood. He was intubated and an upper endoscopy was performed, which did not show any bleeding. He was given large amounts of IV fluids to rehydrate. He required pressors to support his BP. He had worsening respiratory failure, acidosis and arrhythmias. He required dialysis and eventually died of these complications. Autopsy report stated he had massive hepatic necrosis with lymphoplasmacytic response, likely an immune–mediated inflammatory response generally caused by a toxic exposure. The patient only spoke Spanish and admitted through a translator that he had taken nothing else other than some Tylenol (an acetaminophen level was 7.7 [time not stated] and he was treated for acetaminophen

toxicity). He admitted to some alcohol use (8 beers over the previous two weeks). In a follow-up conversation with the reporter, no additional information was obtained to provide further insight into this case.

6.4 *Road traffic accidents*

As of 3/11/2005 there were five reports in AERS of road traffic accidents associated with the use of telithromycin. One of these reports was not an actual case but was an inquiry by a physician to the company to ask about a rumor they had heard about a patient involved in a motor vehicle accident during a telithromycin clinical trial, which was unfounded. In the other four cases, three were from Japan and one was from the United States. The Japanese cases (a 54–year–old male, a 63–year–old female, a 77–year–old male) all involved reports of loss of consciousness leading to an accident (as noted in the demographics for *Loss of consciousness*, above). The US case involved a female in her 40s who experienced a visual disturbance and "totaled her car."

7.0 USAGE DATA

Table 2. Projected Number of Total Prescriptions Dispensed by Retail Pharmacies in the US for Telithromycin Distributed by Calendar Month -- June through December 2004

(Factored by 1000; **DO NOT** ADD THREE 0's**)**

JNE/04	JLY/04	AUG/04	SEP/04	OCT/04	NOV/04	DEC/04	Total 2004
4	602	63,766	121,495	172,254	215,855	285,720	859,696

SOURCE: IMS HEALTH; National Prescription Audit (NPA) Plus™, On-line

**NOTE: DATA NOT TO BE SHARED OUTSIDE OF FDA OR WITH non-FDA STAFF WITHOUT PRIOR CLEARANCE BY IMS HEALTH. Clearance must be requested from IMS HEALTH through the FDA Office of Drug Safety.

NPA Plus measures the retail dispensing of prescriptions, or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. These retail pharmacies include chain, independent, food store, mail order, discount houses, and mass merchandiser pharmacies, as well as nursing home (long-term care) pharmacy providers. Information on the specialty of the prescribing physician can also be collected, except for in the long-term care and mail-order settings.

The number of dispensed prescriptions is obtained from a sample of approximately 22,000 pharmacies throughout the U.S. and projected nationally. The pharmacies in the database account for approximately 40% of all pharmacy stores and represent approximately 45% of prescription coverage in the U.S.

8.0 DATA MINING ANALYSIS

8.1 *Methodology*

The algorithm used for the data mining analysis was the Multi-Item Gamma Poisson Shrinker (MGPS).[10,11] This algorithm analyzes the records contained in large post-marketing drug safety databases and then quantifies potential drug-event associations by producing a ranked set of values or scores which indicate varying strengths of reporting relationships between drugs and events. These scores, denoted the Empirical Bayes Geometric Mean (EBGM), provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs in the database being analyzed. MGPS also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95 respectively.

An examination of the relative frequency of reports for telithromycin was conducted by applying the MGPS algorithm to FDA's AERS database (run 564 on the cdsdmpilot server)[12] and the World Health Organization's Uppsala Monitoring Centre (WHO-UMC) database (output kindly provided by Lincoln Technologies). The WHO-UMC database was analyzed in addition to AERS, because AERS contained only 174 total events for telithromycin as of October 2004. The WHO-UMC database contained 276 total reports for this drug.

8.2 *Results*

EBGM scores for event codes associated with telithromycin are presented in Figure 1 and Table 3 for the AERS data and in Figure 2 and Table 4 for the WHO-UMC data. Number of cases for each DEC is also presented in parenthesis. **Strong** signals (EB05 $\geq$ 2) and **weak** signals (1 < EB05 <2) appear in both databases. Only those drug-event combinations (DECs) with an EB05 > 1 are presented in this analysis.

In the AERS data (Figure 1, Table 3), DECs with an EB05 > 2 are seen for "loss of consciousness," "vision blurred," "malaise," "viral infection," and "drug interaction." Numerous weaker signals (1 < EB05 < 2) are also seen, including those for "blood lactate dehydrogenase increased," "epistaxis," "purpura," "international normalized ratio increased," "hepatitis cholestatic," "hepatitis," "hepatic necrosis," "disturbance in attention," and "alanine aminotransferase increased." Weak signals are also seen for "arrhythmia," "bradycardia," "angina pectoris," "syncope," "congestive cardiomyopathy," "shock," "syncope vasovagal," "bundle branch block right," "circulatory collapse," and "tachycardia."

A total of 15 cases of drug interactions were reported with telithromycin, . Of note is that 5 cases occurred between telithromycin and warfarin (prothromin time increased) in patients 60-75

10 DuMouchel W, Pregibon D. Empirical bayes screening for multi-item associations. Proceedings of the conference on knowledge discovery and data; 2001 Aug 26-29; San Diego (CA): ACM Press: 67-76.

11 Szarfman A, Machado SG, O'Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392.

12 The version of AERS used in this analysis is the CBAERS version. The CBAERS database is a reformatted, integrated (de-normalized) version of the AERS database containing wider tables with more complete data in each table, facilitating systematic retrieval and analyses.

years of age (one case with hemoptysis). There was one case of drug-drug interaction between simvastatin and telithromycin describing myositis, and another case between telithromycin and tacrolimus describing increased tacrolimus levels.

In the WHO-UMC data (Figure 2, Table 4), DECs with an EB05 > 2 are seen for "accommodation abnormal," "vision abnormal," "dizziness," and "parosmia." Numerous weaker signals (1 < EB05 < 2) are also seen, including those for "circulatory failure," "hepatic enzymes increased," and "diplopia."

Table 3. Telithromycin Data Mining Scores and Number of Cases (N) for Preferred Terms, CBAERS Database Stratified by Gender, Age, and Receipt Year, October 2004

Event Code (MedDRA PT)	N	EB05	EBGM	EB95
Loss of consciousness	15	2.656	4.071	6.034
Vision blurred	11	2.598	4.275	6.739
Malaise	13	2.47	3.903	5.932
Viral infection	6	2.089	4.125	7.873
Drug interaction	14	2.039	3.168	4.745
Dermatitis medicamentosa	5	1.824	3.813	7.594
Cough	9	1.783	3.068	5.001
Blood lactate dehydrogenase increased	7	1.761	3.24	5.576
Epistaxis	6	1.741	3.353	5.993
Arrhythmia	6	1.648	3.169	5.648
Bradycardia	7	1.611	2.963	5.092
Acute tonsillitis	3	1.569	12.306	125.659
Bronchitis	5	1.54	3.127	5.827
Blood pressure increased	8	1.487	2.638	4.403
Nephritis interstitial	4	1.486	3.293	6.672
Purpura	4	1.411	3.086	6.115
International normalised ratio increased	6	1.41	2.707	4.812
White blood cell count increased	6	1.371	2.631	4.679
Blood creatine phosphokinase increased	6	1.257	2.413	4.287
Cryptogenic organizing pneumonia	3	1.244	3.259	10.338
Paresis	3	1.233	3.17	7.988
Angina pectoris	4	1.229	2.671	5.229
Syncope	6	1.218	2.338	4.154
Inflammation	4	1.197	2.6	5.086
Generalised erythema	3	1.189	2.949	6.495
Congestive cardiomyopathy	3	1.188	2.942	6.467
Bronchitis acute	3	1.184	2.921	6.399
Emphysema	3	1.155	2.802	6.003
Shock	4	1.149	2.495	4.876
Syncope vasovagal	3	1.148	2.78	5.942
Bundle branch block right	3	1.132	2.728	5.796
Pyrexia	12	1.132	1.818	2.8

Hepatitis cholestatic	3	1.12	2.694	5.709
Eosinophil count increased	3	1.106	2.655	5.613
Hepatitis	4	1.08	2.344	4.579
Hepatic necrosis	3	1.078	2.578	5.431
Thrombocytopenia	6	1.066	2.047	3.637
Circulatory collapse	4	1.054	2.288	4.469
Disturbance in attention	4	1.031	2.237	4.368
Muscular weakness	4	1.03	2.235	4.364
Tachycardia	5	1.025	2.075	3.843
Alanine aminotransferase increased	7	1.01	1.856	3.188
Leukopenia	4	1	2.17	4.234

Table 4. Telithromycin Data Mining Scores and Number of Cases (N) for Preferred Terms, WHO-UMC Database Stratified by Gender, Age, and Receipt Year

Event Code (MedDRA PT)	N	EB05	EBGM	EB95
Accommodation abnormal	13	43.399	70.554	109.695
Vision abnormal	68	12.521	15.359	18.683
Dizziness	34	2.162	2.874	3.766
Parosmia	6	2.134	9.197	24.639
Diarrhoea	24	1.87	2.62	3.596
Circulatory failure	9	1.778	3.313	7.474
Taste perversion	7	1.441	2.748	5.816
Glossitis	5	1.437	4.623	19.044
Vertigo	8	1.418	2.521	4.371
Hepatic enzymes increased	9	1.417	2.426	3.995
Vomiting	21	1.311	1.875	2.617
Nausea	27	1.285	1.764	2.374
Diplopia	5	1.251	2.888	10.482
Face oedema	11	1.194	1.939	3.015
Abdominal pain	17	1.131	1.68	2.422

8.3 *Discussion*

An EBGM of 1 indicates that the particular DEC occurs together as often as would be expected under the assumption of randomly paired drug and event reports (independence assumption). Using an EB05 >1 as a signal definition corresponds to being 95% confident that the DEC in question occurs at least at a higher-than-expected rate.

An EB05 value of greater than 2.0 ensures with a high probability that the particular DEC occurs in these patient data records at least twice as often as expected under the independence assumption. Using an EB05 ≥2 as a signal definition indicates 95% confidence that the DEC is occurring at least at twice the expected rate when considering all other drugs and events in the database.

The higher the EB05 score, the higher the association between the drug and event, as reported in the database being analyzed. Note that this "association" is a factor of the relative reporting of various events among all drugs in the database and that it does not automatically imply causality. These signal scores provide an indication of the potential toxicity of telithromycin; however, the exact degree of this potential toxicity cannot be elicited from the data mining analyses of WHO and AERS data alone. Signal scores indicate higher-than-expected drug-event reporting associations, not necessarily causality or the degree of risk. Conversely, absence of an increased signal score does not rule out a potential drug-event association.

8.4 *Conclusion*

Because the AERS data and the WHO-UMC databases contain different reports of adverse events[13], the data mining analysis of each of these databases will generate somewhat different results. However, some interesting patterns in both databases were manifested:

Visual Adverse Events: Signals (EB05 >2) are seen for visual adverse events in both the AERS and WHO-UMC databases. In AERS, a signal is seen for the term "vision blurred" (EB05 = 2.6 In the WHO-UMC data, strong signals are seen for the terms "accommodation abnormal" (EB05 = 43.4 and "vision abnormal" (EB05 = 12.52).

Hepatic Adverse Events: In AERS, weak signals (1 < EB05 < 2) are seen for "blood lactate dehydrogenase increased," "international normalized ratio increased," "hepatitis cholestatic," "hepatitis," "hepatic necrosis," and "alanine aminotransferase increased." In the WHO-UMC data, a weak signal is seen for "hepatic enzymes increased."

Syncope/Loss of Consciousness: In the AERS data, weak signals are seen for "syncope," "shock," "syncope vasovagal," and "circulatory collapse." Weak signals are also seen in AERS for several cardiac events, including "arrhythmia," "bradycardia," "angina pectoris," "congestive cardiomyopathy," "bundle branch block right," and "tachycardia." In the WHO-UMC data, a weak signal is seen for the term "circulatory failure."

In addition MGPS identified signals of drug-drug interaction in the cbaers database that requires close and continuous monitoring:

9.0 SUMMARY AND RECOMMENDATIONS

In reviewing the cases of visual adverse events, hepatic adverse events, loss of consciousness and road traffic accidents associated with telithromycin reported to the agency since the drug's approval in April 2004, it appears the cases of visual and hepatic adverse events are consistent with those seen prior to approval in worldwide experience and as described in the current labeling. The data mining analysis of AERS and WHO-UMC databases demonstrated signals for various visual adverse events, hepatic adverse events, and syncope/loss of consciousness associated with telithromycin (see Sections 8.2 and 8.4).

[13] Approximately 50 percent of the reports in the WHO-UMC data are AERS reports submitted to WHO by the FDA.

Therefore, there are no recommendations for a major change in labeling for these events as they are adequately described in the **PRECAUTIONS** section. However, we recommend including a statement in the **PRECAUTIONS** section, following the current statement about hepatic dysfunction, that the hepatic dysfunction may be severe (as is currently stated in the **Post-Marketing Adverse Event Reports** section of the **Adverse Reactions** section).

Loss of consciousness is not adequately described in the labeling, but the sponsor proposes to add a statement under Nervous System in the **Post-Marketing Adverse Event Reports** section of the **Adverse Reactions** section noting rare reports of syncope usually associated with vagal syndrome. It appears that the loss of consciousness is related to a vagal syndrome as nine cases noted concomitant bradycardia or conditions possibly related to increased vagal tone. As there is a high number of reports of this event that can potentially lead to serious consequences such as road traffic accidents while driving (as seen in the cases received for that event), we agree with the Medical Officer's recommendation to include a statement about loss of consciousness in the **PRECAUTIONS** section with increased emphasis on patient information concerning the use of telithromycin while driving a vehicle, operating machinery or engaging in other potentially hazardous activities. This information should also be included in the **Information for Patients** section so that it is included in the patient handouts when a prescription is dispensed. Consideration should be given to conducting clinical studies to elucidate the scope of these effects and the pathophysiology behind them (e.g., anti-cholinergic, cardiac conduction, and circulatory effects).

We will continue to monitor these events for a change in frequency or character, which may necessitate further refinement of the product label.

_____

Ronald Wassel, Pharm.D.
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Concur:

_____

Melissa Truffa, R.Ph.
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cc:
NDA # 21-144
HFD-520 Division File / Alexander / Cooper / Moledina / Milstein
HFD-430 Avigan / Truffa / Kang / Chron / Drug

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

PID# D050633

DATE: May 16, 2006 [updated October 24, 2006*]

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THROUGH: Mark Avigan, M.D., C.M., Director
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TO: Janice Soreth, M.D., Director
Division of Anti-Infective and Ophthalmologic Products

SUBJECT: An evaluation of hepatic adverse events associated with telithromycin

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/ non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

1.0 EXECUTIVE SUMMARY

This review is written in response to a request from the Division of Anti-Infective and Ophthalmologic Products (DAIOP) to assess serious hepatic injuries in association with telithromycin. The detailed analysis consists of recovery and hands-on characterization and adjudication of domestic, spontaneous cases within the Adverse Event Reports System (AERS) database. Enumeration of US case reports of acute liver failure (ALF) and quantification of telithromycin exposure in the US have provided the basis for reporting rate measurement. Comparisons to US reporting rates of ALF associated with members of the fluoroquinolone class of antibiotics (levofloxacin, gatifloxacin and moxifloxacin) as well as the macrolides azithromycin and clarithromycin have been provided. Important caveats concerning the interpretation of such reporting rate comparisons are discussed.

*Estimates of teleithromycin use were included in the memorandum dated May 16, 2006 as validated telithromycin use data for April 2006 were not available at the time of its completion. This updated version includes actual numbers and revised calculations (where necessary). These changes do not impact upon the memorandum's conclusions.

From a total of 110 unduplicated domestic reports of liver events in association with telithromycin received in AERS through April 2006, DDRE classified **12** cases of telithromycin-associated ALF and **23** cases of telithromycin-associated acute serious liver injury (ASLI). ***Selected case reports of telithromycin-associated ALF are clinically remarkable. Cases ranged in age from adult to elderly, with more females than males (9 versus 3). Importantly, the median latency (as time to onset of liver injury) among these cases was 4 days - although one case experienced symptoms shortly after only one (1) dose. Following symptom onset, these cases were marked by a profound degree of hepatic injury. Among cases which provided pertinent laboratory data, the medium reported peak bilirubin level was 18.3 mg/dl; the median reported peak ALT level was 2,489 IU/L. Death was reported as an outcome for four (4) cases and another case underwent orthotopic liver transplant. Three (3) of the other cases were evaluated for orthotopic liver transplant but recovered. Many of these cases appear to have few confounding factors and occurred in individuals who were generally healthy. Although dermatologic and hematological derangements were not prominently reported (or not prominent enough to be reported), the rapid tempo and severity of injuries and the reported presence of eosinophilia in four cases of ASLI suggest an acute hypersensitivity-like process.***

With reference to utilization data, these cases resulted in an observed incidence density of telithromycin-associated ALF in the US of 168 per million person-years exposed through April 2006. Through December 2005, and thus prior to any reporting possibly stimulated in response to a recent publication on telithromycin-associated ALF, the observed incidence density based on 5 cases of telithromycin-associated ALF was 89 per million person-years. These estimates are substantially higher than the expected rate of ALF of 1 per million person-years in the general population and consistent with an association between telithromycin and ALF.

Prescription-based reporting rates were calculated in order to place the prescription-based ALF reporting rate calculated for telithromycin in context with certain other antibiotics, specifically other members of the macrolide class and three recently marketed fluoroquinolones known to cause idiosyncratic liver injuries with a similar clinical signature as telithromycin.[14] Observed prescription-based US reporting rates for telithromycin-associated ALF at selected time points after approval include:

12 per 10 million Rx *through December 05*, based on 5 cases and 4,084,000 Rx

17 per 10 million Rx *through February 06*, based on 8 cases and 4,736,000 Rx, and

23 per 10 million Rx *through April 06*, based on 12 cases and 5,198,000 Rx

It is notable that upon reiterated measurements over time, the telithromycin-associated ALF reporting rate has increased. The most recent calculated rate is 3 to 4-times that of moxifloxacin and gatifloxacin, which had ALF reporting rates of 6.6 and 6 per 10 million Rx, respectively, and also 10-times that of levofloxacin. [Note: On May 1, 2006 it was reported that gatifloxacin will

[14] Memorandum dated August 6, 2004. From Allen Brinker and Sarah Singer to Renata Albrecht. Reports of acute liver failure (ALF) and acute liver injury (ALI) in association with moxifloxacin, gatifloxacin, and levofloxacin.

be removed from the market by its sponsor. This follows articles and spontaneous reports linking gatifloxacin to an increased risk for dysglycemia.] In addition, the most recent telithromycin-associated ALF reporting rate is higher than those measured for azithromycin and clarithromycin. Reporting rates should not be interpreted as incidence rates, although they have been used to support regulatory action in the past in conjunction with other data. In addition to possible differences in actual exposure related risk, these observed differences could also be attributed to 1) secular reporting trends and 2) different (longer) study windows.

At this time, based on analysis and consideration of only spontaneous AE reporting data, it is difficult to definitively determine whether the risk for telithromycin associated ALF and ASLI is qualitatively higher than certain other currently marketed antibiotics that have been associated with idiosyncratic liver injury. Nonetheless, the rising trend of reporting rates associated with telithromycin is of concern.

Previously, as a result of a signal for telithromycin-associated liver injury observed in pre-approval clinical trials, FDA and the telithromycin sponsor agreed to address safety concerns by performing a large simple safety study.[15] Because of irregularities in its execution, results of this study do not provide a meaningful assessment of the hepatic safety concerns.

With this background, it is notable that post-marketing spontaneous report data of liver injury strongly influenced the decision to terminate out-patient prescribing of the fluoroquinolone trovofloxacin, a product with both oral and IV formulations. In the case of trovofloxacin, an ALF reporting rate of 58 per 10 million prescriptions was observed. Despite concerns for stimulated reporting, DDRE recommends that if the telithromycin associated reporting rate of ALF rises to this level, regulatory action other than labeling changes, such as restricted use for only patients who have failed other antibiotic treatments, or possible market withdrawal, should be considered.

At this time because of the concerns regarding telithromycin's hepatotoxic potential we recommend the following actions:

1. Continued regular monitoring for additional cases and re-evaluation of reporting rates.

2. Labeling of events to include a bolded or boxed **WARNING** that contains a description of the clinical characteristics of severe life threatening telithromycin-associated liver injury and liver failure.

3. Communication of appropriate patient selection for telithromycin use to physicians and patients.

[15] Food and Drug Administration Center for Drug Evaluation and Research. Summary minutes of the Anti-Infective Drugs Advisory Committee meeting, April 26 and 27, 2001, Bethesda, MD.

2.0 INTRODUCTION

Telithromycin (Ketek®, NDA# 21-144), a ketolide, is the first of a new class of antimicrobials that was approved in the United States in April 2004 for the oral treatment of acute bacterial sinusitis (ABS), acute exacerbation of chronic bronchitis (AECB), and community–acquired pneumonia (CAP). The ketolides are structurally related to macrolide antibiotics. They have a similar mechanism of action and spectrum of activity with the macrolides.

The original NDA for Ketek® was submitted in February 2000. The drug was discussed at an Anti-Infective Drug Advisory Committee Meeting on April 26, 2001 after which the FDA issued an approvable letter that in part requested the applicant to perform a large safety study to examine the potential toxicities of telithromycin with regard to cardiac, hepatic, visual, and vascular safety following questions that were raised at the meeting.[16] Aventis subsequently began marketing telithromycin outside of the United States in September 2001. In July 2002, the applicant submitted an amended NDA that included results from the safety study (Study 3014). A second Advisory Committee Meeting was held on January 8, 2003 to discuss the safety concerns and focus on the risk-benefit ratio of the drug. It was presented at that meeting that hepatic adverse events were uncommon (about 1%) and an outside expert noted that the hepatotoxicity was in the range of other antibiotics, such as Augmentin® and erythromycin.[17] However, in his 2004 Safety Review, the Medical Officer noted that "[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."[18] Since there was no other way to evaluate the potential hepatotoxicity of telithromycin, another approvable letter was issued to the applicant on January 24, 2003 requesting the submission of post-marketing data from outside the US to further evaluate this issue.

Following review of this additional post-marketing ex-US data, the Medical Officer's 2004 Safety Review noted that "pre-clinical data suggests that telithromycin may be a significant hepatotoxin in humans. However, the available data from Phase 3 trials and [ex-US] post-marketing adverse event reporting are consistent with other macrolide antibiotics, which are well known to cause hepatocanalicular toxicity."

In March 2005, the Division of Drug Risk Evaluation (DDRE) was consulted by the Division of Anti-Infective Drug Products to provide a one–year post-marketing evaluation of the safety profile of telithromycin, which included hepatic adverse events (AE).

The Medical Officer's Safety Review at the time of approval and the 2005 DDRE consult regarding telithromycin and hepatotoxicity are summarized below.

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[16] Food and Drug Administration Center for Drug Evaluation and Research. Summary minutes of the Anti-Infective Drugs Advisory Committee meeting, April 26 and 27, 2001, Bethesda, MD. Available at: http://www.fda.gov/ohrms/dockets/ac/01/minutes/3746m1.htm

[17] Food and Drug Administration Center for Drug Evaluation and Research. Transcript of the Anti-Infective Drugs Advisory Committee meeting, January 8, 2003, Gaithersburg, MD. Available at: http://www.fda.gov/ohrms/dockets/ac/03/transcripts/3919T1.htm

[18] Medical Officer Safety Review of NDA 21-144: Telithromycin (Ketek™), March 31, 2004. Available at: http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek.htm

2.1 *Medical Officer's Pre-Approval Safety Review* (from document dated March 31, 2004)[e]

"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.[19] 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 [ex-US] 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 3.7 million 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."

[19] Telithromycin—137/688; Comparators—91/523 (# of pts. with low level ALT elevations/total # of pts.)

2.2 *June 14, 2005 DDRE consult*[20]

There were a total of 39 unduplicated cases of hepatic adverse events in AERS as of 3/11/2005. Eleven cases were excluded as not associated with telithromycin (other drug therapy as a more likely cause, obstructive jaundice, viral etiology, sepsis with multi-organ failure, temporal relationship undetermined). Of the 28 remaining cases, 13 described a hepatic event (hepatitis [9], cholestatic jaundice [1], hepatocellular necrosis [1], hepatic failure/shutdown [2]), while 15 described increases in liver function tests. Sixteen patients were hospitalized (of which 10 were noted to have recovered), 3 patients recovered without hospitalization, and there were 3 deaths.

The cases of hepatic dysfunction were consistent with those described in the current product labeling (increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, which may be severe and is usually reversible).

In the three cases in which the patient died, two were the result of other causes (endocarditis with a brain abscess; infection and dehydration leading to circulatory failure). The case in which hepatic failure led to death was that of the 26–year–old Hispanic male from North Carolina.

DDRE's analysis at the time was that the cases of hepatic adverse events were consistent with those seen prior to approval in worldwide experience and as described in the current labeling. Therefore, there were no recommendations for a major change in labeling for these events as they were adequately described in the **PRECAUTIONS** section. However, DDRE recommended including the statement that hepatic dysfunction may be severe (as stated in the **Post-Marketing Adverse Event Reports** section of the **Adverse Reactions** section) in the **PRECAUTIONS** section. In addition, DDRE would continue to monitor these events for a change in frequency or character, which could necessitate further refinement of the product label.

Throughout 2005, cases of hepatotoxicity associated with telithromycin were monitored by DDRE and the DAIOP. Another review of these hepatic adverse events was proposed with a comparison of hepatotoxicity associated with other macrolide antibiotics in order to compare reporting rates and determine if differences exist among the products that could lead to changes in labeling. Coincidently, on January 20, 2006, *Annals of Internal Medicine* published an early release article reporting three patients who experienced serious liver toxicity following administration of telithromycin, which were cases that had been previously reported to the Agency.[21]

[20] Memorandum dated June 14, 2005. From Ronald Wassel, Joseph Tonning, Jonathan Levine, and Ana Szarfman to Janice Soreth. One-year post-approval evaluation of the safety profile of telithromycin.

[21] Clay KD, Hanson JS, Pope SD, Rissmiller RW, Purdum PP 3rd, Banks PM. Brief communication: severe hepatotoxicity of telithromycin: three case reports and literature review. Ann Intern Med. 2006 Mar 21;144(6):415-20. Epub 2006 Feb 15.

3.0 CURRENT LABELING

In the **PRECAUTIONS, General** section:

> Hepatic dysfunction, including increased liver enzymes and hepatitis, with or without jaundice, has been reported with the use of KETEK. These events were generally reversible.
>
> Caution should be used in patients with a previous history of hepatitis/jaundice associated with the use of KETEK. (See ADVERSE REACTIONS, Liver and biliary system.)

In the **ADVERSE REACTIONS** section:

> **Liver and biliary system:** abnormal liver function tests: increased transaminases, increased liver enzymes (e.g., ALT, AST) were usually asymptomatic and reversible. ALT elevations above 3 times the upper limit of normal were observed in 1.6%, and 1.7% of patients treated with KETEK and comparators, respectively. Hepatitis, with or without jaundice, occurred in 0.07% of patients treated with KETEK, and was reversible. (See PRECAUTIONS, General.)
>
> **Other possibly related clinically-relevant events occurring in <0.2% of patients treated with KETEK from the controlled Phase III studies included:** anxiety, bradycardia, eczema, elevated blood bilirubin, erythema multiforme, flushing, hypotension, increased blood alkaline phosphatase, increased eosinophil count, paresthesia, pruritus, urticaria.
>
> **Post-Marketing Adverse Event Reports:**
> In addition to adverse events reported from clinical trials, the following events have been reported from worldwide post-marketing experience with KETEK.
> Liver and biliary system: Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been infrequently reported with telithromycin. This hepatic dysfunction may be severe and is usually reversible.

4.0 SEARCH TYPE AND DATE

The AERS database was initially searched on 1/17/2006 (and thus prior to the *Annals* publication). A subsequent search was conducted in March 2006. A final search was conducted in early May 2006 for cases through April 2006.

5.0 SEARCH CRITERIA

Telithromycin was searched under the *ODS Liver All* Reaction Group, which includes the following MedDRA terms:

Hepatic and hepatobiliary disorders (HLGT)
Hepatobiliary investigations (HLGT)
Liver transplant (PT)

Note: The HLGT Hepatobiliary investigations is included to capture any cases coded with any hepatobiliary histopathology and imaging procedures, or liver function tests. The PT Liver transplant is included to capture any cases of liver transplants that may not have been coded as hepatic failure. This PT is under the Surgical and Medical Procedures SOC and would not be captured under the hepatic disorders group.

This search was further narrowed to: 1) domestic (U.S.) reports (for the purpose of calculating reporting rates based on U.S. drug use data); and 2) reports with an outcome of death, hospitalization, disability, life-threatening, or intervention required to prevent permanent injury (consistent with the DDRE review of hepatotoxicity associated with fluoroquinolones dated August 2004 [i]).

Although foreign cases were not included in the analysis as data is not available to accurately calculate reporting rates, a summary review of those cases was undertaken because of the large ex-US use prior to and following US approval.

6.0 SEARCH RESULTS (from marketing [April 2004] through April 2006)

A total of 110 unduplicated domestic reports of liver events were retrieved (68 pre-*Annals*, 42 post-*Annals*). Of these, 31 were excluded as confounded and probably unrelated to telithromycin (reports that were actually inquiries about hearsay; other causes such as viral infections including Epstein-Barr and cytomegalovirus, sepsis, pancreatitis, hemolytic anemia, rhabdomyolysis, hepatic carcinoma, biliary cirrhosis; other drugs). The remaining 79 cases were reviewed in order to categorize them as acute liver failure (ALF) or acute serious liver injury (ASLI) as defined below:

- **Acute Liver Failure (ALF):** a case of ALF was defined as a report containing a diagnosis of acute "liver failure" with or without supporting clinical information; a clinical scenario outlining acute and severe liver injury with encephalopathy; liver transplant following acute illness; or death in the setting of acute severe liver injury as a primary cause

- **Acute Serious Liver Injury (ASLI):** a case of ASLI was defined as a report of transaminase elevations, or hyperbilirubinemia, or clinical jaundice leading to hospitalization. Since the element separating ASLI from ALF is the presence of

encephalopathy, all ASLI cases were screened for the presence of mental status changes suggestive of encephalopathy.

These case definitions are identical to that applied in a recent review of serious liver injury in association with newer fluoroquinolones.[22]

Because of the variability in quality between spontaneous ("MedWatch") reports, attempts were made to contact the reporter or treating institution. In many instances multiple calls were made in order to gather more clinical information. Out of the 79 cases reviewed, a total of **35** cases met the criteria for ALF or ASLI. The remaining 44 cases involved elevations of liver function tests or reports of hepatitis in which the cases were not deemed serious and the patients were not hospitalized. Of these 44 non-serious cases, 7 were noted to have jaundice, but no concomitant coagulopathy. Table 1 shows the clinical characteristics of the ALF (n=12) and ASLI (n=23) cases and Appendix 1 provides a brief summary of the ALF cases.

Table 1. Clinical characteristics of ASLI and ALF in association with telithromycin (U.S. cases from beginning of marketing through April 2006)

	ASLI* (n=23)	**ALF** (n=12)**
Age	Range—22 to 90 years Median—52 years (n=21)	Range—26 to 85 years Median—52 years
Gender	Female (18), Male (5)	Female (9), Male (3)
Indication for use (verbatim from report)	Sinusitis—9 URI—5 Bronchitis—2 Pneumonia—2 Cellulitis—1	Sinusitis—5 Pneumonia—2 URI—2 Bronchitis/pneumonia—1 Bronchitis—1 Respiratory tract infection—1
Latency (time to onset of symptoms from initiation of treatment)	Range—2 to 30 days Median—10 days (n=15)	Range—1 to 20 days Median—4 days (n=11)
Jaundice reported at Dx	6	8
Highest reported bilirubin (mg/dL)	Range—0.5 to 27 Median—1.75 (n=14)	Range—1.7 to 24.3 Median—18.3 (n=10)
Highest reported AST (IU/L)	Range—83 to >2800 Median—461 (n=18)	Range—812 to 34,423 Median—3638 (n=11)
Highest reported ALT (IU/L)	Range—69 to 1700 Median—740 (n=18)	Range—833 to 19,888 Median—2489 (n=11)
Eosinophilia reported	4	0
Death / transplant	0 / 0	4 / 1
Geographic distribution		

[22] Memorandum dated August 6, 2004. From Allen Brinker and Sarah Singer to Renata Albrecht. Reports of acute liver failure (ALF) and acute liver injury (ALI) in association with moxifloxacin, gatifloxacin, and levofloxacin.

* Acute Serious Liver Injury: report of transaminase elevations, or hyperbilirubinemia, or clinical jaundice leading to hospitalization; no evidence of encephalopathy

** Acute Liver Failure: a report containing a diagnosis of acute "liver failure" with or without supporting clinical information; a clinical scenario outlining acute and serious liver injury with encephalopathy; liver transplant following acute illness; or death in the setting of acute liver injury as a primary cause.

6.1 *Non-US Cases*

The review of foreign cases found only two possible cases of ALF (both from Japan), although one of them may have been related to circulatory failure secondary to arteriosclerosis with sepsis and dehydration (see Appendix 2 for a description of these cases). There were four cases that met the criteria for ASLI (one each from Japan, Puerto Rico, Canada, and Greece) and three cases that were probably related to other causes (one each from Canada, Germany, and France).

7.0 CLINICAL CHARACTERISTICS OF TELITHROMYCIN-ASSOCIATED ACUTE LIVER FAILURE CASES

Selected case reports of telithromycin-associated ALF are clinically remarkable. Cases ranged in age from adult to elderly, with more females than males (9 versus 3). Importantly, the median latency (as time to onset of liver injury) among these cases was 4 days - although one case (included below) experienced symptoms shortly after only one (1) dose. Following symptom onset, these cases were marked by a profound degree of hepatic injury. Among cases which provided pertinent laboratory data, the medium reported peak bilirubin level was 18.3 mg/dl; the median reported peak ALT level was 2,489 IU/L. Death was reported as an outcome for four (4) cases and another case underwent orthotopic liver transplant. Three (3) of the other cases were evaluated for orthotopic liver transplant but recovered. Many of these cases appear to have few confounding factors and occurred in individuals who were generally healthy. Although dermatologic and hematological derangements were not prominently reported (or not prominent enough to be reported), the rapid tempo and severity of injuries and the reported presence of eosinophilia in four cases of ASLI suggest an acute hypersensitivity-like process.

7.1 *Selected Case Summaries*

ISR #4579921-5 (direct report); Mfr. Control #200513491US—A 26-year-old Hispanic man was admitted to the hospital after an 8-day history of jaundice, fever, melena, and hematemesis. Two weeks before admission, the patient had computed tomography of the sinuses that showed an enhancing lesion in the nasal cavity and nasopharynx on the left, possibly a neoplasm. The patient was prescribed and completed a course of telithromycin, 400 mg, 2 tablets once daily for 5 days. The patient and his wife reported that he drank eight 12-ounce beers every 2 weeks. He

reported no long-term use of nonsteroidal anti-inflammatory drugs and no history of hepatitis, intravenous drug use, tattoos, or herbal medication use before admission. On physical examination, the patient appeared severely ill and diaphoretic. The patient had jaundice and his abdomen was firm and tympanic, with notable hepatomegaly. There was notable tenderness to palpation in the mid-epigastric region and the right upper quadrant, with no rebound or guarding noted. Initial laboratory tests showed alkaline phosphatase level of 575 U/L, aspartate aminotransferase level of 3638 U/L, alanine aminotransferase level of 2200 U/L, and total bilirubin level of 13.6 mg/dL. The prothrombin time was 25.7 seconds, partial thromboplastin time was 38 seconds, and international normalized ratio was 2.3. Abdominal radiography showed no high-grade obstruction or gross pneumoperitoneum. Computed tomography without contrast of the abdomen and pelvis showed moderate ascites and bowel-wall thickening. Acetylcysteine therapy was initiated, but levels of acetaminophen, salicylate, and ethylene glycol were subsequently found to be normal. The patient had upper endoscopy, which showed only gastritis. During the procedure, the patient became hypotensive and developed cardiopulmonary failure requiring resuscitation. General surgeons were consulted for possible abdominal catastrophe and performed a deep peritoneal lavage with removal of nonbloody ascitic fluid. On the second hospital day, the patient required pressors and continued ventilator support. He had metabolic acidosis despite bicarbonate infusion. Dialysis was begun but did not correct his acidotic state. Results of all serologic tests-including tests for HIV infection; Epstein-Barr virus infection; hepatitis A, B, and C virus infection; antinuclear antibody; and leptospirosis antigen-were negative. On day 3, despite aggressive therapy, the patient was hypotensive and had continued refractory acidosis; his respiratory status worsened. Despite receiving fluid resuscitation and pressors, the patient became asystolic and died.

ISR #4892304-3 (direct report); Mfr. Control #200513250US—51–year–old female with no significant past medical history presented to her Primary Care Physician with a 2 week history of URI symptoms. Patient was given telithromycin 400 mg twice daily for 5 days and developed icterus with elevated liver enzymes two days after completing the course of therapy. Patient was seen by a gastroenterologist and had an abdominal ultrasound that showed a small liver (echogenic) with ascites. Patient continued to have worsening of her liver function (maximum total bilirubin 24.1 mg/dL; AST and ALT > 1000 U/L) requiring a liver transplant on ……. The explanted liver was only about one third of the normal size (480 g) and consisted predominantly of diffuse collapse. Islands of surviving intact lobular parenchyma consisted of regenerative nodules.

ISR #4907442-6 (direct report); Mfr. Control #200611392US—26–year–old otherwise healthy female was being treated for a sinus infection and took one dose of Ketek 800 mg. She began to develop nausea and vomiting and eventually became unresponsive and was transported via EMS to the emergency department. The patient was admitted to the ICU as a case of possible sepsis with coagulopathy, with elevated liver enzymes, acute renal failure, and moderate dehydration. Peak liver function tests included a total bilirubin of 1.7 mg/dL, AST 34,423 U/L, and ALT 19,888 U/L. The patient was assessed as having fulminant liver failure and was transferred to another facility for possible liver transplantation. A liver biopsy showed 70% nonspecific necrosis. LFTs and mental status improved throughout the course of her admission and a transplant was not required. She was transferred to a rehab facility (secondary to multiple cerebral infarcts) and will have hepatology follow-up.

8.0 EPIDEMIOLOGY / REPORTING RATES

Several epidemiologic approaches can be used to analyze spontaneous ADE reports. Reporting rates (based on division of the number of case reports for an event by the number of prescriptions) can be used to compare one drug against another. Such comparisons are most appropriate when the drugs are very similar, including indication and initial marketing date (+/- 2-3 years). However, such comparisons are subject to uncertainty in the numerator and, to a lesser extent, uncertainty in the denominator. Uncertainty in the numerator is afforded by differential reporting. At baseline, studies have estimated that the fraction of reports received by FDA to be only 1% to 10%, but the absolute percentage for any individual drug is unknown. Notoriety of a drug-event combination (stimulated reporting[1,2]), the reporting practices of different clinicians in disparate populations, the clinical severity of the event, different drug sponsors, and secular reporting trends may all affect reporting. A large difference in reporting rates between similar drug products may support an association between an event and one of the drugs, especially when combined with other information. Another method that has been used to assess a potential drug-event association involves comparison of the reporting rate to an expected rate for the event in the population (observed-to-expected analysis). Since background rates are usually available as incidence densities (rates per person-time), such comparisons often require transformation of the reporting rate into a rate as person-time based on typical length of therapy for the drug under study.

Reporting rates, both as cases per prescription and as an incidence density (per person-time) were calculated in order to assess the association between telithromycin and acute liver failure. As has been done in previous reviews, such as the recent fluoroquinolone one highlighted above, national prescription use data was used to adjust for utilization by prescription and was combined with average length of therapy to estimate person-time on drug. For the purposes of this analysis, the study window for collection of cases and drug utilization is from initial marketing appearance in July 2004 through April 2006 and includes 12 domestic cases that met the ALF case definition.

The observed-to-expected comparison requires a background rate of ALF. For the purposes of this review, a background rate of 1 per million person years will be used. This rate was developed by Dr. David Graham during review[3] of troglitazone-associated ALF and has been used in previous DDRE analyses.

8.1 *US Utilization Data*

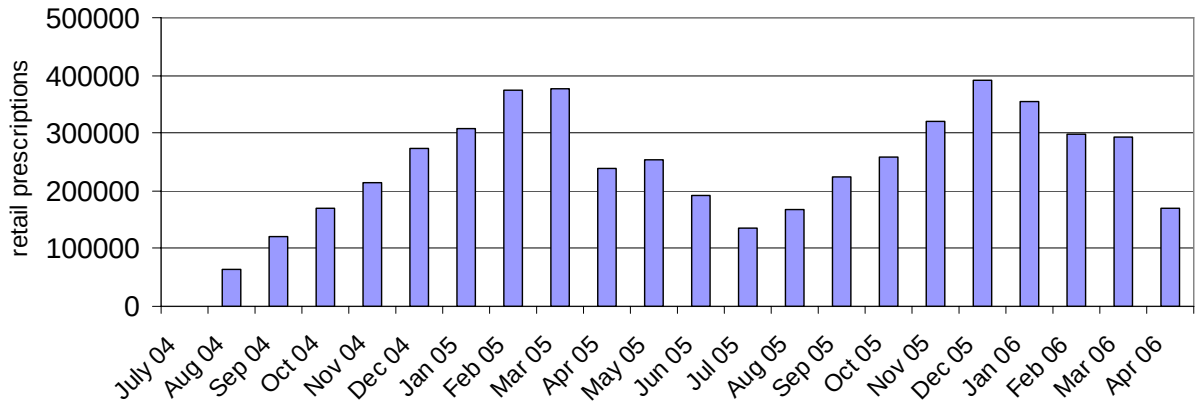
Utilization data was provided by an analysis of the Verispan VONA audit which measures retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Prescriptions are captured from a sample of approximately 51,000 pharmacies throughout the U.S. The pharmacies in the database account for nearly all retail pharmacies and represent approximately 55% of retail prescriptions dispensed nationwide. These data are then projected to reflect national prescription patterns. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients

that are continuing or new to therapy are also collected. The VONA database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Verispan currently receives over 2 billion prescription claims per annum representing pharmaceutical claims from over 160 million unique patients.

Verispan Vector One® estimates of utilization of telithromycin from launch (July 2004) through April 2006 as dispensed, retail prescriptions are shown in Figure 1 (below).

Figure 1. Telithromycin prescriptions dispensed from U.S. retail pharmacies, July 2004 (market appearance) through April 2006.

Verispan Vector One®:National, months May 2004-April 2006, extracted May 2006.



8.2 *US reporting rate calculations*

Prescription-based US reporting rate calculations*

Observed ALF prescription-based US reporting rates for telithromycin at selected time points include:

12 per 10 million Rx *through December 05*, based on 5 cases and 4,084,000 Rx

17 per 10 million Rx *through February 06*, based on 8 cases and 4,736,000 Rx, and

23 per 10 million Rx *through April 06*, based on 12 cases and 5,198,000 Rx

*Comment on these rates follows below under 8.3

Person-time-based US reporting rate calculations

A comparison of the rate of ALF observed through spontaneous reports to that expected in the population requires an estimate of the typical time-course for a treatment cycle with telithromycin. Based on the approved label, which includes a 5-day course of therapy for both bronchitis and sinusitis, a 5-day interval was chosen as the typical length of therapy. These result in the following estimates of telithromycin-exposed person-time:

56,000 person-years through *December 05*, based on 4,084,000 Rx

65,000 person-years through *February 06* based on 4,736,000 Rx

71,200 person-years through *April 06* based on 5,198,000 Rx

Incidence densities at these same time points are then calculated after inclusion of case counts:

89 per 1,000,000 person-years through *December 05*

123 per 1,000,000 person-years through *February 06*

168 per 1,000,000 person-years through *April 06*

Through December 2005, and thus prior to reporting *potentially* stimulated[1,2] in response to the *Annals* publication by Clay et al on telithromycin-associated ALF, the observed incidence density based on 5 cases of telithromycin-associated ALF was 89 per million person-years. Through April 06, the observed US incidence density for telithromycin-associated ALF is 167 per million person-years. These estimates are substantially higher than the expected rate of ALF of 1 per million person-years in the general population and consistent with an association between telithromycin and ALF. These results should prompt changes to approved labeling for telithromycin and consideration for other regulatory actions (see **SUMMARY AND RECOMMENDATIONS**).

8.3 *Comparison of prescription-based reporting rates for telithromycin with newer fluoroquinolones and azithromycin and clarithromycin*

In order to place the prescription-based reporting rates into context, comparisons were made to the recently marketed fluoroquinolones and the newer macrolides, azithromycin and clarithromycin. Comparison to the recently marketed fluoroquinolones was afforded by a recent consult, which described cases of ALF associated with these products, as mentioned previously (Table 2).

Table 2. Prescription-based acute liver failure reporting rates for recently-marketed fluoroquinolones as reviewed in a 2004 consult.[tt]

IMS Health, National Prescription Audit *Plus*™, Years 1997 through September 2003, extracted July 2004.

	levofloxacin	gatifloxacin	moxifloxacin
U.S. Outpatient Oral Prescriptions (Rx)[1]	57,436,000	10,068,000	7,563,000
U.S. Outpatient Cases of ALF with Oral Drug	12[2]	6[3]	5
Rate per 10 million Rx[4]	2.1	6.0	6.6

[1]through September 30, 2003

[2]excludes four cases of oral therapy from in-patient setting

[3]excludes two cases that received gatifloxacin and ciprofloxacin or levofloxacin.

[4]For reference, regulatory action was undertaken on trovafloxacin with 12 probable cases and 2,073,000 Rx: reporting rate = 58 per 10 million Rx

[tt]Memorandum dated August 6, 2004. From Allen Brinker and Sarah Singer to Renata Albrecht. Reports of acute liver failure (ALF) and acute liver injury (ALI) in association with moxifloxacin, gatifloxacin, and levofloxacin.

The most recent US reporting rate for telithromycin-associated ALF is 3 to 4-times that of moxifloxacin and gatifloxacin, which had ALF reporting rates of 6.6 and 6 per 10 million Rx, respectively and 10-times that of levofloxacin. Comparison of the most recent ALF-reporting rate for telithromycin to the rates of newer fluoroquinolones should include consideration for secular trends in reporting (higher rates are expected for newer drugs in comparison to older drugs). Therefore, the relative reporting rate ratios of 3-4 in comparison to (moxifloxacin, gatifloxacin) may/may not represent remarkable differences of incidence. A 2-fold difference in relative reporting rate ratios was observed between moxifloxacin/gatifloxacin and levofloxacin and attributed to 1) secular reporting trends and 2) the 6.5 year study window used for levofloxacin in comparison to the 3.5 year interval for moxifloxacin and gatifloxacin. These same limitations may also apply in consideration of the relative reporting rate ratio of 10 based on comparison of the ALF reporting rate for telithromycin to levofloxacin, except that both the time period between marketing appearance and the difference in study windows are larger. This could be cited to explain the higher rate calculated for telithromycin in comparison to levofloxacin.

As noted above, in an effort to compare to members of the macrolide class a review was undertaken to generate ALF reporting rates for clarithromycin (approved 10/31/1991) and azithromycin (approved 11/1/1991). Identical searches to that which was done with telithromycin were conducted with azithromycin and clarithromycin. The searches were conducted using a criteria of reports submitted with an FDA received date up to 12/31/1995, which would include the first three years of marketing for each drug (1991 – 1994) with an extra year in case there were any follow-ups reported after the third year. Only those cases that occurred in the first three years of marketing were selected for review. Reports recovered in searches were then subjected to hands-on adjudication. No effort was made to obtain more information on reports given the 10+ year interval since report submission.

The review for clarithromycin resulted in 7 cases of ALF and 22 cases of ASLI. The review for azithromycin resulted in 2 cases of ALF and 9 cases of ASLI. The clinical signatures of these cases with reference to both time of liver injury after initiation of treatment and tempo of injury may be different than that associated with telithromycin. As these cases are over 10 years old, the lack of detailed information makes compilation of clinical characteristics of limited value. Of note, there was one death in the azithromycin associated ALF group and four deaths and one transplant in the clarithromycin associated ALF group.

Calculation of reporting rates for these products was conducted using the IMS Health National Prescription Audit (NPA) as this study period predates Verispan data. These data are accessible only through review of archived, hardbound books. Inspection of these data resulted in the following estimates of dispensed, retail prescriptions (Table 3):

Table 3. Dispensed, retail prescriptions for clarithromycin and azithromycin during first three complete years of marketing.
IMS Health, National Prescription Audit *Plus*™, Years 1991 through 1994, Hardcopy book.

Drug	1992	1993	1994
clarithromycin	2,774,000*	5,610,000	8,140,000
azithromycin	626,000	1,837,000	2,905,000

*includes 130,000 Rx from 1991

ALF prescription-based reporting rate (clarithromycin) =
7 cases / 16,526,000 Rx = 4.2 per 10 million Rx

ALF prescription-based reporting rate (azithromycin) =
2 cases / 5,368,000 Rx = 3.7 per 10 million Rx

Thus, rates of ALF associated with these macrolides were lower than those presently associated with telithromycin. However, the same caveats raised above concerning interpretation of a comparison of the telithromycin ALF reporting rate to the newer fluoroquinolones apply to comparison to the macrolides. Specifically, differences in the rates could also be attributed to 1) secular reporting trends (10+ year difference between initial marketing) and 2) a longer study interval.

Although not included in this review, a comparison of the ALF reporting rate of telithromycin with the rates of cefditoren pivoxil and gemifloxacin (oral drugs with similar indications) is being undertaken.

9.0 SUMMARY AND RECOMMENDATIONS

At the time of telithromycin's approval in April 2004, the drug was regarded as a potentially significant hepatotoxin in humans. However, the data at the time suggested the hepatotoxicity appeared to be similar in severity and pattern to drugs in the macrolide class. The one–year post-

approval safety review found one case of liver failure resulting in death, but most case reports were generally consistent with those seen prior to approval in worldwide experience and consistent with approved labeling. Since that time, several additional cases of severe hepatotoxicity have been reported with telithromycin, including cases resulting in death and liver transplantation. These cases are characterized by a remarkable clinical signature of rapid onset and tempo of liver injury after initiation of telithromycin treatment. The finding prompts a need for a bolded or boxed warning of ALF in the telithromycin product labeling with a description of the clinical signature of serious liver injuries.

The 5 adjudicated cases of ALF reported to FDA through December 2005 - coupled with use data for the same period - result in an ALF incidence density for telithromycin 89-times the expected rate of 1 per million patient-years. The magnitude of this effect size is consistent with an association between telithromycin and ALF.

Prescription-based reporting rates were calculated in order to place the prescription-based ALF reporting rate calculated for telithromycin in context with certain other antibiotics including members of the macrolide class and three fluoroquinolones known to cause idiosyncratic liver injuries with a similar clinical signature as telithromycin.[23] Observed ALF prescription-based US reporting rates for telithromycin at selected time points after approval include:

12 per 10 million Rx through December 05, based on 5 cases and 4,084,000 Rx

17 per 10 million Rx through February 06, based on 8 cases and 4,736,000 Rx, and

23 per 10 million Rx through April 06, based on 12 cases and 5,198,000 Rx

It is notable that upon reiterated measurements over time, the telithromycin-associated ALF reporting rate has increased. The most recent calculated rate is 3 to 4-times that of moxifloxacin and gatifloxacin, which had ALF reporting rates of 6.6 and 6 per 10 million Rx, respectively and 10-times that of levofloxacin. [Note: On May 1, 2006 it was reported that gatifloxacin will be removed from the market by its sponsor. This follows articles and spontaneous reports linking gatifloxacin to an increased risk for dysglycemia.] In addition, the most recent telithromycin-associated ALF reporting rate is higher than those measured for azithromycin and clarithromycin. In addition to possible differences in actual exposure related risk, these observed differences could also be attributed to 1) secular reporting trends and 2) different (longer) study windows.

In the case of trovofloxacin, an ALF reporting rate of 58 per 10 million prescriptions was observed. Despite concerns for stimulated reporting, DDRE recommends this rate should serve as a frame of reference to prompt consideration of regulatory actions for telithromycin such as restricted use for only patients who have failed other antibiotic treatments or even market withdrawal.

[23] Memorandum dated August 6, 2004. From Allen Brinker and Sarah Singer to Renata Albrecht. Reports of acute liver failure (ALF) and acute liver injury (ALI) in association with moxifloxacin, gatifloxacin, and levofloxacin.

At this time because of the concerns regarding telithromycin's hepatotoxic potential we recommend the following actions:

1. Continued regular monitoring for additional cases and re-evaluation of reporting rates.

2. Labeling of events to include a bolded or boxed **WARNING** that contains a description of the clinical characteristics of severe life threatening telithromycin-associated liver injury and liver failure

3. Communication of appropriate patient selection for telithromycin use to physicians and patients.

DDRE has proposed the following language to be incorporated into the labeling:

CONTRAINDICATIONS

KETEK should not be re-administered in patients currently recovering from KETEK associated liver injury or in patients with previous history of hepatitis/jaundice associated with the use of KETEK.

WARNINGS

Hepatotoxicity:

Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant hepatitis, hepatic necrosis and hepatic failure, have been reported in patients treated with KETEK. These hepatic reactions were observed during or immediately after treatment. In some of these cases, liver injury progressed rapidly and occurred after administration of a few doses of KETEK. Mainly in less severe cases, recovery from liver injury has also been reported.

Physicians and patients should monitor for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. Patients with signs or symptoms of hepatitis must be advised to discontinue KETEK and immediately seek medical evaluation, which should include liver function tests (See ADVERSE EVENTS, See Information to Patients). If clinical hepatitis or transaminase elevations combined with other systemic symptoms occur, KETEK should be permanently discontinued.

Due to the possibility of hypersensitivity-related liver injury, KETEK should not be re-administered in patient with a previous history of liver injury associated with the use of KETEK (see CONTRAINDICATIONS). Caution is advised in the use of KETEK in patients with previous history of drug-induced hepatitis/jaundice.

ADVERSE EVENTS: Post-Marketing Adverse Event Reports:

Liver and biliary system: Severe, life-threatening, and in some cases fatal hepatotoxicity, including fulminant hepatitis, hepatic necrosis and hepatic failure, have been reported in patients treated with KETEK. These hepatic reactions were observed during or immediately after

treatment. In some of these cases, liver injury progressed rapidly and occurred after administration of only a few doses of KETEK. Mainly in less severe cases, recovery from liver injury has also been reported.

Information for Patients:

Patients should be informed of the possibility of severe liver disease associated with Ketek that may result in liver transplantation or death. Patients developing signs or symptoms of liver disease should be instructed to discontinue KETEK and seek medical attention immediately, including performance of laboratory monitoring. Symptoms of liver disease include nausea, fatigue, anorexia, jaundice, dark urine, light-colored stools, pruritus, or tender abdomen. KETEK should not be re-used in patient with previous history of hepatitis/jaundice associated with the use of KETEK. Caution is advised in the use of KETEK in patients with previous history of hepatitis/jaundice with the use of other drugs.

Appendix 1. SUMMARY OF DOMESTIC ACUTE LIVER FAILURE CASES (n=12) ASSOCIATED WITH TELITHROMYCIN THROUGH APRIL 2006

ISR # MFR # State	Age Sex	Outcome	Indication Dose Time to onset (from day 1 of tx)	Event	Concomitant medications	Medical history	Maximum liver function tests
4579921-5 (direct report) 200513491US	26 M	Death	Sinusitis 400 mg BID about 5 days 14 days	A 26-year-old Hispanic man was admitted to the hospital after an 8-day history of jaundice, fever, melena, and hematemesis. Two weeks before admission, the patient had computed tomography of the sinuses that showed an enhancing lesion in the nasal cavity and nasopharynx on the left, possibly a neoplasm. The patient was prescribed and completed a course of telithromycin, 400 mg, 2 tablets once daily for 5 days. The patient and his wife reported that he drank eight 12-ounce beers every 2 weeks. He reported no long-term use of nonsteroidal anti-inflammatory drugs and no history of hepatitis, intravenous drug use, tattoos, or herbal medication use before admission. On physical examination, the patient appeared severely ill and diaphoretic. The patient had jaundice and his abdomen was firm and tympanic, with notable hepatomegaly. There was notable tenderness to palpation in the mid-epigastric region and the right upper quadrant, with no rebound or guarding noted. Initial laboratory tests showed alkaline phosphatase level of 575 U/L, aspartate aminotransferase level of 3638 U/L, alanine aminotransferase level of 2200 U/L, and total bilirubin level of 13.6 mg/dL. The prothrombin time was 25.7 seconds, partial thromboplastin time was 38 seconds, and international normalized ratio was 2.3. Abdominal radiography showed no high-grade obstruction or gross pneumoperitoneum. Computed tomography without contrast of the abdomen and pelvis showed moderate ascites and bowel-wall thickening. Acetylcysteine therapy was initiated, but levels of acetaminophen, salicylate, and ethylene glycol were subsequently found to be normal. The patient had upper endoscopy, which showed only gastritis. During the procedure, the patient became hypotensive and developed cardiopulmonary failure requiring resuscitation. General surgeons were consulted for possible abdominal catastrophe and performed a deep peritoneal lavage with removal of nonbloody ascitic fluid. On the second hospital day, the patient required pressors and continued ventilator support. He had metabolic acidosis despite bicarbonate infusion. Dialysis was begun but did not correct his acidotic state. Results of all serologic tests-including tests for HIV infection; Epstein-Barr virus infection; hepatitis A, B, and C virus infection; antinuclear antibody; and leptospirosis antigen-were negative. On day 3, despite aggressive therapy, the patient was hypotensive and had continued refractory acidosis; his respiratory status worsened. Despite receiving fluid resuscitation and pressors, the patient became asystolic and died.	Acetaminophen	None reported	Bili—13.6 AST—3638 ALT—2200

Appendix 1 (continued)

ISR # MFR # State	Age Sex	Outcome	Indication Dose Time to onset (from day 1 of tx)	Event	Concomitant medications	Medical history	Maximum liver function tests
4809109-1 (direct report)	45 F	Recovered	Pneumonia 400 mg BID for 3 days 4 days	Patient was started on Ketek 400 mg twice daily for pneumonia. Patient took Ketek for three days when she presented to the ER with decreased level of consciousness and increased liver enzymes. Patient was switched from Ketek to Levaquin. The next morning the patient was awake, alert, and oriented. On third day lungs clear. Patient says she is feeling well and wants to go home. Patient was discharged that afternoon.	None reported	None reported	Bili—4.4 AST—>5000 ALT—>5000
4892304-3 (direct report) 200513250US	51 F	Transplant	URI 400 mg BID for 5 days 7 days	51 year old female with no significant post medical history presented to her Primary Care Physician with 2 wk h/o URI symp. Patient was given Ketek (telithromycin) and developed icterus with elevated liver enzymes. Patient seen by gastroenterologist and had a Abdominal Ultrasound that showed a small liver (echogenic) with ascites Patient continued to have worsening of her liver function requiring a liver transplant on……. The explanted liver was only about one third of the normal size (480 g) and consisted predominantly of diffuse collapse. Islands of surviving intact lobular parenchyma consisted of regenerative nodules.	Aspirin, multivitamin, vitamin E	None reported	Bili—24.1 AST—>1000 ALT—>1000
200514291US 200513490US (considered the same patient)	57/58 M	Recovered	Bronchitis/ Pneumonia Unknown 2 days	A 57/58 year-old male patient initiated Ketek (telithromycin) on 20-Apr-05 for bronchitis and pneumonia. The patient developed a reaction, together with jaundice, liver failure, liver toxicity, and bleeding two days later and was admitted to the hospital on……... An office assistant stated the patient's liver transaminases were elevated. The patient also received a liver biopsy. He was transferred to with right upper quadrant pain and hypotension. He was hospitalized and was given broad antibiotics for less than 12 hours. He was found to have multiple system organ failure with elevated bilirubin, coagulopathy and renal failure without need of dialysis. The initial diagnosis was septic shock secondary to gangrenous gallbladder. The surgeon was called for consultation. After exploratory laparotomy, gangrenous gallbladder, gallbladder stone, and intra-abdominal sources were ruled out. A liver biopsy confirmed acute ischemic hepatic injury with acute congestion and extensive hemorrhage. Patient was treated with broad antibiotics and fluid support. He was discharged on …… with a diagnosis of multiple system organ failure due to systemic inflammatory response syndrome. Outcome of the organ failure was 'resolved'. The patient returned to the office for a blood test on 17-May-05. Hepatic panel was normal. His prothrombin time (PT) time was 17.6, and international normalized ratio (INR) was 2.1.	Spironolactone, ramipril, warfarin, furosemide	Atrial fibrillation, COPD	Not provided

Appendix 1 (continued)

ISR # MFR # State	Age Sex	Outcome	Indication Dose Time to onset (from day 1 of tx)	Event	Concomitant medications	Medical history	Maximum liver function tests
4822395-7 and 4838056-4 (direct reports) 200518509US	73 F	Recovered	Sinusitis 400 mg BID for 16 days 13 days	73 y/o healthy active female initiated telithromycin on 9/29/05 for chronic sinusitis. Approx 10/11/05 noted dark urine and jaundice. Went to PCP 10/14: AST-ALT 300-600, total bili 12. Telithromycin dc'd. 10/17 patient called PCP and said she felt fine, appt made for for follow-up labs. Patient did not come for appt, did not answer phone, so ambulance was sent to patients home. ER admission for confusion and fulminant hepatic failure. Patient became more obtunded and required intubation @2300, given IV acetylcystine. VSs stable except for SBP 180-190. No hepatosplenomegaly or ascites. Transferred to … hospital for evaluation for liver transplantation …….. 11/13 follow up with PCP, patient declined liver transplantation, "improved", residing in a nursing home.	Advair, mometasone inh, ipratroprium inh, albuterol inh, cetirizine, guaifenesin, valdecoxib, glucosamine, atenolol, aspirin, estrogen, amitriptyline, atorvastatin, multivitamin	Asthma, mital valve prolapse, rhinosinusitis, osteoarthritis, hypertension, hyperlipidemia	Bili—23 AST—4100 ALT—7200
4907442-6 (direct report) 200611392US	26 F	Recovered	Sinusitis 800 mg once 1 day	26 y/o otherwise healthy female was being treated for a sinus infection and took one dose of Ketek. She began to develop nausea and vomiting and eventually became unresponsive and was transported via EMS to the emergency department. The patient was admitted to the ICU as a case of possible sepsis with coagulopathy, with elevated liver enzymes, acute renal failure, and moderate dehydration. The patient was assessed as having fulminant liver failure and was transferred to another facility for possible liver transplantation. A liver biopsy showed 70% nonspecific necrosis. LFTs and mental status improved throughout the course of her admission and a transplant was not required. She was transferred to a rehab facility (secondary to multiple cerebral infarcts) and will have hepatology follow-up.	Montelukast, fluticasone	None	Bili—1.7 AST—34,423 ALT—19,888
200612457US	37 M	Recovered	Bronchitis Unknown Unknown	37 y/o male presented to the ER with increased RUQ abdominal pain, nausea, and fevers. The patient was seen approximately one week ago for acute bronchitis and treated with telithromycin. Labs revealed AST 697, ALT 1146, total bili 2.3. Transaminases continued to elevate and the patient was ultimately transferred to …. Hospital for further treatment and possible liver biopsy. At …., the patient's condition resolved very quickly; all serologies were negative. Follow-up LFTs to be performed monthly.	Hyoscyamine, cetirizine	Irritable bowel syndrome	Bili—3.9 AST—812 ALT—1385

Appendix 1 (continued)

ISR # MFR # State	Age Sex	Outcome	Indication Dose Time to onset (from day 1 of tx)	Event	Concomitant medications	Medical history	Maximum liver function tests
4935122-X (direct report)	49 F	Death	Respiratory tract infection 800 mg daily 4 days	A 49 y/o African American lady with polycystic kidney disease. She had bilateral nephrectomies and has been on chronic ambulatory peritoneal dialysis for several years. Two weeks prior to the event she had chills, fevers, aches and diarrhea. She tried to treat symptoms herself, but as they progressed she went to her primary care physician for ceftriaxone 1 gram injection and began Ketek 800 mg po daily. She took one or two doses of Ketek, but did not take any more because of her nausea and vomiting. Her symptoms progressed and she was hospitalized five days later. At that time she had leukopenia, thrombocytopenia, and abnormal liver enzymes. She progressed to respiratory failure, DIC, and fulminant liver failure. A CT scan did show a cyst on her liver which was thought related to her polycystic kidney disease. Her neurologic status deteriorated. She was too unstable for a liver biopsy. She continued to deteriorate and was moved to hospice care where she died.	Cinacalcet, calcium acetate, atorvastatin, losartan, KCl, levothyroxine	Breast cancer in remission, parathyroidectomy	Bili—3.1 AST—9112 ALT—2489
4894737-8 4897570-6 (direct reports) 200610952US	53 F	Recovered	Sinusitis 800 mg daily 6 days	A 53 y/o female received Ketek 800 mg daily for sinusitis from 1/18-22/06. She saw her physician on 1/24/06 with complaints of malaise and nausea. The physician found her to be icteric and obtained LFTs. She was admitted to a local hospital on …….. with drug induced jaundice. On……. when her lab results were available, her SGOT 2800, SGPT 1200, direct bili 7.1 and total bili 12.1. Per physician's discussion with the physician in the hospital, he learned that the pt.'s LFTs were a little higher in hospital, sonogram normal, and viral hepatitis diagnosis was negative. On……., the pt. was transferred to a general hospital. Per pt.'s husband's report, bili was 16 and LFTs were 3000 (unspecified test). On…… the LFTs went even higher, but on 2/2/06, the pt. stabilized a little bit. Biopsy was done on showing extensive acute damage. On……., the pt. was transferred to another hospital, in which bili was noted to be 21. Additional information 2/13/06: the pt. has no history of liver or biliary disease, no known prior hepatic reactions to medications. She has no history of alcohol use, cardiac problems/heart failure, or malignancy. The patient was transferred to another hospital for close monitoring and consideration of liver transplant. She had had elevated PT associated with the hepatic injury, but no encephalopathy. Autoimmune work-up was "negative" and the physicians felt the event was "probably" related to telithromycin. The event outcome is ongoing but improved; no transplantation is required. The pt. was discharged from the hospital and will be followed-up in 2 weeks.	HCTZ, mometasone, azelastine, pantoprazole, Prempro, aspirin, Ocuvite	Type II diabetes, chronic sinusitis, allergic rhinitis	Bili—23 AST—1244 ALT—2821

Appendix 1 (continued)

ISR # MFR # State	Age Sex	Outcome	Indication Dose Time to onset (from day 1 of tx)	Event	Concomitant medications	Medical history	Maximum liver function tests
4913613-5 4916980-1 (direct reports) 200611473US 200611868US	69 F	Death (family withdrew care after post-op compli-cations following perforated duodenal ulcer repair)	URI 800 mg daily 2 days	A 69 y/o Asian female began Ketek for an URI on approx. 12/4/05. She stopped taking Ketek after two days because of severe abdominal pain and switched to Bactrim. She became jaundiced on the first day of therapy and went to an outside hospital where she was admitted with jaundice and severe fluid retention in the lower extremities and abdomen. Bilirubin and LFTs continued to rise and pt. was referred to Hospital on ……. for possible transplant. Liver biopsy on……..demonstrated cirrhosis of unknown etiology possibly due to hepatitis B or autoimmune hepatitis. Bilirubin and LFTs decreased and pt. was discharged on …… on a prednisone taper. Pt. was readmitted on …… with a perforated duodenal ulcer. Admission INR 9.6, AST 286, ALT 690, total bili 13.8. Pt. taken to OR for surgical repair; post-op course complicated by bleeding, acute renal failure, acute respiratory distress, and cardiovascular failure. Family withdrew care and pt. expired …….	Acetaminophen (2 to 4 gm per day)	Osteoarthritis	Bili—24.3 AST—1114 ALT—833
4945339-6 (direct report) 200612213US	85 F	Death	Pneumonia 800 mg daily 6 days	An 85 y/o female took Ketek from 2/25/06 to 2/28/06 with improvement, but on 3/1/06 complained of nausea, inability to urinate, muscle weakness, dizziness, and SOB. On…….. pt. was so weak she could not get out of bed and was taken to the ER where she presented with metabolic acidosis, acute renal and liver failure. Lab work revealed liver enzymes in the 5000's and blood cultures were negative. BUN 43, Cr 5.0, CK 877, MB 134, Troponin 27.6. Pt. had a junctional rhythm in the 50s. The pt. passed away on…… due to liver failure.	Valsarten, atenolol	Hypertension, mastectomy (1973)	Bili—N.S. AST—5525 ALT—4351

Appendix 1 (continued)

ISR # MFR # State	Age Sex	Outcome	Indication Dose Time to onset (from day 1 of tx)	Event	Concomitant medications	Medical history	Maximum liver function tests
4958310-5 (direct report) 200612961US 200613843US	71 F	Recovered	Sinusitis 400 mg daily 20 days	A 71 year old female was prescribed telithromycin (Ketek) on 2/17/06 for sinusitis. On 3/8/06 she developed weakness, fatigue, nausea, decreased appetite, and jaundice. On …….., liver function tests were elevated. On ……., the patient was hospitalized due to hepatic failure, Ketek was discontinued. The results of liver function tests from ……., were reported without reference ranges or units: bilirubin was 23.1, aspartate aminotransferase 885, alanine aminotransferase 1172, lactate dehydrogenase (LDH) 832, alkaline phosphatase 337, amylase 151, lipase 690. On an unknown date, bilirubin peaked at 24.3 and LDH peaked at 1383. She was treated on an unknown date for an increased international normalized ratio (value not reported) with vitamin K. Test results for EBV, CMV, Hepatitis A,B & C were all negative. The patient had no heart failure, sepsis, cancer or history of alcohol or tobacco abuse. History of acetaminophen use was not known. The patient was discharged on …….. and is recovering. Medical history included diabetes mellitus type 2, asthma, osteoporosis, degenerative joint disease, hypertension, and previous cholecystectomy. Concomitant medications included clarithromycin, moxifloxacin, montelukast (Singulair), fexofenidine (Allegra), lisinopril, fluticasone/salmeterol (Advair), hydrochlorothiazide, triamcinolone (Nasacort), alendronate (Fosamax), esomeprazole (Nexium), multivitamins and glucosamine. The patient has been taking all concomitant medications at the same time she has been taking Ketek, except Clarithromycin and Moxifloxacin. These two drugs had been prescribed for sinusitis, but since they didn't work the patient was prescribed Ketek. The diagnosis of liver failure is based on clinical manifestations. No biopsy has been done.	Montelukast, fexofenidine, lisinopril, Advair, HCTZ, triamcinolone, alendronate, esomeprazole, MVI, glucosamine Clarithromycin and moxifloxacin had been prescribed previously to telithromycin.	Diabetes (type II), asthma, osteoporosis, DJD, hypertension	Bili—24.3 AST—885 ALT—1172

Appendix 2. SUMMARY OF FOREIGN ACUTE LIVER FAILURE CASES (n=2) ASSOCIATED WITH TELITHROMYCIN

ISR # MFR #	Age Sex	Outcome	Indication Dose Time to onset (from day 1 of tx)	Event
200412840JP	85 F	Recovered	Pneumonia 600 mg daily 2 days	An 85 y/o male patient received 600mg of Ketek from 8/2/04 to 8/2 or 3/04 for pneumonia. No information of relevant history and concomitant disease provided. Concomitant drugs include leuprorelin acetate, hydroxyzine hydrochloride, famotidine, brotizolam, sodium picosulfate. On ……., the patient experienced hepatitis fulminant. On 8/2 or 3/04, Ketek was discontinued. Progress: 7/30/04: azithromycin hydrate for 3 days was prescribed. 8/2/04: Ketek for 5 days was prescribed. 8/3/04: The patient was transferred to municipal medical center due to loss of consciousness. ……..: GOT 4790, GPT 3220, LDH 4810, CRTN 3.2 ……: GOT 35, GPT 123, LDH 223, CRTN 1.21. 8/20/04: The patient returned to nursing care home. The physician's comment: Ammonia was not measured, but the loss of consciousness might have been caused by increase of it. Addendum on 9/17/04: The clinical event has been changed from "hepatitis fulminant" to "multiple organ failure", and "loss of consciousness" has been added. Chief complaint: Deterioration of level of consciousness History: The patient is in nursing home for MD, prostate cancer, dementia. The patient was receiving Zithromac for pain pharynx and abnormal auscultatory finding at right lung field since 7/30/04. It was replaced by Ketek since 8/3/04. The patient developed consciousness disturbed, irregular respiration, apnoea since evening of……. The patient was transferred to department of cranial nerve surgery for detailed examination. Since there was no abnormal CT findings, the patient was transferred to another department. Findings on admission: BT: 37.0c BP: 153/93 mmHg conj: not anemic, not icteric Heart: clear no murmur Lung: right rhonchi Respiration irregular, with apnea for around 20 to 30 seconds frequently occurs. Lab data on admission: WBC: 10700 RBC: 3550000 Hb: 10.9 Ht: 33.2 plt: 1230000 Na: 140 K: 5.4 Cl: 106 BUN: 75.1 Cr: 3.29 T-Bil: 1.7 GOT: 4790 GPT: 3220 LDH: 4810 ALP: 434 chE: 124 T-Ch: 153 CRP: (-) PT: 29.4% Chest X-ray: Infiltrative shadow with right interlobar pleural effusion. Congestion is suspected rather than pneumonia. ECG: ischemic change (-) Progress after hospitalization: Marked hepatic function disorder and renal impairment, cardiac failure-like pulmonary congestion were confirmed. Inflammatory reaction was low, no pyrexia, it was unlikely sepsis or ischemic cardiac event, according to ECG. Fluid, diuretic, ceftriaxone, LMWH 3000U s.c since D dimer was high) were administered. All internal drugs were discontinued then hepatic and renal functions gradually improved. Administration of internal drugs at previous physician were famotidine, chlorpromazine, sennoside A, B, bicalutamide, include macrolide and ketolide antibiotics which administered this time. Gaster, Contomin, Alosenn were reintroduced and no aggravation was confirmed. Casodex was not reintroduced since severe liver disorder was reported, however, it was unlikely the cause because it had been administered for years. The physician consider MOF is unlikely to relate to ketek. The patient was discharged on Aug,20 and transferred back to where he was, with marked improvement. However, the cause remains unknown. The reporting physician who prescribed ketek reported as follows. After the patient was transferred to another hospital, GOT and GPT rapidly increased. Hepatic function did not fluctuate during about 3 times of administration of Zithromac. Ketek is suspected as the cause of hepatic function aggravated.

Appendix 2. (continued)

ISR # MFR #	Age Sex	Outcome	Indication Dose Time to onset (from day 1 of tx)	Event
200413245JP .	78 F	Death	Bronchitis 300 mg daily (3 occasions) 2^{nd} day of 3^{rd} treatment cycle	This spontaneous case was received via Fujisawa Pharmaceutical Co. Ltd. from a physician on 19-Oct-2004. This case involves a 78-year-old female patient who received 300mg of Ketek (telithromycin) from 28-Sep-2004 to 1-Oct-2004, from 5-Oct-2004 to 8-Oct-2004, from 14-Oct-2004 to 15-Oct-2004 for bronchitis acute. No mention of relevant history. Concomitant diseases include cardiac failure, renal failure. No mention of concomitant drugs. On 15-Oct-2004, the patient experienced hepatic failure showing transaminase 20,000. Ketek was discontinued. The outcome is unknown. The physician assesses the causality between Ketek and hepatic failure as "possible". Addendum on 27-Oct-2004: Additional information: Concomitant drugs include Neuer (cetraxate hydrochloride) , Cleanal (fudosteine) , Theolong (theophylline) , Mucosolvan (ambroxol hydrochloride) , Alesion (epinastine hydrochloride) , Lincocin (lincomycin hydrochloride monohydrate) , Fosmicin (fosfomycin calcium) . The patient had been treated with dialysis since Dec-7-1999 to Oct-16-2004. Adver event reported was changed from hepatic failure to hepatic function disorder. On ……,the patient experienced hepatic function disorder, and she died on…….. due to hepatic failure, cardiac failure at 6 pm. lab data; Alb, ChE, ZTT, WBC, UIBC, Fer, …….. 3.2, 158, 2.6, 8100, 109, 522. ……. 3.8, 14800. The physician mentions Halospor (cefotiam hydrochloride) as possible alternative explanations for the hepatic function disorder. The physician assesses the causality between Ketek and hepatic function disorder as "possible". Addendum on 06-Dec-2004: Additional information: According to information via our license partner, the physician at the hospital where the patient was hospitalized and died states this event occurred due to general circulatory failure and it is unlikely related to Ketek. Addendum on 28-Dec-2004: Progress: On 25-Sep-2004, the patient developed common cold. Halospor (cefotiam hydrochloride) 1g/day was administered after hemodialysis at a nearby hospital, and the symptom transiently abated. On 10-Oct-2004, she developed common cold again. CRP 17, WBC 14800. She had a tendency of diarrhoea after hemodialysis on 14-Oct-2004. On 15-Dec-2004, she was almost bedridden. Neighbor physician made a house call, and glucose and Fosmicin (fosfomycin sodium) was intravenously administered. On ……, she made an emergency visit to the reporting hospital due to depressed level of consciousness. JCS (Japan Coma Scale) : II-1 , BP 80/40. Hypoglycaemia was significant. Acidosis (-19) . GOT/GPT 1200/971. She was urgently hospitalized around 13:00. After that, the acidosis got better. Blood pressure persisted low as around 60 even after catecholamine was administered. On ……., she deceased. The physician's comment: The patient developed severe arteriosclerosis accompanied dehydration and infection, it caused generalized circulatory failure. Therefore, Ketek is unlikely related. Lab data …… BT 36, 37.5, 38.0; Pulse 110; BP(mmHg) 60/47; RBC(10000/mm3) 428, 350, 328; HGB(g/dL) 14.6, 12.5; HCT(%) 36.5; WBC(/mm3) 15302, 13500; Band neut(%) 575; Seg(%) 6.5; Eos(%) 0; Baso(%) 0; L(%) 2.0; Mo(%) 1.0; plt(10000/mm3) 7.2, 4.3, 2.2 PT(%); AST(IU/L) 1201, 18121, 15150; ALT(IU/L) 991, 4240, 4340; LDH(U/L) 126, 7787, 23570; T-Bil(mg/dL) 1.3, 2.0; D-Bil(mg/dL) 0.7, 1.5; TP(g/dL) 0.1, 5.1; BUN(mg/dL) 64, 93; CRTN(mg/dL) 4.63, 5.23; Na(mEq/L) 131, 145; K(mEq/L) 4.7; Cl(mEq/L) 95; CRP CK(U/L) 857, 1875; BS(mg/dL) 28 Addendum on 12-Jan-2005: The physicians at the hospital where the patient was admitted assesses Ketek is unrelated with the events. The other hand, physician who prescribed still assesses the causal relationship with Ketek and hepatic shock can not be excluded.

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cc:
NDA # 21-144
HFD-520 Division File / Alexander / DeBellas
HFD-430 Avigan / Johann-Liang / Truffa / Beam / Chron / Drug

MEMORANDUM **DEPARTMENT OF HEALTH AND HUMAN SERVICES**
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

RCM # 2006-195

DATE: October 10, 2006

TO: Janice Soreth, M.D., Director
Division of Anti-Infective and Ophthalmologic Products

FROM: Allen Brinker, M.D., M.S., Epidemiologist and Team Leader
Division of Drug Risk Evaluation

Melissa M. Truffa, R.Ph., Safety Evaluator Team Leader
Division of Drug Risk Evaluation

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

SUBJECT: Exacerbation of Myasthenia Gravis

PRODUCTS: Ketek® (telithromycin) Tablets, NDA 21-144

****This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/non-FDA personnel without contractor approval obtained through FDA's Office of Surveillance and Epidemiology. ****

1.0 EXECUTIVE SUMMARY

This review was conducted to document exacerbation of myasthenia gravis in association with telithromycin because cases of exacerbation of myasthenia gravis including four fatal cases continue to be reported to the Adverse Event Reporting System (AERS) despite warnings in the Ketek® label. The labeling with regard to exacerbation of myasthenia gravis was recently changed as of June 2006 to include theses fatal cases. In addition to other changes, the following text was advanced from the body of text within the WARNINGS section of the label to the first, or introductory, sentence under a new, discrete section called, "Exacerbations of myasthenia gravis."

"Telithromycin should not be used in patients with myasthenia gravis unless no other therapeutic alternatives are available"

Labeling changes were advanced with a *Dear Healthcare Professional* letter in addition and other communication avenues, including the FDA's MedWatch program.

Although telithromycin is the most recently marketed of selected antibiotics (see Table 3), it is currently associated with more cases of exacerbation of myasthenia gravis than all eight comparator agents combined (n=7). Furthermore, at least 6 cases of telithromycin associated MG resulted in intubation. A formal quantitative (i.e., reporting rates) analysis has not been conducted, however, these data nonetheless suggest exacerbation of MG may be more frequent with telithromycin than similar antibiotics.

To further address concerns which prompted the June 2006 measures other strategies should also be considered 1) a Medication Guide, 2) to facilitate the Medication Guide unit-of-use packaging with printing specific to myasthenia gravis, and/or 3) the addition of the statement "Telithromycin should not be used in patients with myasthenia gravis" to CONTRAINDICATIONS section of the label.

2.0 BACKGROUND

The March 2004 Medical Officer's safety review[24] for NDA 21-144 for Ketek® (telithromycin) states: "*Review of post-marketing data revealed a total of 13 patients with likely telithromycin-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."* A warning stating that telithromycin is not recommended in patients with myasthenia gravis unless no other therapeutic alternatives are available was included in Ketek's product labeling[25] at the time of the April 2004 U.S. approval. A statement that "telithromycin is not recommended in patients with myasthenia gravis" was also included in Information for patients. However, the patient package insert (PPI) only states that there have reports of "worsening myasthenia gravis symptoms in patients with myasthenia gravis" but does not state that use is not recommended in these patients or advises patient to talk to their doctors before starting therapy with telithromycin.

Despite strong warnings about the use of telithromycin in patients with myasthenia gravis cases including fatalities continue to be reported post-approval. A review of post-marketing AERS from U.S. marketing (April 2004) through May 2006 identified 26 reports of exacerbation of myasthenia gravis including 3 deaths. In June 2006 the Ketek® labeling was revised to add stronger recommendations about the exacerbation of myasthenia gravis including reports of death to Warnings, Information for Patients, and Patient Package Insert (see Section 3.0, Product Labeling below).

This document intends to summarize the AERS reports of exacerbation of myasthenia gravis as of August 8, 2006 and explore the possibility of contraindicating the use of telithromycin in all patients with myasthenia gravis.

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[24] Medical Officer Safety Review of NDA 21-144: Telithromycin (Ketek™), March 31, 2004. Available at: http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek.htm

[25] April 2004; Ketek® (telithromycin) Package Insert, 2004 Aventis Pharmaceuticals Inc.

3.0 PRODUCT LABELING

Ketek® (telithromycin) Labeling for Myasthenia Gravis approved June 26, 2006[26] (2006 revisions are in italics):

Warnings
Exacerbation of myasthenia gravis: Telithromycin *should not be used* in patients with myasthenia gravis unless no other therapeutic alternatives are available *(moved to the beginning of paragraph from the body of the text).* Exacerbations of myasthenia gravis have been reported in patients with myasthenia gravis treated with telithromycin. This has sometimes occurred within a few hours after intake of the first dose of telithromycin. Reports have included *death* and life-threatening acute respiratory failure with a rapid onset in patients with myasthenia gravis treated for respiratory tract infections with telithromycin. If other therapeutic alternatives are not available, patients with myasthenia gravis taking telithromycin must be closely monitored. Patients must be advised that if they experience exacerbation of their symptoms, they should discontinue treatment with KETEK and immediately seek medical attention. Supportive measures should be instituted as medically necessary.

Precautions/Information for Patients: *Patients with myasthenia gravis should not take KETEK, unless there are no other therapeutic alternatives. Exacerbations of myasthenia gravis have been reported in patients treated with KETEK. This has sometimes occurred within a few hours after taking the first dose. Reports have included death and life-threatening respiratory failure that occurred rapidly in patients with myasthenia gravis (see* ***WARNINGS).***

Patient Package Insert:
Worsening of myasthenia gravis has been reported in patients treated with KETEK. *This has sometimes occurred within a few hours after taking the first dose. Reports have included death and life-threatening breathing problems that happens fast in myasthenia gravis patients. If you have myasthenia gravis, you should talk with your doctor before taking KETEK.*

Contraindications: No applicable text for myasthenia gravis.

4.0 DRUG USE DATA

VERISPAN, LLC
Vector One®: National (VONA)
Verispan's VONA is a nationally projected database which measures the retail dispensing of prescriptions or the frequency with which drugs move out of retail pharmacies into the hands of consumers via formal prescriptions. Information on the physician specialty, the patient's age and gender, and estimates for the numbers of patients that are continuing or new to therapy are available.

[26] June 2006; Ketek® (telithromycin) Package Insert, 2006 sanofi-aventis U.S. LLC

The Vector One® database integrates prescription activity from a variety of sources including national retail chains, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2.0 billion prescription claims, representing over 160 million unique patients. The number of dispensed prescriptions is obtained from a sample of virtually all retail pharmacies throughout the U.S and represents approximately half of the retail prescriptions dispensed nationwide. Verispan receives all prescriptions from approximately one-third of the stores and a significant sample of prescriptions from the remaining stores. Mail order prescriptions are not included in the sample at this time.

Table 1. Projected number of total prescriptions for Ketek® (telithromycin) dispensed by retail pharmacies in the US (through May 2006)[1]
(NUMBERS ARE IN THOUSANDS: ADD THREE ZEROS [000].)

REDACTED

5.0 AERS SEARCH STRATEGY

Search Criteria:

- Date of Search: August 8, 2006
- All reports in AERS from date of US marketing (April 2004) until August 8, 2006
- MedDRA: Myasthenias, a group of high level terms (HLT), Neuromuscular Junction Dysfunction (HLT), Respiratory Failure (EXCL Neonatal) (HLT)*, Respiratory Arrest, a preferred term (PT), and Cardio-pulmonary Arrest (PT)
- All post-approval telithromycin reports with outcome of death were searched to capture potential reports of a possible myasthenia gravis-related fatal outcome.

***Note**: The respiratory failure and arrest terms were included as a surrogate to capture reports of myasthenia gravis (MG) exacerbation or crisis with a serious respiratory outcome that did not specifically mention myasthenia gravis.

Myasthenia Gravis Crisis: A crisis occurs when a person with myasthenia gravis develops difficulty in breathing, requiring hospitalization and usually a mechanical respirator. The crisis may be brought on by any stress on the body, such as infection, emotional upset, physical activity, menstruation, pregnancy, or even adverse reaction to medication. The patient in crisis requires swift medical attention to treat life-threatening respiratory problems.

6.0 AERS SEARCH RESULTS (n=33)

A total of 62 reports were retrieved from the AER database. After removing 3 duplicate reports and excluding 26 reports because they were unrelated to exacerbation of myasthenia gravis, **33** unduplicated cases were identified for further review.

6.1 Case Characteristics (Table 2)

Table 2. Clinical characteristics of Exacerbation of Myasthenia Gravis in Association with Telithromycin (from marketing through 8/8/2006)	
Number of Cases	**N=33**
Age (n=28)	Range—34 to 85 years Median—59 years
Gender (n=31)	Female (20), Male (11)
Source	US (28), Non-US (5)
Outcome	Death (4) Hosp (15) Life-threatening (7) Medically significant (7)
Average Daily Dose	800 mg
Indication for use (verbatim from report) (N=27)	Sinusitis--11 Bronchitis--5 Pneumonia--4 URI--2 1 each--bacterial infection, pharyngitis, chest congestion, flu-like illness
Latency (time to onset of symptoms from initiation of treatment)	Range—0.5 hours to 14 days Median— 1.25 hours (n=16) Average—1.5 hours After 1st dose of Ketek (n=23)
History of MG	29
Patients requiring a ventilator or intubation	12

A summary of all **33** cases can be found in the Table 3 (see Appendix).

6.2 Fatal Cases (n=4)

AERS Case # 5940271, Mfr# US-Aventis-200519884US: An 80-year-old female consumer initiated therapy with Ketek (telithromycin) 800mg daily on 27-Nov-2005, for a sinus infection. Relevant medical history includes myasthenia gravis, and allergies to penicillin and sulfa. Concomitant medications include Prednisone, Mestinon (pyridostigmine bromide), and Duo neb (salbutamol with ipratropium bromide). On ……., the patient took her first dose of Ketek at 9:30pm and around midnight she began experiencing "respiratory problems." The patient was taken to the emergency room where they treated her with oxygen. The patient was a "DNR" so no drastic measures were performed. She died at 1:30am on …….

AERS Case # 6101315 and 5768411; Mfr# 200512341US and Direct Consumer Reports: A 71-year-old female patient was given samples of Ketek (telithromycin) on 18-Feb-2005 for acute

bronchitis. The patient took her first dose of 800 mg on …….. and experienced an anaphylaxis reaction with respiratory failure 30 minutes thereafter. The patient was described by the health care professional to have significant tongue and facial swelling. The patient was transported to the hospital, intubated, and placed on mechanical ventilation. Additional treatment measures included prednisone, intravenous steroids, blood pressure support, and therapy for myasthenia in which she did not respond. The patient "collapsed" and fell into a coma for several days and died on …….. No autopsy was performed. The health care professional stated he has not seen the death certificate. The discharge summary indicates the patient died of acute respiratory failure. The patient has no known drug allergies. Laboratory values provided include a potassium level of 3.1. The health care professional stated her blood test was otherwise normal. Medical history includes ocular myasthenia (mild) for several years. The health care professional feels her death was attributed to anaphylaxis due to Ketek therapy since respiratory failure occurred 30 minutes after the first dose was taken. Concomitant medications include Mestinon (pyridostigmine bromide).

AERS Case # 5750251, Mfr# 200510488EU, Spain: This 72-year-old female patient who was given Ketek (telithromycin), 800 mg/d, since 01 January, 2005, for a non-specified bacterial infection, developed respiratory insufficiency on ……. and died on the same day from a cardiac arrest. Myasthenia gravis was given as a contributory factor of the fatal event. Additional treatment: salbutamol. The Spanish Health Authorities considered telithromycin as the only suspect drug.

AERS Case# 5988058, Mfr#200611454US: This case was reported via a sales representative from a physician who gave a lecture on drug-drug interactions to a myasthenia gravis group on medications to avoid. When Ketek was discussed, an unknown member stated that one of our members died while taking Ketek (telithromycin). Patient demographics were not provided. The lecturer was not the patient's physician.

7.0 EPIDEMIOLOGY

In order to assess reporting of myasthenia gravis (MG) exacerbation in association with telithromycin in comparison to other, similar antibiotics, a complementary epidemiology analysis was undertaken. This analysis was different than the one outlined above as the primary focus was for quantitative comparison. In addition, the large number of AERS reports for some of the older comparator products required a specific, rather than sensitive, report recovery algorithm.

Methods: This analysis was conducted on 14 September 2006 and restricted to reports classified as domestic within the AERS database. Reports were recovered for telithromycin and 8 comparator antibiotics as listed in Table 3 based on the presence of a event (as a *preferred term*) listed under the *high level terms* of ***myasthenias*** or ***neuromuscular junction dysfunction.***

Reports recovered under this search process were then subjected to hands-on evaluation for case status. Cases were defined as unique, domestic reports of MG exacerbation following initiation of an oral course of therapy with one of the selected antibiotics. Reports of MG presenting with initiation of antibiotic therapy (i.e., new diagnosis) were excluded.

Table 3. Domestic MedWatch reports of exacerbation of myasthenia gravis in association with selected antibiotics: crude counts, cases, and cases with report of intubation. Data from AERS database of MedWatch reports.				
Drug	Marketing appearance	Reports captured in search	Cases After review	Intubated (N)
azithromycin	1992	24	3	1
clarithromycin	1992	3	0	0
levofloxacin	1997	8	3	1
cefdinir	1998	0	0	0
moxifloxacin	2000	9	1	0
gatifloxacin	2000	2	0	0
cefditoren	2001	0	0	0
gemifloxacin	2003	0	0	0
telithromycin	2004	20	15	6

Results/Discussion: Results are shown in Table 3. As of the time this search was conducted, telithromycin was associated with 15 cases of exacerbation of myasthenia gravis. Although telithromycin is the most recently marketed of these selected antibiotics, it is currently associated with more cases of exacerbation of myasthenia gravis agent than all eight comparator agents combined (n=7). Furthermore, 6 cases of telithromycin associated MG resulted in intubation.

It is problematic to calculate reporting rates for this event as patients with MG might enter into a crisis/exacerbation as a result of the illness under treatment, and so attribution to a drug is confounded. Also, choice of comparator is difficult. Cefditoren and gemifloxacin would be potential comparators given labeled indications and time-on-market but have limited utilization in comparison to telithromycin. Although a formal quantitative (i.e., reporting rates) analysis has not been conducted, these data nonetheless suggest exacerbation of MG may be more frequent with telithromycin than similar antibiotics.

8.0 DISCUSSION

In the United States the prevalence of myasthenia gravis is estimated at 14/100,000 population (incidence of 5-10 cases per million population) resulting in approximately 25,000- 36,000 patients currently living with myasthenia gravis.[27],[28] Previous studies show that women are more often affected than men and the most common age at onset is second and third decades in women and the seventh and eight decades in men. In people who present with MG at < 40 years of age, 75% are women and those > 40 years of age are 60% men.

Approximately 12-16% of patients will at some point in their illness experience crisis. This occurrence is most likely in patients with history of previous crisis, oropharyngeal weakness, or thymoma. Possible temporally associated triggers with development of crisis (see Table 4)

[27] http://www.myasthenia.org/information/summary.htm Howard JF, Department of Neurology, UNC
[28] http://info.med.yale.edu/neurol/programs/neuromuscular/mg.html Neurology Department Yale University School of Medicine

include infections, emotional and physical stress, aspiration, and changes in medications (see Table 5)[29,30].

Table 4. Possible Triggers for Myasthenia Gravis Crisis
• Infections (30-40%) of crisis (most common are viral upper respiratory tract infections, bronchitis, bacterial pneumonia).
• Aspiration pneumonitis (10%) of crisis
• Emotional and Physical Stress (trauma or surgery)
• Changes in medicines (including recent initiation of medicine in Table 5, recent increases in dose of AChE inhibitor, and recent tapering of corticosteroids)
• No obvious trigger (30-40%)

Table 5. **Medications that may exacerbate weakness and trigger a myasthenia crisis**
• **Anti-arrthythmic agents :** quinidine, procainamide
• **Antibiotics:** aminoglycosides (gentamicin, tobramycin, others), tetracyclines (tetracycline, doxycycline, others), macrolides (erythromycin, clarithromycin, azithromycin), quinine derivatives (ciprofloxacin, other quinolones), ampicillin, peptide antibiotics (polymyxin B, Colistin)
• **Beta Blockers:** (propanolol, atenolol, others)
• **Calcium Channel Blockers**: (verapamil, others)
• **Neuromuscular junction blocking agents:** succinylcholine chloride, curare derivatives, others
• **Steroids**
• **Others:** Quinine, Thyroid hormones, Anticonvulsants (phenytoin, carbmazepine)

Exacerbation of myasthenia gravis has been reported in the medical literature in association with the use of medications. Anti-infectives (aminoglycosides, macrolides, and quinolones) caution against use in patients with myasthenia gravis; neuromuscular junction blocking agents and Botox® warn against use in these patients. Quinine is contradicted in myasthenia gravis patients. Currently, the labeling for Ketek warns that "*Telithromycin should not be used in patients with myasthenia gravis unless no other therapeutic alternatives are available"* and if therapy is warranted in these patients that they be closely monitored.

Post-approval reports of exacerbation of myasthenia gravis have been received with use of telithromycin despite the **Warning** to only us when no alternative therapies are available. This includes 4 reports of fatalities one of which may have been due to an anaphylaxis reaction however, exacerbation of myasthenia gravis cannot be definitively ruled out as contributory (see Section 6.2). In additional to these deaths there were 15 hospitalization and 7 reports of life-threatening event. The severity of these reports is reflected by the number of patients who required intubation for exacerbation of myasthenia gravis (12/29 or 41%) and in the rapid onset on symptoms after (median time = 1.25 hours) a dose of telithromycin. The majority (23/33) of these patients experienced symptoms after the first dose.

[29] Bedlack RS, Sanders DB. How to handle myasthenia crisis: essential steops in patient care. Postgrad Med 2000: 107 (4): 211-22

[30] Mayer S. Intensive care of the myasthenia patient. Neurology 1997:48(Suppl 5): 70-75S

Although underreporting and reporting biases complicate drug against drug comparisons, this review includes an epidemiology analysis that identified 15 cases of exacerbation of myasthenia gravis in association with telithromycin verses 7 cases for all eight comparator agents. Furthermore, 6 cases of telithromycin associated MG resulted in intubation. These data suggest the risk for exacerbation of MG may be greater with telithromycin than other agents. This is particularly important when the condition for treatment is acute bacterial sinusitis or acute exacerbation of chronic bronchitis in contrast the risk:benefit ratio given treatment for a condition such as pneumonia.

9.0 CONCLUSIONS/RECOMMENDATIONS

This review was conducted to document exacerbation of myasthenia gravis in association with telithromycin and follows labeling changes to the telithromycin (Ketek) label as of June 2006. In addition to other changes, the following text was advanced from the body of text within the WARNINGS section of the label to the first, or introductory, sentence under a new, discrete section called, "Exacerbations of myasthenia gravis."

> "Telithromycin should not be used in patients with myasthenia gravis unless no other therapeutic alternatives are available"

Labeling changes were advanced with a *Dear Healthcare Professional* letter in addition and other communication avenues, including the FDA's MedWatch program.

Although telithromycin is the most recently marketed of selected antibiotics (see Table 3), it is currently associated with more cases of exacerbation of myasthenia gravis than all eight comparator agents combined (n=7). Furthermore, at least 6 cases of telithromycin associated MG resulted in intubation. A formal quantitative (i.e., reporting rates) analysis has not been conducted, however, these data nonetheless suggest exacerbation of MG may be more frequent with telithromycin than similar antibiotics.

To further address concerns which prompted the June 2006 measures other strategies should also be considered 1) a Medication Guide, 2) to facilitate the Medication Guide unit-of-use packaging with printing specific to myasthenia gravis, and/or 3) the addition of the statement "Telithromycin should not be used in patients with myasthenia gravis" to CONTRAINDICATIONS section of the label.

APPENDIX: Table 6: Summary of Myasthenia Gravis Cases Associated With Telithromycin as of August 8, 2006 (N=33)

# Case # MFR # Location	Sex	Outcome	Indication Dose/Duration Time to onset of symptoms	Event(s)	Concomitant medications	History of Myasthenia Gravis	Required ventilator or intubation
1 **5811403** **200514571US**	Unk M	Hosp	Bronchitis 1 dose Not reported	Myasthenia gravis	Non reported	Yes	Not Reported
A male patient initiated therapy with Ketek for bronchitis on…….. Subsequent to taking the first dose, the patient experienced myasthenia crisis and was hospitalized. The patient only had one lung which is now functioning at 48% of its capacity.							
2 **5855445** **200513857US** .	Unk	Hosp	Not reported Not reported 14 days	Myasthenia gravis dysphasia	None reported	No	Not Reported
An elderly patient initiated Ketek (indication and therapy dates not provided) and 2 weeks later developed dysphasia and was hospitalized. Patient may have developed myasthenia gravis. Outcome of adverse event, treatment measures taken and tests performed not provided.							
3 **5857385** **200514520US** .	Unk F	Hosp	Not reported 1 dose 45 minutes	Myasthenia gravis Throat tightness dysarthria	None reported	Yes (remission 15 years)	Almost
A female patient initiated Ketek and experienced exacerbation of her myasthenia gravis characterized by throat constriction. They almost had to intubate her but they didn't. The nurse stated that the patient took 1 dose of Ketek and 45 minutes later she experienced slurred speech. The patient consulted her physician and Ketek was discontinued. The nurse stated she seemed fine when she left the office. Outcome of adverse event, treatment measures taken and tests performed not provided. Patient's physician stated that she had been in remission for 15 years and has taken fluoroquinolones without exacerbating the condition.							
4 **5770074** **200512391US** .	34 M	Hosp	Pneumonia 800mg x 1 dose Not reported	Myasthenia gravis Throat tightness	Pyridostigmine	Yes	Yes (admitted to ICU)
A 34 year old male patient received two 400mg tablets of telithromycin (Ketek) once on 21-Mar-2005 for pneumonia. On ……., the patient was presented to the emergency room for shortness breath (pointing to his throat), cyanosis, sweating, blood pressure of 200/100 and heart rate of 110. Rhonchi were noted to his breath sounds. The patient was given 2 ampules of Atropine and intubated. He was transferred to ICU the same day and place on a ventilator. He remained on a ventilator in ICU at the time of the report. The physician confirmed the therapy date of telithromycin to be 21-Mar-2005, and that the event abated after the use of telithromycin was stopped. Clinical outcome is resolved. Physician's causal assessment is possible: "Interaction between pyridostigmine and Ketek versus myasthenic exacerbation with Ketek."							
# **Case #**			**Indication Dose/Duration**				**Required**

MFR # Location	Sex	Outcome	Time to onset of symptoms	Event(s)	Concomitant medications	History of Myasthenia Gravis	ventilator or intubation
5 **5768409** **200511054FR**	38 F	Medically significant	Sinusitis 800 mg x 1 dose 3 hours	Myasthenia gravis Dysphonia Dyspnea	Prednisolone Levothyroxine Ibuprofen acetylcysteine	No	No
A 38-year-old female patient with a medical history of benign multinodular goiter and total thyroidectomy on 24-FEB-03 with substitutive treatment well controlled, but no diabetes mellitus and no other autoimmune disease. The patient had also a medical history of drug intolerance to dihydroergotamine (tinnitus, vertigo, cold finger). On 11-OCT-05, treatment with telithromycin was started for rhinosinusitis. The concomitant drugs were prednisolone sulfobenzoate PO 60 mg/d from 11 to 13-OCT-04 and acetylcysteine PO 30 mg/d for 5 days and levothyrox 100 microg/d. Three hours later, the patient experienced drunken sensation, marked asthenia and dyspnea. The same day, treatment with telithromycin was discontinued and no corrective treatment was administered. It was the first treatment with telithromycin. The patient had previously been treated with roxitromycin and penicillin with a good tolerance. Thoracic CT scan showed a remaining thymus and on 16-MAR-05, EMG was reportedly contributive. Asthenia, difficulties in speaking, swallowing, masticating, writing or combing her hair persisted. According to the neurologist's report, since the beginning of the year, the patient experienced marked fatiguability, dysphonia, swallowing disorder and proximal weakness of limbs. The patient's condition had improved on treatment with pyridostigmine bromure PO 5 tablets/d. Osserman's score was 74/100. Level of antibody to acetylcholine receptors was high. Surgery was planned for thymic remaining. According to the GP, myasthenia gravis was diagnosed after the treatment with telithromycin and he suspected its role in the onset or revelation of the disease. The GP assessed the role of telithromycin as highly probable.							
6 **5815855** **200512120US**	43 F	Medically significant	Not reported 800mg x 2 doses Not reported	Myasthenia gravis Eyelid disorder	Pyridostigmine Antibiotic (unspecified)	Yes	No
A 43 year old female patient started Ketek 800 mg on 05-Mar-05 (indication unspecified). She took 2 doses and experienced worsening of her myasthenia gravis with difficulty opening her left eyelid. Patient increased her dose of Mestinon for the MG symptoms. The following day she was switched to another antibiotic (unspecified). It took about 3 weeks for complete resolution of symptoms.							
7 **5756777** **200417457US**	45 F	Medically significant	Pneumonia (CAP) 800mg x 1 dose 1 hour	Myasthenia gravis	None reported	Yes (Diagnosis 15 years ago with associated history of weakness, visual and balance problem; in remission for 10 years)	No
A 45 year old female patient started Ketek for CAP on 22-Sept-04. Approximately 1 hour after receiving her first dose, the patient experienced blurred vision. The patient was taken to the ER by her husband on ……. with complaints of weakness, throat closing, problems focusing, N/V, and severe headache with pressure behind her eyes. The patient was given Reglan for the N/V as well as IV fluids. She was monitored in the ER and discharged the same day feeling much better. Oxygen saturation was 99% with no soft tissue swelling of the airway. Chest X-ray revealed no pneumonia. The patient never had an event like the one reported. Ketek was discontinued due to the event after taking the initial dose and the visual disturbances began 1 hour after the dose and lasted for 10-12 hours.							
# **Case #**			**Indication** **Dose/Duration**				**Required**

MFR # Location	Sex	Outcome	Time to onset of symptoms	Event(s)	Concomitant medications	History of Myasthenia Gravis	ventilator or intubation
8 **5771953** **CTU 244596**	46 F	Life-threatening	Sinusitis 400 mg x 1 dose Not Reported	Myasthenia gravis Respiratory distress	None Reported	Yes	Not Reported
Patient had respiratory distress after taking one dose of Ketek. Oxygen saturation 84%							
9 **5686299** **200418120US**	46 F	Hosp	Sinusitis/pneumonia 800mg x 1 dose 20 minutes	Myasthenia gravis	Hydrochlorothiazide Pyridostigmine Maxzide	Yes	Yes
A 46 year old Caucasian female with history of myasthenia gravis diagnosed in 2001 and history of hypertension developed a fever of 101 or 102 with dry cough. She was diagnosed with bacterial sinusitis and given Ketek 800mg daily on …….. Approximately 20 minutes later while driving with a friend she noticed weakness , blurred vision, and tiredness then the patient started having shortness of breath, and cough. She went to the ER and was found to be hypoxic with pulse oximetry of 84%, received albuterol nebulizer treatments and IV Solumedrol with no improvement and was sedated and intubated. She was felt to be in myasthenia crisis. She was transferred to the acute care facility. Her temperature was 100.8, blood pressure 109/56 and pulse 111. Pulse oximetry of 100% on ventilator. She was admitted to the MICU with respiratory failure and myasthenia gravis. Neurology and hematology were consulted. She was placed back on Mestinon and given 2 runs of plasmaphresis ……. with improvement. Patient was switched from Ketek to moxifloxacin for pneumonia/ sinusitis. CT scans of head and chest were negative. Patient discharged on ……...							
10 **5705466** **5708236** **CTU 235024** **200419776US**	48 M	Life-threatening	Sinusitis 800mg x 1 dose 1.5 hours	Myasthenia gravis Respiratory failure Vision blurred	Valsartan Serevent Paroxetine Singular (montelukast) Aspirin	Yes	Yes
48-year old male patient experienced breathing difficulty and blurred vision 45 minutes to 1.5 hours after receiving the first dose of Ketek of 800 mg for sinusitis on …….. The patient had not taken Ketek in the past and was had an allergy to cephalosporins. Patient was taken to via ambulance to the hospital in respiratory failure (on a respirator). He was admitted with exacerbation of myasthenia gravis (treated with Mestinon and steroids) and respiratory failure. Patient was on a ventilator for 13.5 hours. Blurred vision appeared 20 minutes after first dose and lasted for more than 12 hours. Patient recovered with symptoms of myasthenia gravis. Patient had been treated with azithromycin in Sept 2004 with no reaction.							
11 **5977792** **BE-Aventis-200610836GDDC**	50 F	Hosp	Pharyngitis 800mg x 1 dose 2 hours	Myasthenia gravis Paresis Quadriparesis Respiratory failure	Corticosteroids Mestinon	Yes	Not reported
50 year old female initiated Ketek 800mg daily on …….. for pharyngitis and 2 hours after first 2 tablets developed severe quadric-paresis and respiratory failure. Patient was hospitalized and made a complete recovery.							

# Case # MFR # Location	Sex	Outcome	Indication Dose/Duration Time to onset of symptoms	Event(s)	Concomitant medications	History of Myasthenia Gravis	Required ventilator or intubation
12 5977791 US-Aventis-200610980US	50 F	Medically Significant	Sinus infection 800mg x 1 dose 1 hour	Myasthenia gravis Aphasia Fatigue paralysis	Kaletra, Hivid, dapsone, Sustiva, ibuprofen, sertraline, garlic, ambient, grape seed, medroxypra AC, cenestin, cephalexin, metronidazole	No	Not reported
A 50-year-old female consumer received Ketek (telithromycin) 400mg 2 tabs QD once on 05Jan06 for sinusitis. Med hx: AIDS diagnosed 1985, recurrent varicella zoster virus of L lower extremity, chicken pox 2X as an adult, chronic hepatitis C with elevated LFT, bilateral tubal ligation, insomnia, gastroenteritis with nausea and diarrhea, cervical dysplasia, abnormal pap smears, trichomonas vaginalis, cryotherapy, benign breast lumpectomy, multiple cystoscopies, occasional tachycardia since 14 yrs and occasional constipation and diarrhea. 05Jan06, pt called MD's office with c/o of sore throat, dry cough, green mucous, sinus pain, and pressure, fever and body aches. She missed 4 days of work. Pt was aware MD was not in on Thurs.'s and went to ……, where the dx was sinusitis and Ketek was given. Pt took 2 pills that night and within 1 hr had no feeling or movement to the body. She went to ER and was told it was Myasthenia Gravis. No neurologic tests performed to dx myasthenia gravis. All symptoms resolved by 23Jan06. ER released her and gave her erythromycin (previously reported as a hospitalization). 18Jan06, prescription was finished; however, she still had Sx of a sinusitis. 23Jan06, returned to her MD with c/o a sore throat, nasal discharge, and headaches. Impression: chronic sinusitis times 2 months. TX included Azithromycin 250 mg 2X that day then 1 tab PO QD for 4 days and steam to nasal passage BID No further info was provided. She took 2 tabs of Ketek 400 mg at 2 PM with NyQuil and by 3PM she complained of general weakness with decreased strength and increased lethargy. VS at 4:43PM, T 97.5, HR 82, R 18, BP 156/101, and POx 99% on room air. 6:30PM, VS were HR 90,R 18, BP 126/75 and POx 97% on room air. Pt was given IV fluids of NS 1 L. CT findings: no acute intracranial abnormality, but R max sinus disease. Abnormal lab results: alk phos 150, ALT 81, AST 65, and RBC 4.09. MD reported pt was sick for about a wk with SX of sinusitis. Pt saw her MD who prescribed Ketek. She took Ketek with NyQuil and took a nap. When she awakened, she felt foggy, out of it and things were in slow motion. She came to the ER and c/o a mild headache. No other system complaints. Physician exam, pt appeared fatigued. Review of systems were WNL, cranial nerves II-XII were grossly intact. Motor 5/5. Sensory intact. Cerebellar revealed no localizing findings. Pt was hydrated with a L of fluid. Her Sx resolved and she was up, ambulatory and felt back to herself. Final dx was altered mental status, resolved, and sinusitis. Etiology unclear. There did not appear to be any acute Cerebrovascular disease. Possibly an AE secondary to NyQuil and Ketek. Differentials: CNS infection, ingestion, hypoxemia, and PE. Pt was asymptomatic Medication changed from Ketek to amoxicillin (previously reported as erythromycin) and encouraged to push fluids and continue meds as directed. Pt was discharged home in stable condition with husband. Pt is a smoker. In this received report by ER, there is no mention of dx of drug-induced myasthenia gravis. Dx is altered mental status, which resolved on 05-JAN-2006, in 4 hr. Per internal review, it is found that patient's sinusitis wasn't resolved by 23JAN-2006, and she was prescribed Azythromycin. It was found that elevated ALT & AST weren't serious.							
13 5759826 200419794US	53 F	Hosp	Unknown 800mg x 1 dose 40 minutes	Myasthenia crisis	Pyridostigmine Pioglitazone Benezepril Venelafaxine Carvedilol glimepiride	Yes	Yes
53 year old female took 800mg of Ketek x 1 dose in the physician's office. Approximately 40 minutes later at the …… Pharmacy, she began her myasthenia crisis and was intubated at the …… pharmacy by the rescue squad. She was treated with steroids, famotidine, and diphenhydramine during admission with							

full recovery.							
# Case # MFR # Location	**Sex**	**Outcome**	**Indication Dose/Duration Time to onset of symptoms**	**Event(s)**	**Concomitant medications**	**History of Myasthenia Gravis**	**Required ventilator or intubation**
14 5749808 FR-BMS-12873311	56 F	Hosp	Sinusitis 800mg daily Not reported (9 days of therapy before dc'd)	Myasthenic syndrome Eyelid ptosis headache	Coaprovel	Yes (from another drug)	No
A 56 year old female experienced myasthenia gravis during the use of irbesartan for the treatment of arterial hypertension. Myasthenia worsened after the introduction of telithromycin for the treatment of sinusitis on 26-Aug-2003. On 15-Jul-2003 the patient experienced exacerbation of myasthenia. Neurological exam revealed bilateral right and left ptosis, paralysis of oculomotor nerve and paralysis without extension. Test results: prostigmine was positive, acetylcholine antibody anti-receptor was negative, antinuclear antibody was negative, skeletal antibody anti-muscle was negative and no thymoma was identified. Patient recovered with sequelea. Exacerbation of MG possibly due to both suspect agents. Addendum: On 15-Jul-2003, ptosis and arterial hypertension were diagnosed and treated with indapamide, then valsartan 160, followed by irbesartan + hydrochlorothiazide (HCTZ). Ptosis could be aggravated by irbesartan + HCTZ therapy. In early Aug-2003, the patient was evaluated in the emergency ward for sinusitis, and started on the antibiotic, telithromycin as treatment. Ptosis clearly worsened. On ……, the patient was hospitalized and was diagnosed with myasthenia. Prostigmine test was positive. Irbesartan + HCTZ therapy was stopped on 27-Oct-2003. A neurological exam revealed no pyramidal syndrome. The outcome revealed spreading to other musculature. The patient was treated with pyridostigmine bromide, corticoids, and plasmapheresis (2004). Medical history included osteomalacia since 1995, nephritic colic in 1996, asthma, and tuberculosis for more than 15 years. By the end of Aug-2003, the patient was hospitalized due to ptosis and cephalgias. On ……., an ophthalmologic consultation revealed a marked worsening of ptosis and telithromycin therapy was stopped. At the time of reporting, the patient had not yet recovered.							
15 5937752 200516265US	58 M	Medically significant	Chest congestion 800mg x 1 dose Not reported	Myasthenia gravis Difficulty breathing	Levothyroxine Pyridostigmine	Yes (since 2003)	No
58 year old male received telithromycin 800mg for chest congestion and weakness. On 12-Jul-2005 the patient experienced exacerbation of myasthenia gravis after his first dose of telithromycin (exact time after dose is unknown). Patient contacted doctor when experiencing overall weakness and difficulty breathing. The patient remained home and did not receive any treatment and recovered with 3-4 hours. Ketek was discontinued after the first dose because of exacerbation.							
16 6016061 CTU272657	60 F	Life-threatening	Pneumonia 800mg x 1 dose 3 hours	Myasthenia gravis Respiratory failure	None reported	Yes (congenital myasthenia gravis)	Not reported
Patient took one dose of Ketek on a full stomach and within 3 hours suffered respiratory failure.							
17 5816713 200512104US	60 F	Hosp	Sinusitis 800mg x 1 dose 2 hours	Myasthenia gravis Dyspnea Anaphylactic shock	None	Yes	No
60 year old female prescribed telithromycin 800mg daily for sinusitis on ……. experienced anaphylactic shock and exacerbation of myasthenia gravis 2 hours							

after taking her first dose of Ketek. Patient could not breathe and self-treated herself with Mestinon before being taken to the ER where she was treated with albuterol and sent home the same day. Ketek was discontinued and she recovered with symptoms of myasthenia gravis lasting 4 days.							
# Case # MFR # Location	**Sex**	**Outcome**	**Indication Dose/Duration Time to onset of symptoms**	**Event(s)**	**Concomitant medications**	**History of Myasthenia Gravis**	**Required ventilator or intubation**
18 5766192 200511999US	71 M	Life-threatening	Acute Bronchitis 800mg x 1 dose 1 hour	Myasthenia gravis	None reported	Yes	Yes
71 year old male patient with history of myasthenia gravis and COPD initiated Ketek (telithromycin) 800 mg once a day for acute exacerbation of chronic bronchitis on . One hour after receiving his first dose, the patient experienced blurred vision, double vision, and muscle weakness in neck. He could not hold his head up. The patient's daughter called the paramedics, and the patient was intubated and taken into the intensive care unit. The patient was diagnoses with myasthenia crisis. The patient was placed on a ventilator for a few days, and developed aspiration pneumonia as a complication. He did develop right lower lobe infiltrate, over the next two or three days and this gradually cleared, leaving behind subsegmental atelectasis on his chest X-ray. Treatment included Clindamyacin. Outcome of visual event resolved. The patient's aspiration pneumonia reversed, and was discharged on …….. The patient has never taken Ketek in the past. He received neurological consultation, and it was felt that this is myasthenic crisis from the new antibiotic that was administered. Neurological consultation was compatible with myasthenia crisis secondary to antibiotic taken.							
19 5768411 6101315 200512341US	71 F	Death	Acute bronchitis 800mg x 1 dose 30 minutes	Acute Respiratory failure Anaphylactic reactions Selling face Swollen tongue	Pyridostigmine	Yes (Ocular myasthenia diagnosed 1 year ago)	Yes
71-year-old female patient was given samples of Ketek (telithromycin) on 18-Feb-2005 for acute bronchitis. The patient took her first dose of 800 mg on …… and experienced an anaphylaxis reaction with respiratory failure 30 minutes thereafter. The patient was described by the health care professional to have significant tongue and facial swelling. The patient was transported to the hospital, intubated, and placed on mechanical ventilation. Additional treatment measures included prednisone, intravenous steroids, blood pressure support, and therapy for myasthenia gravis in which she did not respond. The patient "collapsed" and fell into a coma for several days and died on …….. No autopsy was performed. The health care professional stated he has not seen the death certificate. The discharge summary indicates the patient died of acute respiratory failure. The patient has no known drug allergies. Laboratory values provided include a potassium level of 3.1. The health care professional stated her blood test was otherwise normal. Medical history includes ocular myasthenia (mild) for several years. The health care professional feels her death was attributed to anaphylaxis due to Ketek therapy since respiratory failure occurred 30 minutes after the first dose was taken.							
20 5750251 200510488EU	72 F	Death	Bacterial infection 800mg 4 days	Myasthenia gravis Respiratory failure Cardiac arrest	Albuterol	Yes	Not reported
72-year-old female patient was given Ketek (telithromycin), 800 mg/d, since 01 January, 2005, for a non-specified bacterial infection, developed respiratory insufficiency on …….. and died on the same day from a cardiac arrest. Myasthenia gravis was given as a contributory factor of the fatal event.							

# Case # MFR # Location	Sex	Outcome	Indication Dose/Duration Time to onset of symptoms	Event(s)	Concomitant medications	History of Myasthenia Gravis	Required ventilator or intubation
21 5757051 200418413US	78 M	Hosp	Flu-like illness x 1 dose Not reported	Myasthenia gravis	Pyridostigmine Influenza vaccine	Yes	Yes
78 year old male with a long history of myasthenia gravis (several years ago he experienced a protracted exacerbation of his myasthenia requiring ventilator) developed flu-like symptoms or viral prodome over several days and received a dose of Ketek and a flu shot. He developed substantially worsening shortness of breath and required intubation and ventilator support. ER suspected a possible drug reaction although he did not have al of the full manifestations of an anaphylactoid reaction and was hemodynamically stable. He improved after IV steroids and was subsequently weaned from the ventilator in less than 24 hours. However, within 48 hours he developed recurrent hypercapanic respiratory failure and required further mechanical ventilation and at that time it was felt to be a flare of his myasthenia. He recovered and is currently in rehab environment to help regain strength and functional status.							
22 5937576 US-Aventis-200519884US	80 F	Death	Sinusitis 800mg x 1 dose 3 hours	Myasthenia gravis Respiratory failure Dyspnea	Pyridostigmine Salbutamol/ipratropium prednisone	Yes	Not reported
An 80-year-old female consumer initiated therapy with Ketek (telithromycin) 800mg daily on 27-Nov-2005, for a sinus infection. Relevant medical history includes myasthenia gravis, and allergies to penicillin and sulfa. Concomitant medications include Prednisone, Mestinon (pyridostigmine bromide), and Duo neb (salbutamol with ipratropium bromide). On ……., the patient took her first dose of Ketek at 9:30pm and around midnight she began experiencing "respiratory problems." The patient was taken to the emergency room where they treated her with oxygen. The patient was a "DNR" so no drastic measures were performed. She died at 1:30am on …….							
23 6022411 200519935US	82 M	Hosp	Upper respiratory infection 800mg x 1 dose Not reported	Myasthenia gravis crisis	None reported	Yes	Yes (admitted to ICU)
82 year old male received 1 dose of Ketek (telithromycin) 800mg on…… for an upper respiratory infection. He then experienced a myasthenia gravis crisis for which he was hospitalized and had to be intubated. He spent one day in ICU and was later discharged recovered from the hospital.							
# Case #			Indication Dose/Duration				Required

MFR # Location	Sex	Outcome	Time to onset of symptoms	Event(s)	Concomitant medications	History of Myasthenia Gravis	ventilator or intubation
24 5890911 200513137FR	82 M	Life-threatening	Bronchitis 800mg x 1 dose 1 hour	Myasthenia gravis Respiratory failure Respiratory paralysis Coma	Rhinofluimucil Aspegic 325 Pyridostigmine Vastarel Clamoxyl	Yes	Yes (admitted to ICU)
82 year-old male patient with a past medical history of myasthenia gravis diagnosed in 1995, laryngeal episode NOS and arrhythmia by atrial fibrillation not treated was treated with amoxicillin (Clamoxyl), exact doses unknown, for bronchial infection persistent for 15 days then with telithromycin (Ketek) 800 mg daily on 10-FEB-2005 because of failure of first treatment with dyspnea. According to the hospitalization's report, acetylsalicylate lysine had been taken as usual treatment. On …….., within the hour after the first intake of telithromycin, the patient experienced bronchospasm. On the arrival of mobile emergency medical unit, the patient was unconscious, arterial oxygen saturation was markedly decreased but there were no signs of shock or cardiac insufficiency. The patient was intubated with difficulties on etomidate and received treatment with methylprednisolone then was hospitalized in ICU for mechanical ventilation. In the ICU, BP was 144/68 mm Hg, HR was 80/min and body temperature was 35.7 degrees Celsius. Tracheal aspirations were dirty. Physical examination found crepitant rales in the left side. Lab tests revealed Ph= 7.34, Pco2= 6.52 kPa, SaO2: 99.5%. Serum creatinine was 97 micromol/l, Na+: 135 mmol/l, K+: 4.6 mmol/l, serum glucose: 19.6 mmol/l. Hb was 12 g/dl, WBC were 19 500 /mm3 and platelet count was 361 000/mm3. Liver tests showed ALAT of 123 UI/l, ASAT of 237 UI/L, alkaline phosphatase of 171 UI/l, total bilirubin of 9 micromol/l. CPK was 218 UI/l. Troponine was 0.52 microg/l. Chest X-ray revealed left opacities with retracted lung. Bronchoscopy showed inflammation and petechiae compatible with left bronchial inhalation associated with left bronchial congestion. The patient was treated with clavulanate amoxicillin, nasal oxygen, enoxaparin sodium and neostigmine. The patient had seemingly never been treated with macrolides or telithromycin. There was no known allergy to macrolides. The diagnosis suspected by the hospital physician was myasthenic crisis due to telithromycin and pneumonia due to inhalation. On ……., the patient was extubated. On ……., O2 was discontinued and physiotherapy was started. Liver tests returned to normal. On ……., the patient was discharged from the hospital. The patient contacted by the physician between 22-SEP-05 and 26-SEP-05, reported aggravation of myasthenia gravis since the treatment with telithromycin. The patient's son (a physician) considered that his father had psychological and physical sequelea.							
25 5999138 US-Aventis-200611788US	83 F	Hosp	Upper respiratory infection 800mg x 1-2 doses Not reported	Myasthenia gravis Respiratory distress	Mestinon (pyridostigmine), Lasix (furosemide), digoxin, Protonix (pantoprazole), Synthroid (l-thyroxine), Claritin (loratadine), Coreg (carvedilol) and Imdur (isosorbide mononitrate).	Yes	Not reported
83 year old female was prescribed telithromycin (KETEK) 800mg daily on 23-Feb-2006 for an upper respiratory infection. On …….., she went to the emergency department of her local hospital and was admitted for respiratory distress that had started the night before. Ketek was discontinued on 24-Feb-2006. The event was ongoing at the time of this report. Medical history included myasthenia gravis, COPD, dementia, GERD and a pacemaker. She has drug allergies to Combivent (ipratropium/albuterol), sulfa and promethazine. Concomitant medications included							
# Case #			**Indication Dose/Duration**				**Required**

MFR # Location	Sex	Outcome	Time to onset of symptoms	Event(s)	Concomitant medications	History of Myasthenia Gravis	ventilator or intubation
26 **6011396** **CTU272046**	85 M	Medically significant	Sinusitis 800mg (1-2 doses) Not reported	Myasthenia gravis Dysarthria Dysphasia	Pyridostigmine prednisone	Yes	No
Patient with known generalized myasthenia gravis developed severe dysarthria and dysphasia consistent with exacerbation of myasthenia gravis. Exam showed marked facial and bulbar weakness consistent with MG exacerbation. Symptoms approved after discontinuation of Ketek							
27 **5988058** **200611454US** **US**	Unk	Death	Not reported	Death	None reported	Not reported	Not reported
Initial information received on 10-FEB-2006: This is a spontaneous post-marketing case reported via a sales representative from a physician who gave a lecture on drug-drug interactions to a myasthenia gravis group on medications to avoid. When Ketek was discussed, an unknown member stated that one of our members died while taking Ketek (telithromycin). Patient demographics were not provided. The lecturer was not the patient's physician. Additional information was requested.							
28 **5892236** **200515325US**	64 M	Life-threatening	Bronchitis 800mg x 1 dose 2 hours	Respiratory arrest	Pyridostigmine bromide Nebulizer (NOS)	Yes	Yes
A 64-year-old patient with history of myasthenia gravis and bronchitis was seen in the physician's office and given a nebulizer treatment for bronchitis. He was also given a prescription for Ketek. Later that same day, the patient rook one dose of telithromycin and 2 hours later he experienced respiratory arrest. The patient was intubated in the field and transferred to the hospital where he was admitted with respiratory arrest. PE, CHF, MI, and all other respiratory cayses were ruled out.							
29 **6068828** **200610503US**	60 F	Hosp	Pneumonia 800mg x 1 dose 1.5 hours	Respiratory arrest	escitalopram	Yes	Yes
A 60-year-old patient with history of myasthenia gravis and apnea with a Bi-Pap machine at home was seen by her physician and received an x-ray that showed minor infiltrates. She was afebrile. She was placed on Ketek and sent home. An hour and half after her first dose of telithromycin the patient called her doctor and said she did not feel right. She called 911 and when the ambulance arrived the patient was in respiratory arrest and was intubated. She was admitted and on a respirator for 2.5 days. She was extubated and placed on a Bi-pap machine. 4 days later she was transferred to tertiary care facility and received plasmaphresis and was re-intubated.							
30 **6073344** **200611786US**	45 F	Medically significant	Atypical URI 800mg QD x 5 days	Exacerbation of Myasthenia gravis Asthenia, diplopia, extraocular muscle paresis	Pyridostigmine bromide levothyroxine	Yes (diagnosed in 2005)	Not reported
A 45 year old woman with past history of myasthenia gravis and thymoma started Ketek and had exacerbation of her myasthenia gravis that included weakness							

and double vision due to weak eye muscles. She recovered promptly (no date specified).							
# Case # MFR # Location	**Sex**	**Outcome**	**Indication Dose/Duration Time to onset of symptoms**	**Event(s)**	**Concomitant medications**	**History of Myasthenia Gravis**	**Required ventilator or intubation**
31 6073345 200611748US	Unk F	Hosp	Not reported 800mg QD x 2 doses	Myasthenia gravis	Not reported	Yes	Not reported
The patient experienced an exacerbation of myasthenia gravis after their second day of treatment. They were hospitalized over night and have recovered. Comment from reporter: "2 pharmacists knew of no contraindication of Ketek with myasthenia gravis; however, the hospital was made acutely aware."							
32 5708907 200419892US	48 M	Life-threatening	Sinusitis 800mg x 1 dose 40 minutes	Cardiac arrest Loss of consciousness Respiratory arrest	Pyridostigmine bromide Diovan, diazepam, Singular, Serevant, prednisone, Paxil, ASA	Yes	Yes
This is a 48-year-old male patient who on …..expced respiratory arrest requiring ventilator support within 40 minutes of taking the first dose of Ketek. Patient was prescribed Ketek 800mg daily on 20-Dec-2004 for sinusitis. Patient has had Zithromax (azithromycin) x 3 days in September 2004 with no problems. Patient survived after the ventilator support. The physician reports that the patient experienced sudden shortness of breath with loss of consciousness which was witnessed. Patient does not have a history of coronary artery disease. Patient does not have an implantable Cardioverter Defibrillator or a pacemaker. Patient was not evaluated by a cardiac specialist. Patient was not diagnosed with an acute myocardial infarction within one week of the event.							
33 6074253 200611851US	63 F	hosp	Sinusitis 800mg QD 10 days	Myasthenia gravis Vision blurred Dysphasia, dyspnea, Asthenia	Not reported	Yes (undiagnosed)	No
This 63-year-old patient was treated with telithromycin 800mg QD x 5 days in Jan06 for sinusitis. Approximately 10 days after stating Ketek, experienced blurred vision, difficulty swallowing, difficulty breathing and speaking and general weakness that impairing her normal daily living. Approximately 4-5 days after onset of event she was hospitalized in another state and diagnosed with myasthenia gravis. Patient seen by neurologist on …….s was acute exacerbation of myasthenia gravis (undiagnosed). Patient was treated with IVIG x 5 days and prednisone and she slowly improved. Discharged 3 weeks after onset of event.							

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY

RCM#: 2006-75

DATE: 10/10/06

FROM: Ronald Wassel, Pharm.D., Safety Evaluator
Division of Drug Risk Evaluation

THROUGH: Mark Avigan, M.D., C.M., Director
Division of Drug Risk Evaluation

TO: Janice Soreth, M.D., Director
Division of Anti-Infective and Ophthalmologic Products

SUBJECT: Update of visual adverse events and loss of consciousness reported with telithromycin from March 1, 2005 through July 7, 2006

This document contains proprietary drug use data obtained by FDA under contract. The drug use data/information cannot be released to the public/ non-FDA personnel without contractor approval obtained through the FDA/CDER Office of Surveillance and Epidemiology.

1.0 EXECUTIVE SUMMARY

A review was undertaken to assess the cases of visual adverse events and loss of consciousness reported with telithromycin since March 2005 (to update a previous review) in order to determine if there is more information concerning the frequency or character of these events, which may necessitate further regulatory action. The review included a data mining analysis for visual disorders with selected antibiotics for comparison with telithromycin.

During the 16 months this review encompassed (3/1/05 to 7/7/06), an additional 276 reports of visual adverse events and 85 reports of disturbances in consciousness were retrieved, supplementing 114 reports of visual events and 52 reports of disturbances in consciousness identified in the previous review, (4/1/04 to 3/11/05) (all of these figures are crude counts). Numbers of serious cases (crude counts), defined as having an outcome of death, disability, hospitalization, life-threatening, required intervention to prevent permanent impairment/damage, or other serious important medical event, were 95 for visual events and 72 for disturbances in consciousness (compared to 51 and 51 for the 2005 review, respectively). The proportion of reports between the two review periods and between the total number of reports and those

considered serious has remained relatively constant and consistent with the longer review period and increased drug usage of the current review.

From the crude numbers, the most frequently reported visual events were vision blurred (197), visual disturbance (77), and diplopia (70). The most frequently reported central nervous system events were loss of consciousness (37), syncope (15), and depressed level of consciousness (13).

In identifying cases that were judged serious by outcome, a total of 89 unduplicated cases were found for vision disorders and 61 unduplicated cases were found for disturbances in consciousness. Of these, **71 cases of visual events** and **23 cases of disturbances in consciousness** were considered possibly related to telithromycin. None of the cases resulted in the death of the patient, and three cases occurred while the patient was driving (one of blurred vision and two of loss of consciousness), one of which resulted in an accident killing a pedestrian.

The data mining analysis indicates that compared with each of a number of other antibiotics used to treat acute exacerbation of chronic bronchitis (AECB), acute bacterial sinusitis (ABS), and community–acquired pneumonia (CAP), the strength of association of telithromycin with visual disorders is substantially stronger. It is notable that the predominant effect of blurred vision seen with telithromycin is not associated with any of the comparators at an EB05 limit of greater than one, except for gatifloxacin, which is no longer marketed.

This review documents the continued reporting of these events with similar characteristics to what was found in the previous review. Since there does not appear to be a change in the character of these events and the new labeling initiative combines warnings and precautions into one section, we do not recommend a change from the current Precautions section for these events. However, given that the current label already delineates these adverse event risks as a precaution, it is important to improve communication of these problems to patients, particularly those who are automobile drivers and operators of heavy machinery. As the cumulative experience consistently points to risk for these events, it appears that telithromycin is distinct among comparator antibiotics for its association with visual adverse events. Because of the potential disability that visual impairment and loss of consciousness can cause, particularly on a patient's ability to drive, better communication and education of these risks to both prescribers and patients are warranted.

In view of the potential seriousness of these effects (road traffic accidents; six reports to date) in conjunction with other identified serious adverse events (hepatic, exacerbation of myasthenia gravis), we recommend that the sponsor develop a plan to inform and educate prescribers regarding these risks. Also, consideration should be given to the development of a Medication Guide (MedGuide) for telithromycin to be provided to patients when the drug is dispensed.

On a separate note, while some of the cases reporting disturbed consciousness appear to have had a vagal component leading to syncope, not all can be explained by this mechanism and we would recommend changing the wording from "syncope" to the more general "disturbances in consciousness." We would also reiterate the recommendation from the June 2005 consult that consideration should be given to conducting clinical studies to elucidate the scope of these

effects and the pathophysiology behind them (e.g., anti-cholinergic, cardiac conduction, and circulatory effects).

We will continue to monitor the events for any further changes in frequency or character.

2.0 INTRODUCTION

In March 2005, the Division of Anti-Infective and Ophthalmologic Products (DAIOP) requested the Division of Drug Risk Evaluation (DDRE) to review Adverse Event Reporting System (AERS) data for several adverse events reported for telithromycin as the drug approached its one–year approval anniversary. Two of the events of interest were visual adverse events and loss of consciousness. Visual adverse events were a known finding at the time of U.S. approval (April 2004) and represented the most commonly reported post-marketing events for telithromycin since approval in Europe and South America (July 2001). These included the preferred terms vision blurred, visual disturbance NOS, accommodation disorder, diplopia, and visual acuity reduced, which together accounted for 96% of the visual adverse event reports.[31] Table 1 provides the incidence of all treatment-emergent visual adverse events in controlled Phase III studies by age and gender. The group with the highest incidence was females under the age of 40, while males over the age of 40 had rates of visual adverse events similar to comparator-treated patients.[32]

Table 1. Incidence of All Treatment-Emergent Visual Adverse Events in Controlled Phase III Studies		
Gender/Age	**Telithromycin**	**Comparators***
Female	2.1%	0.0%
≤40	(14/682)	(0/534)
Female	1.0%	0.35%
>40	(7/703)	(2/574)
Male	1.2%	0.48%
≤40	(7/563)	(2/417)
Male	0.27%	0.33%
>40	(2/754)	(2/614)
Total	1.1%	0.28%
	(30/2702)	(6/2139)
* Includes all comparators combined		

[31] Medical Officer Safety Review of NDA 21-144: Telithromycin (Ketek™), March 31, 2004. Available at: http://www.fda.gov/cder/foi/nda/2004/21-144_Ketek.htm

[32] Product Information: KETEK® (telithromycin) Tablets. sanofi-aventis, Bridgewater, NJ, June 2006.

Reports of loss of consciousness associated with the use of telithromycin that were submitted to the agency following approval also generated concern.

In the first DDRE review of postmarketing reports of visual adverse events submitted between April 1, 2004 and March 11, 2005 (Division Files System (DFS), June 14, 2005[33]) we concluded that these events were consistent with those seen prior to approval in worldwide experience and as described in the then current labeling (which listed them under PRECAUTIONS). No recommendations for a major change in labeling for these events were made at that time. It was also concluded that loss of consciousness was not adequately described in the labeling, but the sponsor proposed at the time to add a statement under Nervous System in the Post-Marketing Adverse Event Reports subsection of the Adverse Reactions section noting rare reports of syncope usually associated with vagal syndrome. As there were a high number of reports of loss of consciousness that could potentially lead to serious consequences such as road traffic accidents while driving (in which there were four cases reported; three from Japan and one from the US; no deaths), we agreed with the Medical Officer's recommendation to include a statement about loss of consciousness in the PRECAUTIONS section. The sponsor subsequently added a statement concerning syncope in the PRECAUTIONS section in addition to the Post-Marketing Adverse Event Reports section.

This review was undertaken to assess the cases of visual adverse events and loss of consciousness reported with telithromycin since March 2005 in order to determine if there is more information concerning the frequency or character of these events, which may necessitate further regulatory action.

When interpreting the new data, the following caveats should be taken into account: (1) the reporting period for the first review was 8 months and the period for this review was 16 months, and (2) domestic use for the reporting period of the first review was approximately 1.5 million prescriptions, while the usage for this review was approximately 4 million prescriptions (these figures are not meant to provide reporting rates since they only represent U.S. usage, but to illustrate the increased drug usage when comparing crude adverse event counts between the two periods).

3.0 CURRENT LABELING (June 2006)

Under **PRECAUTIONS—*General***

> **KETEK may cause visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation.** Visual disturbances included blurred vision, difficulty focusing, and diplopia. Most events were mild to moderate; however, severe cases have been reported.
>
> There have been post-marketing adverse event reports of syncope usually associated with vagal syndrome.

[33] Memorandum dated June 14,2005. From Ronald Wassel, Joseph Tonning, Jonathan Levine and Ana Szarfman to Janice Soreth. One-year post-approval evaluation of the safety profile of telithromycin.

Patients should be cautioned about the potential effects of these visual disturbances and syncope on driving a vehicle, operating machinery or engaging in other potentially hazardous activities.

Under **PRECAUTIONS—*Information for Patients***

KETEK may cause problems with vision particularly when looking quickly between objects close by and objects far away. These events include blurred vision, difficulty focusing, and objects looking doubled. Most events were mild to moderate; however, severe cases have been reported. Problems with vision were reported as having occurred after any dose during treatment, but most occurred following the first or second dose. These problems lasted several hours and in some patients came back with the next dose. (See **PRECAUTIONS, General** and **ADVERSE REACTIONS.**)

If visual difficulties occur:

- patients should avoid driving a motor vehicle, operating heavy machinery, or engaging in otherwise hazardous activities.

- avoiding quick changes in viewing between objects in the distance and objects nearby may help to decrease the effects of these visual difficulties.

- patients should contact their physician if these visual difficulties interfere with their daily activities.

Patients should be aware of the possibility of experiencing syncope (fainting), and its impact on the ability to drive, especially if they are experiencing vagal symptoms (severe nausea, vomiting, and/or lightheadedness).

If patients experience these symptoms, they should avoid driving a motor vehicle, operating heavy machinery, or engaging in otherwise hazardous activities.

Under **ADVERSE REACTIONS—*Special senses***

Visual adverse events most often included blurred vision, diplopia, or difficulty focusing. Most events were mild to moderate; however, severe cases have been reported. Some patients discontinued therapy due to these adverse events. Visual adverse events were reported as having occurred after any dose during treatment, but most visual adverse events (65%) occurred following the first or second dose. Visual events lasted several hours and recurred upon subsequent dosing in some patients. For patients who continued treatment, some resolved on therapy while others continued to have symptoms until they completed the full course of treatment. (See **PRECAUTIONS, General** and **PRECAUTIONS**, **Information for patients**.)

Females and patients under 40 years old experienced a higher incidence of telithromycin-associated visual adverse events.

Under **ADVERSE REACTIONS—*Post-Marketing Adverse Event Reports***

Nervous system: syncope usually associated with vagal syndrome.

4.0 SEARCH TYPE AND DATE

AERS was searched on 7/10/2006.

In addition, a data mining analysis of the AERS database for visual disorders with selected antibiotics was conducted on 9/21/2006 using WebVDME 5.2.

5.0 SEARCH CRITERIA

AERS was searched for reports with an FDA received date between 3/1/2005 and 7/7/2006 (inclusive) with the same reaction terms as used in the June 2005 review:

5.1 Visual disorders

MedDRA group term: Vision Disorders (HLGT)

The HLGT Vision Disorders is one of the highest level group terms within the Eye Disorders SOC. This group contains the HLTs related to amblyopia, blindness, color blindness, partial vision loss (under which the PT Vision blurred appears), refractive and accommodative disorders, visual color distortion, visual disorders NEC (which includes such terms as diplopia, halo vision, optic nerve disorder, and visual disturbance), visual field disorders, and visual pathway disorders.

Note: This MedDRA term was chosen to capture a wide array of visual adverse events as different preferred terms may be 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. However, the limitation in searching over a wide group of visual adverse events is that it does not account for related pathology among the different events.

5.2 Disturbances in consciousness

MedDRA group term: Disturbances in consciousness NEC (HLT)

Note: The HLT Disturbances in consciousness NEC contains several PTs including Consciousness fluctuating, Depressed level of consciousness, Loss of consciousness, Syncope, and Syncope vasovagal.

This first search provided crude case counts, which were categorized by primary system organ class (SOC) and corresponding preferred terms (PTs). A second search was conducted using the same MedDRA terms but with outcome criteria of death, disability, hospitalization, life-threatening, required intervention to prevent permanent impairment, or other serious important medical event, in order to identify the most serious cases, which then underwent a hands–on review.

The data mining analysis was included to provide a crude comparison of the relative frequency of reports of visual adverse events for telithromycin with other antibiotics used for AECB, ABS, and CAP. The MedDRA search terms were identical to those used above, which included the PTs from the Vision Disorders HLGT. The comparator antibiotics were selected based on the treatment regimens for the above indications as outlined in the Johns Hopkins Antibiotic Guide.[34] These included amoxicillin, azithromycin, cefpodoxime, cefuroxime, clarithromycin, doxycycline, gatifloxacin, levofloxacin, and moxifloxacin. Cefditoren and gemifloxacin were also included.

6.0 SEARCH RESULTS

6.1 Search #1: AERS Reports of Visual Disorders and Disturbances in Consciousness (Crude counts)

A comparison of the number of reports received by AERS for the June 2005 review and this updated review is presented in Table 2. Case numbers are crude counts (foreign and domestic reports), which do not take into consideration duplicate reports or cases that could be excluded due to other reasons (therefore, the crude counts presented in the 2005 Review column in Table 2 below are higher than those reported in the final June 2005 review document because that document reports unduplicated, non-excluded cases). The data are not presented as cumulative totals because of potential overlap between the review periods.

[34] Bartlett JG, editor. Johns Hopkins Antibiotic Guide. Available at http://www.hopkins-abxguide.org/main.cfm.

Table 2. AERS data (crude counts*) for Vision Disorders and Disturbances in Consciousness reported with Ketek for the June 2005 Review and the 2006 Review.

	2005 Review	2006 Review
Period of FDA receipt of reports	8 months (4/1/2004 to 3/11/2005)	16 months (3/1/2005 to 7/7/2006)
Total reports received (all reactions)	421	1319
REDACTED		
Vision disorders (total)	114	276
Vision disorders (serious‡)	51	95
Disturbances in consciousness (total)	52	85
Disturbances in consciousness (serious‡)	51	72

* Foreign and domestic reports; does not take into consideration duplicate reports or cases that could be excluded due to other reasons

‡ Serious cases were defined by the reporter as having an outcome of death, disability, hospitalization, life-threatening, required intervention to prevent permanent impairment/damage, or other serious important medical event

Between the two review periods the total number of reports increased and the proportion of those considered serious has remained relatively constant and reflective of trends in drug usage.

As stated previously, the crude case counts were categorized by system organ class (SOC) and corresponding preferred terms (PTs) to determine the most frequently reported events, which are shown below (case counts of 10 or more; each case may have multiple PTs).

Search Criteria—Vision Disorders (High Level Group Term, HLGT)
System Organ Class (SOC)—Eye Disorders

PTs—Vision blurred	197
Visual disturbance	77
Diplopia	70
Visual acuity reduced	15
Eye pain	14
Photopsia	11
Visual brightness	11

Search Criteria—Disturbances in Consciousness Not Elsewhere Classified (NEC) (High Level Term, HLT)
SOC—Nervous System Disorders

PTs—Loss of consciousness	37
Syncope	15
Depressed level of consciousness	13
Somnolence	12
Dizziness	11
Lethargy	11

6.2 Search #2: AERS Reports of Visual Disorders and Disturbances in Consciousness with Serious Outcome (3/1/2005 to 7/7/2006)

A second search was conducted to narrow down these results to those cases that were considered the most serious as defined by an outcome of death, disability, life-threatening, hospitalization, required intervention to prevent permanent impairment/damage, or other serious important medical event. This search produced 95 cases within visual adverse events and 72 cases related to disturbances in consciousness (crude counts). These cases underwent a hands-on review and are summarized below.

6.2.1 Visual disorders with serious outcome (n=95)

Of the 95 reports with serious outcome in this update (3/1/2005 to 7/7/2006), there were a total of 89 unduplicated cases. Of these, 18 were excluded because of other causes (e.g., cataracts, retinal vein occlusion, myasthenia exacerbation, brain tumor, temporal arteritis), questionable temporal relation, or other confounding factors. The remaining **71** cases reported the following events (individual cases could contain multiple PTs):

-- Blurred vision	49
-- Diplopia	24
-- Visual changes/disturbance	7
-- Vision loss	6
-- Amaurosis fugax	1

Clinical characteristics:

- 57 domestic and 14 foreign cases
- 52 females and 17 males (2 unknown)
- age range from 15 to 83 years (n=63; median 40 years; mean 42.0 years)
- onset typically occurred on the first day of therapy within an hour or two of the dose (n=39), with one case reporting the onset one week after completing a five day course of therapy

- outcomes—
  - 9 cases reported emergency room visits (4) or hospitalization (5)
  - 1 case described an intervention (use of an eye patch for diplopia)

- 1 case was considered life-threatening as it occurred while the patient was driving (did not result in an accident)
- 13 cases were considered disabling as the event impacted activities of daily living such as reading, watching television, driving, working, walking, and writing
- 47 cases were reported as other serious medical events
- 47 patients discontinued telithromycin
- 53 of the cases reported resolution of the events and the patients recovered (outcome was not reported in 18 cases)
- no deaths

- duration of effect—
  - < 3 hours (n=5)
  - 3 to 7 hours (n=5)
  - 7 to 12 hours (n=5)
  - 12 to 24 hours (n=8)
  - 4 cases reported lingering effects for 5 days, 2½ to 3 weeks, 3 to 5½ weeks, and 6 weeks, respectively

It is noteworthy that in five cases of diplopia a diagnosis of a cranial nerve disorder was given (sixth cranial nerve palsy, Bell's palsy). Whether these represent an alternate etiology for the diplopia excluding telithromycin as a causative factor, or whether telithromycin was the cause of these disorders is unknown. However, since myasthenia gravis has the ability to mimic some cranial motor neuropathies, it is possible these were actually cases of ocular myasthenia and may represent the mechanism by which telithromycin affects vision given its known effect for exacerbating myasthenia gravis (there was no indication of a history of myasthenia gravis in these cases).

Representative cases[35]

ISR # 4736165-1; Mfr. report # 200511305US—A 17–year–old female initiated therapy with Ketek 400 mg daily on 2/14/2005 for sinusitis. Approximately four hours after her dose she experienced blurred vision and diplopia. She reported dizziness and generalized pruritis and was treated with Benadryl. The blurred vision occurred when looking from far to near, but no change with changes in the plane of vision. She also experienced difficulty or slowness in focusing on objects. She did not experience abnormalities in color vision, increased brightness, flashing lights or darkness of vision. The event resolved after a given dose, only to recur with subsequent doses. Therapy with telithromycin was discontinued due to the event and the event resolved. The event lasted about 12 hours. The event prevented the patient from engaging in normal activities of daily living including a general impairment in activity, reading, watching television, driving, working, walking and writing.

ISR # 4805727-5; Mfr. report # 200519202GDDC (Canada)—A 35–year–old male patient initiated therapy with Ketek 800 mg daily for bronchitis. The patient was not taking any relevant concomitant medications and has no relevant medical history. On an

[35] Narratives are taken verbatim from text provided in the MedWatch reports.

unknown date, a physician reported his patient experienced vision loss while taking Ketek. The patient took his first dose at suppertime and a few hours later could only see light, dark and colors, but could not see shapes. His life was affected and he was unable to go anywhere. This adverse event resolved by morning, approximately 12 hours later. The doctor discontinued the medication. Outcome: Complete recovery.

ISR # 4736164-X; Mfr. report # 200419342US—A 40–year–old female initiated Ketek 800 mg once a day for sinusitis from 2/10/2005 through 2/20/2005 and experienced blurred vision when looking from near to far. No change with changes in the plane of vision was noted. The patient experienced difficulty or slowness in focusing on objects, with no diplopia, abnormalities in color vision, increased brightness, flashing lights, or darkness of vision noted. The visual adverse event was persistently or significantly disabling, impacting reading, working, and writing. Ketek was not discontinued due to the visual event. The visual episode began 2 hours after the most recent dose of Ketek and lasted 3 to less than 7 hours on average. The visual episode was continuous for the entire course of therapy. "Drug was finished with no lasting effects." The outcome of the visual event was resolved.

6.2.2 *Disturbances in consciousness with serious outcome* (n=72)

Of the 72 reports with serious outcome in this update (3/1/2005 to 7/7/2006), there were a total of 61 unduplicated cases. Cases in which the disturbance in consciousness was part of a constellation of symptoms of a disease process were excluded (n=31). These included:

-- sepsis
-- hepatic failure
-- Stevens-Johnson syndrome/toxic epidermal necrolysis
-- respiratory distress/acute asthma/hypoxemia
-- hypersensitivity/anaphylaxis
-- seizure
-- acute myocardial infarction/cardiac arrest
-- renal failure
-- gastrointestinal bleed.

The focus of this update was to identify cases that occurred in relatively otherwise healthy patients in which a disturbance in consciousness was unexpected and could be directly attributable to the drug. Thirty-one cases were excluded because disturbance in consciousness was part of a constellation of symptoms of a disease process. Four additional cases were excluded as a loss of consciousness was not observed (reports were of somnolence and confusional state), and three reports were excluded as they were follow-ups to reports that were included in the June 2005 review, leaving a total of **23** cases. The reported events were:
-- loss of consciousness 14
-- syncope/fainting 7
-- disturbed consciousness 2

Clinical characteristics:

- 14 domestic and 9 foreign cases
- 9 females and 12 males (2 unknown)
- age range from 18 to 78 years (n=16; median 46 years; mean 46.9 years)
- onset—
  - within 2 hours (n=7)
  - first day of therapy (n=5)
  - days 3 to 5 of therapy (n=4)
  - one day after completion of therapy (n=1)
- outcomes—
  - 8 patients were hospitalized (7) or presented to the emergency room (1)
  - 2 cases occurred while the patient was driving (in one case no accident occurred; in the other case an accident occurred in which a pedestrian was killed and the patient was injured)
  - 1 case resulted in a disability as the patient fell and sustained a vertebral compression
  - 12 cases were reported as other serious medical events

A common explanation for the events, such as a vagal reaction, could not be discerned. One case reported hypoglycemia temporally associated during telithromycin treatment (12 unduplicated cases of hypoglycemia searched with telithromycin are in AERS; a causal effect is not clear), and one case reported the loss of consciousness with torsade de pointes (a known labeled effect).

Representative cases

ISR # 4730221-X; Mfr. report # 200511318FR (France)—A female (age not specified) was started on telithromycin 400 mg daily for bronchitis. Concomitant treatments and medical history were not specified. One hour after the first intake, the patient experienced vomiting, diarrhea, and loss of consciousness resulting in a fall, which caused a vertebral compression.

ISR # 4890970-X; Mfr. report # JP-AVENTIS-200610081JP (Japan)—A 32–year–old male received telithromycin for an unknown indication. One hour after the drug was administered, the patient experienced transient loss of consciousness, difficulty in standing, and weakness of the limbs. He was hospitalized and improved after 500 ml of intravenous drip was given. He was discharged the next day.

ISR # 4634999-5; Mfr. report # 200510604JP (Japan)—A 71–year–old male with chronic sinusitis, hypertension, diabetes (diet controlled), and previous cerebral infarction was prescribed telithromycin for nasal congestion. Concomitant medications include theophylline, tulobuterol (a $beta_2$ agonist; bronchodilator), aspirin, serrapeptase (proteolytic enzyme; anti-inflammatory), loxoprofen (NSAID), nilvadipine (calcium antagonist), and possibly another anti-hypertensive agent. On ……patient visited the

reporting hospital for type A influenza. A mild increasing in CRP was observed as 4.6 and WBC was 8100. The patient's throat was very red at the time. Due to infectious disease, pharyngitis and sinusitis that evolved concomitantly, telithromycin 600mg/day, carbocisteine, serrapeptase, and loxoprofen were prescribed for 5 days. The patient started to dose the medications on 2/15/2005. On 2/17/2005, in the evening, tinnitus (started from dorsal to both, and lasted for 3 to 5 seconds) evolved as prodromal symptom, and the patient remembered the moment that he was about to step on the brake pedal, but he couldn't remember the things happened during his LOC. The patient's co-worker was driving right behind the patient and the co-worker thought strange that the patient pulled over and stopped on the side of the road without turn signal, and the co-worker got off the car and went to check the patient. The patient came back to consciousness recognizing someone was watching him (it was assumed that lasted for 15 seconds). There was no injury or fatal accident happened and no property was damaged. Ketek was discontinued on this day. On ……patient visited the hospital and reported that he lost his consciousness. The patient didn't have pyrexia, and the nasal condition was fine in spite of rhinitis remaining a little. On this day, no examination was performed because the primary disease resolved and for LOC, electrocardiogram, electroencephalogram and brain CT scans weren't performed because there was no sequela observed. On ……., the patient revisited the hospital and no sequela was observed. The patient said that he slept well despite having done no hard work the day before and he felt fine on the day the event evolved. As prodromal symptom, the patient had tinnitus but not nausea. As parenthetic explanation, the patient never had LOC and epilepsy before and antidiabetic and insulin weren't administered for diabetes mellitus. Physician's Comment: The reporting physician states that choosing drugs for the patient is difficult, because many antibacterial agents do not agree with the patient. When Ketek was prescribed previously, the reason that LOC didn't evolve was perhaps because olopatadine (antihistamine) was taken concomitantly. The physician assessed the causal relationship between Ketek and "LOC" as "probable." Addendum on 4/72005: It was newly reported that there was no alternative explanation for both LOC and sleep excessive. It was specified that antihypertensive agent that the patient had been on apart from nilvadipine was valsartan. The physician assessed causal relationship between Ketek and sleep excessive as "probable."

ISR # 4761859-1; Mfr. report # 200512134US—An 18–year–old male initiated telithromycin (Ketek) 800 mg once a day on 1……... The patient lost consciousness while driving to school, ran a red light, and struck and killed a pedestrian. The patient also experienced a syncopal episode and was injured from the accident. Physician provided follow up information. All tests so far were negative. Patient visited the cardio-physiologist and did not undergo an aggressive electrophysiology test, because the physician indicated that there was no need for this test based on his evaluation. MD received the ER record and found no drug test was done in the ER. Other information is non-contributory. Patient doing well and remained academically competitive (4.7). Follow-up received on 29-Aug-2005: per the patient's parents, their son "took Ketek on the evening of ……. and the next morning he passed out while driving and tragically killed a pedestrian" (change in therapy date and event date from previously reported). As per parents, multiple medical evaluations have been conducted, including neurology,

cardiology, and cardiac electrophysiology evaluations. As per parents, other evaluations include: MRI, EKG, EEG's, echocardiograms, and multiple lab evaluations. The parents reported that all evaluations have been normal and revealed no abnormalities.

6.3 Data Mining Analysis of Selected Antibiotics for Vision Disorders

The data mining analysis evaluates the records contained in AERS and then quantifies potential drug-event associations by producing a ranked set of values or scores which indicate varying strengths of reporting relationships between drugs and events.[36] These scores, denoted the Empirical Bayes Geometric Mean (EBGM), provide a stable estimate of the relative reporting rate of an event for a particular drug relative to all other drugs in the database being analyzed. The analysis also calculates lower and upper 90% confidence limits for EBGM values, denoted EB05 and EB95 respectively.

An EBGM of 1 indicates that the particular drug-event combination occurs together as often as would be expected under the assumption of randomly paired drug and event reports (independence assumption). Using an EB05 score of greater than 1 as a signal definition corresponds to being 95% confident that the drug-event in question occurs at least at a higher-than-expected rate. An EBGM value of greater than 2 ensures with a high probability that the particular drug-event occurs in these patient data records at least twice as often as expected under the independence assumption. Using an EB05 $\geq$2 as a signal definition indicates 95% confidence that the drug-event is occurring at least at twice the expected rate when considering all other drugs and events in the database.

The higher the EB05 score, the higher the association between the drug and event, as reported in the database being analyzed. Note that this "association" is a factor of the relative reporting of various events among all drugs in the database and that it does not automatically imply causality. Signal scores indicate higher-than-expected drug-event reporting associations, not necessarily causality or the degree of risk.

When the analysis was first run with an EB05 score limited to a value greater than 2, the only antibiotic of the group defined as above to generate any results was telithromycin (Table 3).

Table 3. Data Mining Analysis of Selected Antibiotics for Vision Disorders with an EB05 Score > 2.

[36] Szarfman A, Machado SG, O'Neill RT. Use of Screening Algorithms and Computer Systems to Efficiently Signal Higher-Than-Expected Combinations of Drugs and Events in the US FDA's Spontaneous Reports Database. Drug Safety 2002; 25:381-392.

Ingredient	PT	N*	EB05
Telithromycin	Visual brightness	17	65.267
Telithromycin	Accommodation disorder	15	28.287
Telithromycin	Colour blindness	11	19.919
Telithromycin	Diplopia	82	14.813
Telithromycin	Vision blurred	289	13.609
Telithromycin	Visual disturbance	114	8.492
Telithromycin	Photopsia	14	4.845
Telithromycin	Visual acuity reduced	26	2.092

* N=crude number of cases

The analysis was repeated with an EB05 score limited to a value greater than 1, which captured additional drug-event combinations for azithromycin, clarithromycin, doxycycline, gatifloxacin, levofloxacin, and moxifloxacin (Table 4).

Table 4. Data Mining Analysis of Selected Antibiotics for Vision Disorders with an EB05 Score > 1.*

	Accommodation disorder	**Amblyopia**	**Blindness**	**Blindness transient**	**Color blindness**	**Diplopia**	**Photopsia**	**Vision blurred**	**Visual acuity reduced**	**Visual brightness**	**Visual disturbance**	**Visual field defect**	**Xanthopsia**
Telithromycin	15 *28.3*			7 *1.43*	11 *19.9*	82 *14.8*	14 *4.84*	289 *13.6*	26 *2.09*	17 *65.3*	114 *8.49*		
Doxycycline			10 *1.03*		5 *1.92*	11 *1.06*						8 *1.14*	
Moxifloxacin		9 *1.77*							25 *1.12*		48 *1.47*		
Gatifloxacin								41 *1.04*					3 *1.06*
Azithromycin												15 *1.01*	
Clarithromycin						33 *1.0*							
Levofloxacin											71 *1.22*		
Amoxicillin													
Cefditoren													
Cefpodoxime													
Cefuroxime													
Gemifloxacin													

*The top number in each cell represents the crude number of cases and the bottom italicized number is the EB05 score. An empty cell indicates that the EB05 score was < 1.

7.0 DISCUSSION

In the 16 months from 3/1/2005 to 7/7/2006 since the June 2005 review, AERS has received an additional 276 reports of vision disorders and 85 reports of disturbances in consciousness (crude counts). These findings are consistent to those seen in the first review (114 and 52, respectively) given the longer review period and increased drug usage. In identifying cases that were judged serious by outcome, a total of 89 unduplicated cases were found for vision disorders and 61 unduplicated cases were found for disturbances in consciousness. Of this subset of serious cases, **71 cases of visual events** and **23 cases of disturbances in consciousness** were considered possibly related to telithromycin. Although none of the cases resulted in the death of the patient, three cases occurred while the patient was driving, one of which resulted in an accident killing a pedestrian.

The data mining analysis indicates that compared with each of a number of other antibiotics used to treat AECB, ABS, and CAP, the strength of association of telithromycin with visual disorders is substantial. It is notable that the predominant effect of blurred vision seen with telithromycin is not associated with any of the comparators at an EB05 limit of greater than one, except for gatifloxacin, which is no longer marketed.

Currently, visual disorders and disturbances in consciousness are expressed as precautions in the labeling and communicated to the patient in the patient information sheet. A review of other drug labeling for statements that caution about the ability to drive found inconsistencies in the presentation of information. A search of the Physician's Desk Reference for the term *driving* in the Warnings and Precautions sections was conducted to determine how this information is conveyed for other drugs. The search retrieved 85 results for the term *driving* in the Warnings section and 84 results for it in the Precautions section. Examples of drugs in which a statement appears in the Warnings section that cautions against driving include zolpidem (Ambien), estazolam (ProSom), cevimeline (Evoxac), terazosin (Hytrin), alprazolam (Xanax), and indomethacin (Indocin). Examples of those drugs in which it appears in the Precautions section include carvedilol (Coreg), tamsulosin (Flomax), oxycodone (OxyContin), pregabalin (Lyrica), brinzolamide (Azopt), and mefloquine (Lariam). Of particular note, for comparative purposes, carvedilol, pregabalin, and brinzolamide contain statements in the Precautions section for syncope (carvedilol) and blurred vision (pregabalin and brinzolamide) while terazosin has a statement regarding syncope in the Warnings section. Of the antibiotic drugs, only telithromycin, minocycline, moxifloxacin, and ciprofloxacin contain statements about driving.

8.0 CONCLUSIONS/RECOMMENDATIONS

This review documents the continued reporting of visual adverse events and disturbances in consciousness with similar characteristics to what was found in the previous review. Since there does not appear to be a change in the character of these events and the new labeling initiative combines warnings and precautions into one section[37], we do not recommend a change from the current Precautions section for these events. However, given that the current label already delineates these adverse event risks as a precaution, it is important to improve communication of these problems to patients, particularly those who are automobile drivers and operators of heavy

[37] Food and Drug Administration Center for Drug Evaluation and Research. New requirements for prescribing information. Available at: http://www.fda.gov/cder/regulatory/physLabel/default.htm.

machinery. As the cumulative experience consistently points to risk for these events, it appears that telithromycin is distinct among comparator antibiotics for its association with visual adverse events. Because of the potential disability that visual impairment and loss of consciousness can cause, particularly on a patient's ability to drive an automobile or operate heavy machinery, better communication and education of these risks to both prescribers and patients are warranted.

In view of the potential seriousness of these effects (road traffic accidents; six reports to date) in conjunction with other identified serious adverse events (hepatic[38], exacerbation of myasthenia gravis[39]), we recommend that the sponsor develop a plan to inform and educate prescribers regarding these risks. Also, consideration should be given to the development of a Medication Guide (MedGuide) for telithromycin to be provided to patients when the drug is dispensed.

On a separate note, while the current labeling for disturbances in consciousness refers to syncope usually associated with vagal syndrome, and some cases had that characteristic, many cases did not and a common explanation could not be discerned. Syncope is technically defined as loss of consciousness and postural tone caused by diminished cerebral blood flow. While some of the cases appear to have a vagal component leading to syncope, not all can be explained by this mechanism and we would recommend changing the wording from "syncope" to the more general "disturbances in consciousness." We would also reiterate the recommendation from the June 2005 consult that consideration should be given to conducting clinical studies to elucidate the scope of these effects and the pathophysiology behind them (e.g., anti-cholinergic, cardiac conduction, and circulatory effects).

We will continue to monitor the events for any further changes in frequency or character.

_____

Ronald Wassel, Pharm.D.
Safety Evaluator

Concur:

_____

Melissa Truffa, R.Ph.
Team Leader

cc:
NDAs 21-144

[38] Memorandum dated May 16, 2006. From Ronald Wassel and Allen Brinker to Janice Soreth. An evaluation of hepatic adverse events associated with telithromycin.
[39] Memorandum dated October 10, 2006. From Allen Brinker and Melissa Truffa to Janice Soreth. Exacerbation of myasthenia gravis.

DAIOP Division File / Alexander / DeBellas
DDRE Avigan / Truffa / Lyndly / Chron / Drug