Medical Officer's review of NDA 21144/Labeling Supplement 004

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	January 10, 2005
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Amendment Submitted:	October 25, 2005

Applicant: Aventis Pharmaceuticals, Inc.
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Drug: Ketek® (Telithromycin) 400 mg tablet

Documents submitted:

- Labeling history;
- Labeling text – proposed, currently used, and last approved;
- Final printed US Prescribing Information (USPI)/Patient Package Insert (PPI); and
- Supporting documentation – *Reasoned Statement – pancreatitis, Reasoned Statement – palpitations,* and *Reasoned Statement – syncope-loss of consciousness.*
- *January 10, 2005 submission: Update to Reasoned Statement of September 2004: Cumulative Review of Syncope and Loss of Consciousness Associated with Telithromycin Use.*
- January 14, 2005 submission: An English translation of the Blue Letter distributed to health care professionals in Japan on January 14, 2005 (*Follow-up - Japanese Regulatory Actions re: Syncope and Loss of Consciousness Associated with Telithromycin Use).*
- October 25, 2005 submission: Amendment to the original submission.

MEDICAL OFFICER'S REVIEW:

Proposed Changes to the Labeling:

Aventis is proposing the following changes to the labeling:

Post-Marketing Adverse Event Reports:

Under Cardiovascular: addition of "rare reports of palpitations"

Aventis received 21 reports of palpitations during the six month review period covering January 10, 2004 until July 9, 2004. This 6-month review period corresponds to an estimated exposure of 4.11 million courses of treatment. Of these 21 reports, 14 were excluded because the drug was not considered to be a likely cause of palpitations.

In the remaining 7 cases, a causal association cannot be excluded. In several of these cases, other medications (carbemazepine, Chinese herbal medication, amlodipine) could have contributed in the development of palpitations. Although other medications have been administered, the temporal relationship is most suggestive of a telithromycin etiology, as telithromycin is the only drug stopped and this discontinuation is associated with symptom resolution. All but one of these events occurs within the first few hours of the first dose, consistent with the kinetics of absorption from the gastrointestinal tract, and all resolve rapidly with discontinuation of telithromycin. In only one of the 7 cases (200410805JP – 54-year old female), an electrocardiogram revealed sinus tachycardia with a rate of 129 beats per minute. None of the adverse event reports led to a serious outcome, and all were reversible.

In conclusion, reports of palpitations have been reported with the marketed use of telithromycin (reporting rate of less than 1 report per half million exposures) in which a causal association to telithromycin cannot be excluded. These events are non-serious and short-lived.

Medical Officer's comments:

The post-marketing reports of palpitations associated with use of telithromycin were few, non-serious and reversible. The addition of the following statement under the section of the labeling Post-Marketing Adverse Event Reports: Cardiovascular: "rare reports of palpitations" should be as follows:

Under Post-Marketing Adverse Event Reports: Cardiovascular: "palpitations."

The adverse events should be listed in the Post-Marketing section without qualifiers.

Post-Marketing Adverse Event Reports:

Under Gastrointestinal system: addition of "rare reports of pancreatitis."

A review of the Aventis database was performed on July 14, 2004 to identify all reports of pancreatitis. These cases were searched using the following Medical Dictionary for Regulatory Activities (MedDRA) terms: High Level Group term (HLGT) "exocrine pancreas conditions", High Level term (HLT) "digestive enzymes", and preferred term (PT) "pancreatic cyst". This search included reports of acute and chronic pancreatitis, pancreatic injury, amylase and lipase increases, and pancreatic cysts. During this time period, global exposure of telithromycin was estimated at greater than 10 million courses of treatment.

A total of 12 reports were identified, 9 of which have been assessed previously. A summary of the 9 reports is as follows:

- There was insufficient information (laboratory or imaging confirmation) of diagnosis of pancreatitis in three cases.
- In three cases, all young patients with ages ranging from 30 years to 55 years, there were minor amylase increases on routine monitoring, which later on resolved, and diagnosis of clinical pancreatitis diagnosis was never made in these patients.
- Two patients had history of chronic alcohol use.
- One patient had underlying gallbladder disease which was the likely cause of pancreatitis, particularly as the symptoms began before first dose of telithromycin was administered.

A review of the cases at that time revealed no safety signal for pancreatitis. The three new reports are reviewed in this submission.

200410080FR: A 71year-old male patient with history of extrinsic allergic alveolitis, melanoma 4 years prior, and Parkinson's disease was treated with telithromycin 800 mg daily for 3 days for bronchitis. He had no history of hypertriglyceridemia, cholelithiasis, or alcoholism. Concomitant long-standing treatment consisted in levodopa-benserazide hydrochloride and piribedil for Parkinson's disease. Other medications included furosemide, perindopril, acetylsalicylate lysine, pravastatin sodium, lansoprazole, beclometasone dipropionate and lorazepam. On day 3 of treatment, the patient experienced abdominal pain without icterus and was hospitalized on (b)(6)----------
Lab results on admission and follow-ups were as follows:

Table 1 – Lab results for Case 200410080FR

Analyte						Normal values
ALT	679	227	110	52	29	30-65 U/L
AST	953	33	22	25	18	15-40 IU/L
Alkaline phosphatase	-	115	107	101	-	< 40 IU/L
g-GT	2029	1055	542	246	60	-
Total bilirubin	37.9	-	15.4	-	-	0-17
Conjugated bilirubin	23	-		-	-	0-5
Amylase	-	-	"normal"	-	-	-
Lipase	12,500	-	"normal"	-	-	-
CRP	31	12	-	-	-	-
WBC	9000	4720	-	-	-	-

IU- International Units, L- litre, '-' – not indicated

A diagnosis of acute pancreatitis and acute hepatitis was made, and treatment with telithromycin was discontinued (other chronic medications were continued). Abdominal ultrasound and CT scan showed slight hepatomegaly with no cholelithiasis or choledochus dilatation. Abdominal CT scan performed a few days later showed normal pancreas and liver. Serology studies for hepatitis A, B, C, CMV, EBV, HIV, Q fever,

Mycoplasma pneumoniae, Chlamydia pneumoniae and Legionella pnemophila were all negative. The patient recovered.

200410898JP: An 89 year-old female patient received telithromycin 600 mg for pneumonia for 4 days. Concomitant diseases were scabies and reflux esophagitis, treated with chlorpheniramine maleate and lansoprazole, respectively. Baseline laboratory results were as follows: AST 20U/l and ALT 11U/l. Four days later, AST had increased to 453U/l and ALT to 263U/l. Telithromycin was discontinued and patient was started on ceftriaxone sodium, with improvement in liver enzymes. The physician stated in his report that this patient had previous history of pancreatitis. Additional information has been requested by the physician.

200411721FR: A 55 year-old female with a medical history of systemic lupus erythematous-related polyarthritis treated in 1982 with corticosteroids for 9 months. In March 2003, diagnosis of autoimmune hepatitis was suspected but not confirmed because of quick normalization of hepatic enzymes and negative anti-tissue antibodies. On an unspecified date in March 2004, treatment with telithromycin PO, daily dose not specified and betamethasone PO, daily dose not specified was started for an unspecified indication. Four days later, the patient experienced intense abdominal pain. Serum amylase and serum lipase levels were elevated and acute pancreatitis was diagnosed. Abdominal ultrasound scan revealed no gallbladder lithiasis and abdominal CT scan showed normal pancreas. Pancreatic enzymes were normal at the time of the report, and the patient recovered completely.

In conclusion, of these three reports, the first report contains the best clinical documentation for causality assessment. Common causes of pancreatitis (alcohol, cholelithiasis, hyperglyceridemia, hypercalcemia, and infectious causes like CMV) have been carefully excluded. The second report lacks adequate details. In the third report, betamethazone is the likely cause of transient pancreatitis.

Medical Officer's Comments:

Aventis has received a total of 12 reports involving pancreatic injury in patients taking telithromycin. In one of the 12 reports, a causal relationship cannot be excluded. The addition of the following statement under the section of the labeling Post-Marketing Adverse Event Reports: "Gastrointestinal system: rare reports of pancreatitis." should be changed to:

Post-Marketing Adverse Event Reports: "Gastrointestinal system: pancreatitis."

The adverse events should be listed in the Post-Marketing section without qualifiers.

Post-Marketing Adverse Event Reports:

Under Nervous system: addition of "rare reports of syncope usually associated with vagal syndrome."

Aventis safety database was searched on July 1, 2004 for the MedDRA preferred terms (PTs) “syncope” and “loss of consciousness” (LOC) recorded as either diagnosis or symptoms. The search identified 56 cases. Of the 56 cases, 21 reported a specific cardiovascular etiology. The remaining 35 case reports included syncope in 11 patients, loss of consciousness in 11 patients, fainting and vertigo in 6 patients, epilepsy in 2 patients, anaphylactic reaction in 2 patients, hypoglycemia in 2 patients and cholestatic hepatitis in 1 patient.
Of the 56 cases identified for this review, 28 cases were excluded because they had the following:

- Lacked a plausible temporal relationship to telithromycin dosing
- Did not have a true loss of consciousness
- Lacked information to make an assessment
- Had a documented cause for loss of consciousness

The remaining 28 cases can be further categorized as follows:

- Cases with significant and confounding underlying disease or concomitant medications
- Cases which have a plausible temporal relationship, but lack sufficient information to assess further
- Cases with probable vagal effects secondary to associated gastrointestinal effects
- Cases for which a primary drug cause appears likely

Of the 28 assessable reports, 11 have significant underlying disease or concomitant medications that are likely to have a causal association to the syncopal episode than the administration of telithromycin.

Four of the 28 reports lack adequate detailed information to make an assessment. Two of those reports also lacked basic information, such as vital signs, clinical symptoms and physical examinations, which are needed to adequately evaluate them.

Eight of the reports had probable or possible secondary vagal etiologies for the syncopal episode. Cases included in this “vagal” category incorporated those with preceding gastrointestinal symptoms or dizziness where vasovagal syncope might be expected with combined hypotension and bradycardia. All the eight cases are summarized as follows:

Case 200020069EU: A 71 year-old female with aortic stenosis and hypertension 4 hours after taking a 1600 mg dose of telithromycin (twice the daily recommended dose) reported the onset of flatulence, malaise and epigastric pain. Heart rate was 35 beats per minute at the time of the event, and blood pressure not reported. ECG revealed no abnormalities. The syncopal episode was followed by mild diarrhea. During a subsequent phase of the study, no symptoms recurred when the patient was given an 800 mg dose.

The occurrence of syncope/bradycardia associated with gastrointestinal complaints strongly suggests a vagally-mediated event.

Case 200313016FR: A 68 year-old female reported massive diarrhea preceded the onset of loss of consciousness, making a secondary vagally-mediated syncope likely.

Case 200211062DE: A 36 year-old female with Type II diabetes mellitus developed dizziness, followed by loss of consciousness and fall 1 hour after the first dose of telithromycin. Concomitant medications are unknown. ECG performed shortly after the event revealed sinus bradycardia (rate 50 beats per minute, with no repolarization abnormalities). A normal QT interval shortly after the event makes a drug-related malignant arrhythmia unlikely. However, a drug related bradycardia (a listed event), possibly via a vagal mechanism, cannot be excluded.

Case 200212354DE: An 82 year-old female with coronary artery disease, hypertension and chronic atrial fibrillation develops loss of consciousness. The preceding gastrointestinal symptoms followed by hypotension with systolic BP of 70 mmHg suggest a vagal cause. However, in this case, a primary hypotension with a blocked compensatory heart rate increase due to concomitant digoxin administration cannot be excluded. Propafenone is a CYP 3A4 substrate that can cause hypotension; however, lacking any other signs of propafenone toxicity (e.g. QT interval prolongation, conduction blocks), propafenone toxicity secondary to a drug interaction appears unlikely. Telithromycin-induced hypotension (a listed event) cannot be excluded.

Case 200310166FR: A 41 year-old female with no cardiopulmonary disease developed witnessed loss of consciousness with palpitations, dyspnea, nausea, and progressive lightheadedness 1 hour after the first dose of telithromycin. Systolic BP was 100 mmHg shortly after recovery and an ECG was normal; heart rate was not reported. Given the preceding nausea and progressive symptoms, a vagally-mediated event is likely.

Case 200313613FR: Age and sex of this patient is unknown. The combination of severe hypotension (blood pressure 60/30 mmHg) and bradycardia (heart rate 55 beats per minute) associated with cold sweats suggests a vagal syncope in this patient with prior coronary artery bypass grafting (CABG) and atrial fibrillation. This may be a primary drug-related event, as no preceding gastrointestinal symptoms occurred; however coronary ischemia (particularly inferior ischemia) needs to be excluded given the coronary artery disease history.

Case 200410493FR: A 95 year-old female had preceding diarrhea and sweats followed by syncope with hypotension (systolic BP of 70 mmHg) and reported bradycardia. However, given the concomitant co-administration with digoxin and amlodipine, any reflex tachycardia due primary hypotension may have been blocked; thus, a drug-related hypotension, either secondary to telithromycin or through interaction with amlodipine via CYP 3A4 cannot be excluded. However, given the relatively rapid onset 1 hour after the first dose of telithromycin, the former cause for primary hypotension, if present, would seem more likely than an interaction.

Case 200214917FR: A 75 year-old woman with a history of hypertension on bisoprolol-hydrochlorothiazide and coronary artery disease developed sudden and unexpected loss of consciousness associated with a fall and nasal bone fracture on Day 2 of treatment with telithromycin. Systolic blood pressure was recorded at 80 mmHg and heart rate at 75 beats per minute. ECG did not reveal QT interval prolongation and Holter monitor was negative. The cause of syncope in this patient is unknown. An extensive cardiac work-up revealed no apparent causes. While hypotension and relative bradycardia (given the degree of hypotension) are reported, it is unclear whether this may represent 1) a vagally-mediated event, 2) primary hypotension with impaired compensatory tachycardia due to concomitant beta-adrenergic blocker administration. Of note, no QTC prolongation was observed in this high-risk patient (QTc 410 msec).

In the remaining 5 cases, a primary drug etiology cannot be excluded. These cases are summarized below:

Case 200310535FR: A 38 year-old man with no significant medical history developed dyspnea, palpitations, and lipothymia (syncope) that resolved with resting in a supine position. The reported events are consistent with presyncope, rather than true loss of consciousness, but no ECG was performed. As additional information, such as vital signs, is also lacking, it is not possible to make an assessment.

Case 200311099FR: A 61 year-old man with hypertension, prior cerebrovascular accident, and mitral insufficiency took telithromycin 800 mg/day for treatment of bronchitis. Concomitant medications were nifedipine, sotalol, and alfuzosin. One hour after the first intake, he experienced loss of consciousness and was found to have a systolic blood pressure of 50 mmHg, for which he was hospitalized but no acute treatment was reported. (Baseline systolic blood pressure was well controlled at 125 mm Hg.) Telithromycin was discontinued, and he recovered and was sent home the next day. Approximately 5 weeks later, he again took telithromycin at an unspecified dose for treatment of bronchitis, and 1 hour later, his systolic blood pressure was 80 mmHg, but there was no loss of consciousness, and he recovered later that day. The recurrence of hypotension with subsequent administration (positive rechallenge) strongly suggests a drug-related etiology, most likely secondary to an interaction with nifedipine (listed event) or alfuzosin.

Case 200311822FR: A 17 year-old female developed syncope leading to a fall with broken teeth 14 hours after the first dose of telithromycin. Examination was unremarkable, and ECG revealed incomplete right bundle branch block (iRBBB) and echocardiogram was normal. Without a baseline ECG, the iRBBB is uninterpretable; however the lack of QT prolongation on this ECG makes a drug-related malignant ventricular arrhythmia, such as torsades de pointes unlikely. The onset of syncope while standing may suggest a vagal effect or primary hypotension; however, vital signs were not performed at the time of the event.

Case 200410971JP involves the occurrence of hypotension (blood pressure 54/28 mmHg) and loss of consciousness without prodrome on the first day of treatment with telithromycin. Concomitant medications include losartan and nifedipine. Both a primary

hypotension from telithromycin and a secondary hypotensive effect due to drug interaction with the antihypertensive medication can be possible causes for the events.

Case 200412060FR: A 70 year-old female with hypertension developed sudden malaise and syncope associated with hypotension (systolic blood pressure 60 mmHg) and bradycardia (heart rate 30-40 beats per minute) 2 hours after the first dose of telithromycin, which resolved after 20 minutes. The combined bradycardia and hypotension suggest a vagal etiology. As there were no preceding gastrointestinal events reported (although the exact meaning of "malaise" is unknown) and no concomitant medications to provide alternative explanations, a primary drug effect is possible.

Medical Officer's Comments:

A precise etiology of the syncopal events is unknown. However, it is observed that 1 report is associated with documented bradycardia, 3 with documented hypotension, and 4 with both hypotension and bradycardia. Moreover, many are preceded by gastrointestinal symptoms. The complex of findings observed in these cases, therefore, appear consistent with a vagal syndrome, which may be associated in rare instances with loss of consciousness. This is compounded by the young age of many of the patients, where increased vagal tone may be more prevalent. One may therefore consider a vagally-mediated drug effect as a plausible alternative explanation.

Of note are 2 cases 200211062DE and 200214917FR where the patients fell when they lost consciousness. One of these patients (200214917FR) sustained a nasal bone fracture.

Medical Officer's Review of additional submissions on syncope and loss of consciousness:

Submissions reviewed:

January 10, 2005 submission: Update to Reasoned Statement of September 2004: Cumulative Review of Syncope and Loss of Consciousness Associated with Telithromycin Use.
January 14, 2005 submission: An English translation of the Blue Letter distributed to health care professionals in Japan on January 14, 2005 (*Follow-up - Japanese Regulatory Actions re: Syncope and Loss of Consciousness Associated with Telithromycin Use).*

Aventis updated the telithromycin safety data in September 2004. The search identified 79 cases (67 from spontaneous reports, 1 from an intensified monitoring study, and 11 from company-sponsored Phase III and IV clinical studies). Fifty-six of these cases were reviewed in the previous analysis, and 23 are new reports since this July 2004 review.

A preliminary review of the cases reported from Japan identified two additional reports reported as depressed levels of consciousness, but which have been considered as syncope due to additional information contained within the case. In addition, these reports involved the occurrence of motor vehicle accidents concurrent with the

disturbance of consciousness. These reports, 200414029JP and 200413606JP, are also included in the review below. Both of these reports were received subsequent to the July 2004 review.

Medical Officer's Review of New Cases of Loss of Consciousness:

Sanofi-aventis Global Pharmacovigilance has received twenty-five new cases, all from spontaneous reports, since the original search of the database in July 2004.

The 25 reports were assessed as follows:

One of these reports, 200413996JP, lacks a temporal relationship to telithromycin, as loss of consciousness occurred 3 days after the end of treatment with telithromycin. Significant underlying disease provides the most likely explanation for the event in this patient with lung cancer with brain metastases.

One report, 200413932FR, was reported as vagal malaise, however full loss of consciousness did not occur. Additionally, the time to onset (15 minutes) was notably very short to be the result of an orally ingested drug.
Twelve of these reports lack adequate information, including details surrounding the events, medical history, concomitant medications, and work-up of the event, precluding a reasonable causality assessment. Of note, this group of indeterminate cases includes one report of sudden death on Day 1 of treatment in a 97 year-old Japanese female (200413992JP). In this patient, however, advanced age and history of cardiac failure, combined with the acute bronchopneumonia and intake of a benzamide may provide significant risk factors for the occurrence of sudden death and may reasonably explain the occurrence of the event. In a second report, 200414029JP, a 64-year old female with unknown medical history drove across several lanes of traffic and hit three other cars on Day 2 of telithromycin treatment. She subsequently stated that she had a moment of unconsciousness (unconfirmed).

The remaining 11 reports (cases with probable loss of consciousness, plausible temporal relationships and adequate information to provide minimal assessment) are summarized below:

Case 200413376FR: A 21 year-old woman with hepatocellular injury (serious adverse event) experienced malaise and vomiting followed by syncope on Day 6 of treatment with telithromycin (time from dosing unknown). The preceding vomiting and malaise is strongly suggestive of a vagal syncope, which is listed in the current Corporate Data Sheet for telithromycin.

Concomitant diseases, including sepsis (*Cases 200413999JP, 200414007JP and 200417865GDDC)*, non-drug related orthostatic hypotension occurring more than 12 hours after the initial dose, and bronchospastic pulmonary disease (*Case 200418619US*) provide possible alternative explanations in 4 of these reports. However, in case 200413999JP, while sepsis appears likely (given the urinary infection with profound

leukocytosis, hypotension, respiratory failure requiring intubation, and acute renal failure), as this patient was also taking amlodipine, a drug interaction leading to hypotension cannot be fully excluded.

Similarly, though somewhat less certain given the paucity of details, adequate information exists to suspect underlying disease (prostate cancer and acute pneumonia in *200412840JP* and subtle heart disease and chest pain in *200419142US*) as a cause or contributor in 2 more reports. It is unclear whether the diaphoresis described in this latter case may be part of a vagal event or is related to the chest pain.

Case 200412695JP likely represents neurogenic syncope, given the witnessed seizure with post-ictal confusion noted after arrival to the medical facility. In this case, the preceding tooth extraction and/or anesthesia confound the causality assessment for the new-onset seizures, as these may also represent a vagal phenomenon.

In three of these reports, *200413869FR, 200416329US, and 200413606JP* a direct role of telithromycin via drug interaction seems possible in the etiology of the syncopal episode. In case 200413869FR, significant hypotension (systolic blood pressure of 70 mmHg) was noted on Day 4 of treatment in a patient taking concomitant amlodipine. As amlodipine is a cytochrome P450 3A4 substrate, an interaction mediated via telithromycin-induced CYP 3A4 inhibition, may have led to an increase in amlodipine levels and subsequent hypotension. However, buflomedil, begun the same day as telithromycin, may also have caused or contributed to the event in an independent and additive way. Similarly, in case 200416329US, a CYP 3A4-mediated interaction between telithromycin and diltiazem cannot be excluded. Lastly, in case 200413606JP, this elderly patient was taking concomitant medications amlodipine and tamsulosin. Both of these drugs have the propensity to induce hypotension, and both are metabolized by CYP 3A4. An interaction with telithromycin, leading to hypotension and syncope on Day 2 in this elderly man, cannot be excluded.

In summary, of these 11 assessable cases, only 6 have a plausible relationship to drug:
Three reports are suggestive of a possible role of telithromycin in the development of syncope and these three events may have occurred via a drug interaction with calcium channel blockers.
In a fourth report, although the presence of sepsis as an alternative explanation seems likely, a drug interaction with amlodipine cannot be excluded.
In two more, a vagally mediated event cannot be completely excluded based upon the presence of nonspecific clinical signs (e.g. sweats) or events known to trigger vagal responses (e.g., tooth extraction performed under local anesthesia).
The remaining 5 assessable cases, as noted above, are likely due to other, nontelithromycin-related causes.

Medical Officer's Comments:

My review of these additional 25 new spontaneous reports of loss of consciousness identified 4 cases leading to a motor vehicle accident. All of these reports were from Japan.

In one of the cases (200412695JP), the loss of consciousness followed by a motor vehicle accident occurred one hour after a single dose of telithromycin was administered. The patient was hospitalized, and a convulsion was witnessed, followed by post-ictal confusion.
In case 200413606JP, this elderly patient was taking concomitant medications amlodipine and tamsulosin. Both of these drugs have the propensity to induce hypotension, and both are metabolized by CYP 3A4. An interaction with telithromycin, leading to hypotension and syncope and motor vehicle accident on Day 2 in this elderly man, cannot be excluded.
A 64 year-old female (200414029JP) had a motor vehicle accident after unverified "moment of unconsciousness". This case lacks adequate information to be assessable.
In the last case (200414030JP), a 48-year old male had loss of consciousness while driving, leading to a minor motor vehicle accident on day 4 of treatment with telithromycin. This episode was witnessed by his wife. This patient was rechallenged without recurrence of loss of consciousness.

Based upon the above reports of loss of consciousness while driving, the company was mandated by the Japanese Ministry of Health, Labor and Welfare (MHLW) to clarify and change the current telithromycin labeling by:

- Modifying the product labeling cautioning against driving a vehicle or operating of heavy machinery
- Issuing a letter to health care professionals (Blue Letter – Appendix 1) to further highlight these adverse events, and the potential consequences for operating machinery to prescribers
- Issuing a patient information leaflet

The previous wording in the Japanese package insert (November 2004):

Important basic precautions

Since Ketek may cause loss of consciousness, visual accommodation disorder and blurred vision etc., patients should be cautioned if they engage in operating potentially hazardous machinery such as driving a vehicle (see Adverse Reaction Section).

The revised wording in the Japanese package insert (January 2005):

Important basic precautions

Patients should be cautioned against engaging in operating potentially hazardous machinery such as driving a vehicle while taking Ketek tablets (see Adverse Reaction Section).

Medical Officer's Comments and Recommendations:

*Based on the review of all cases of loss of consciousness and syncope, the company has proposed the following statement under "**Post-Marketing Adverse Event Reports**":*

Under Nervous system: addition of "rare reports of syncope usually associated with vagal syndrome"

A review of the Aventis safety database revealed 56 reports of syncope or loss of consciousness. Half of the 56 cases occurring in the Aventis safety database could be excluded as likely drug effects. Of the remaining cases, most (13/28, or 46%) lacked adequate information to assess them or contained significant co-morbid conditions or concomitant medications that provided more plausible alternative explanations. Thus, only 13 reports of syncope had possible or plausible relationship to telithromycin, most commonly through secondary vagal complications of more common adverse events such as nausea, vomiting and dizziness.

Thus, after more than 10 million post-marketing exposures, it can be concluded that possibly related syncope associated with telithromycin use is extremely rare (approximately 1.3 per million exposures). These events are usually transient, occurring shortly after the first or second dose, with rapid and full recovery generally observed. Although the mechanism for these events is not known, a frequent association with hypotension and/or bradycardia in these reports may suggest a vagally mediated phenomenon that is usually secondary to other more common adverse events such as nausea, diarrhea or dizziness. Although telithromycin is an inhibitor of CYP 3A4, and thus has the potential for interaction with calcium channel blockers, none of the 3 reports involving dihydropyridine provide convincing evidence for drug interaction leading to syncope. Importantly, given the small effect on cardiac repolarization observed in clinical trials, none of these reports was associated with QT interval prolongation. Though the company has cited these 2 cases of motor vehicle accidents (200414029JP and 200414030JP) as not assessable because of lack of information, I am still concerned that patients who take Ketek may be prone to loss of consciousness. Moreover, the Japanese package insert does not have adequate strong precautionary statement for adaptation into the USA label for Ketek.

My recommendation is as follows:

- *The addition of "Syncope usually associated with vagal syndrome" in the Post-Marketing Adverse Event Section is acceptable; but the repeated use of the term "rare reports of" is not recommended. The adverse events should be listed in the Post-Marketing section without qualifiers. An additional statement should be put in the PRECAUTIONS section of the Ketek label.*

- In the **PRECAUTIONS** section, under **General**, the second paragraph reads:

"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.**)"

The above paragraph should be revised to read:

"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 loss of consciousness and syncope usually associated with vagal syndrome.
Patients should be cautioned about the potential effects of these visual disturbances and loss of consciousness on driving a vehicle, operating machinery or engaging in other potentially hazardous activities. (See ***ADVERSE REACTIONS, CLINICAL STUDIES.)"***

The section **INFORMATION FOR PATIENTS** should be revised as follows:

Information for patients

The following information and instructions should be communicated to the patient.

Patients should avoid driving a motor vehicle, operating heavy machinery, or engaging in otherwise hazardous activities. Auto accidents have occurred in patients who had fainting episodes or visual difficulties when taking KETEK.

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:

- *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 antibacterial drugs including KETEK should only be used to treat bacterial infections. They do not treat viral infections (e.g., the common cold). When KETEK is prescribed to treat a bacterial infection, patients should be told that although it is common to feel better early in the course of therapy, the medication*

should be taken exactly as directed. Skipping doses or not completing the full course of therapy may (1) decrease the effectiveness of the immediate treatment and (2) increase the likelihood that bacteria will develop resistance and will not be treatable by KETEK or other antibacterial drugs in the future.

- *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.*
- *that KETEK should be avoided in patients receiving Class 1A (e.g., quinidine, procainamide) or Class III (e.g., dofetilide) antiarrhythmic agents.*
- *to inform their physician of any personal or family history of QTc prolongation or proarrhythmic conditions such as uncorrected hypokalemia, or clinically significant bradycardia.*
- *that telithromycin is not recommended in patients with myasthenia gravis. Patients should inform their physician if they have myasthenia gravis.*
- *that simvastatin, lovastatin, or atorvastatin should be avoided in patients receiving KETEK. If KETEK is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be stopped during the course of treatment.*
- *that KETEK tablets can be taken with or without food.*
- *to inform their physician of any other medications taken concurrently with KETEK, including over-the-counter medications and dietary supplements.*

The ***POST-MARKETING ADVERSE EVENT REPORTS*** *section should be revised as follows:*

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.
Allergic: face edema, rare reports of severe allergic reactions, including angioedema and anaphylaxis.
Cardiovascular: atrial arrhythmias, palpitations
Gastrointestinal: pancreatitis
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.
Musculoskeletal: muscle cramps, rare reports of exacerbation of myasthenia gravis. (See ***WARNINGS****.)*
Nervous: syncope, usually associated with vagal syndrome

The above recommendations were e-mailed to the applicant on July 25, 2005, August 1, and August 8, 2005. This was followed by a telephone conversation between Dr. John Alexander, Carmen Debellas and Dr. Edelberg (applicant representative).

Subsequent to the above communications, the applicant submitted an amendment to Supplement S-004 on October 25, 2005, and has proposed the following changes to the labeling:

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.

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. (See **ADVERSE REACTIONS, CLINICAL STUDIES.**)

Under **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.
Allergic: face edema, rare reports of severe allergic reactions, including angioedema and anaphylaxis.
Cardiovascular: atrial arrhythmias, palpitations
Gastrointestinal: pancreatitis
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.
Musculoskeletal: muscle cramps, rare reports of exacerbation of myasthenia gravis. (See **WARNINGS**.)
Nervous system: syncope, usually associated with vagal syndrome

Under **Information to Patients Section**

The following information and instructions should be communicated to the patient.

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.

Medical Officer's Recommendations:

The above changes are acceptable and the supplement is approved.

APPENDIX 1

Blue Letter:

— This information is indispensable to the proper use of pharmaceutical products. Please read without fail. —

Ketek 300 mg Safety Information

[Marketed by] Sankyo Co. Ltd., Fujisawa Pharmaceutical Co. Ltd.
[Manufactured by] Aventis Pharma Co. Ltd

Loss of consciousness etc. of Ketek 300 mg (telithromycin) Tablets

Concerning loss of consciousness etc. of Ketek tablets, we revised the package insert of Ketek tablet to add "Since Ketek may cause loss of consciousness, visual accommodation disorder and blurred vision etc., patients should be cautioned if they engage in operating potentially hazardous machinery such as driving a vehicle" into the "Important basic precaution" section and "Clinically important adverse reactions" section based on the instruction issued from the Manager of the Safety Division of MHLW on November 4, 2004, and cautioned HCPs about it.
However, eight additional cases of LOC (cumulative number of LOC cases is fifteen as at 28th December) were reported after informing the revision of the PI [estimated total number of Ketek-treated patients is about 3.4 million by the end of December 2004]. Because two more automobile accident cases were included (cumulative number of automobile accident cases is four), we revised the "Important basic precaution" section and "Adverse reaction" section and cautioned "Patients should be cautioned against engaging in operating potentially hazardous machinery such as driving a vehicle while taking Ketek Tablets".

Please pay careful attention to the following points when using this drug.

1. Should be cautioned against engaging in operating potentially hazardous machinery such as driving a vehicle.

Patients should be cautioned against engaging in operating potentially hazardous machinery such as driving a vehicle during the period of Ketek tablet treatment as loss of consciousness, accommodation disorder, and blurred vision etc. may occur while taking Ketek tablets.

2. Explain fully to patients etc.

When Ketek is prescribed, the patients (their family or persons who taking care of the patients if possible) should receive a full explanation that these ADRs might occur.
If these ADRs occur, the administration should be discontinued and they should consult a doctor.

See the fourth page regarding to the revision of "Precautions" and where to call for more information.