

IMPORTANT PRESCRIBING INFORMATION



KETEK® (telithromycin) DEAR HEALTHCARE PROFESSIONAL LETTER

March 2007

IMPORTANT INFORMATION ABOUT KETEK® (telithromycin)

Dear Healthcare Professional:

Sanofi-aventis U.S. would like to inform you of important updated information regarding KETEK® (telithromycin) tablets. **The prescribing information has been revised to add a boxed warning and contraindication for myasthenia gravis patients. In addition, the indications for the treatment of acute exacerbation of chronic bronchitis (AECB) and acute bacterial sinusitis (ABS) have been removed from the labeling.** These revisions follow discussions with the Food and Drug Administration (FDA) regarding its decision to follow recommendations of a December 2006 Advisory Committee that the balance of the benefits and risks no longer support continued marketing of Ketek for these two indications. It is important to note that Ketek continues to be indicated only for the treatment of community-acquired pneumonia (CAP) of mild to moderate severity due to *Streptococcus pneumoniae*, (including multi-drug resistant isolates [MDRSP*]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydomydia pneumoniae*, or *Mycoplasma pneumoniae*, for patients 18 years old and older.

Safety information regarding visual disturbances and loss of consciousness, previously in the precautions section, has been added to the warnings section. **In prescribing KETEK, it is important for healthcare professionals to inform and discuss with patients the four highlighted toxicities: exacerbation of myasthenia gravis, hepatotoxicity, visual disturbances, and loss of consciousness.**

A Medication Guide has been developed that replaces the Patient Information section of the US prescribing information for KETEK, to better inform and educate patients. The Medication Guide must be provided by pharmacists to patients when KETEK® is dispensed. Healthcare professionals should advise patients to read the medication guide prior to taking KETEK.

Important changes to the updated KETEK® Prescribing Information include:

IMPORTANT DRUG SAFETY INFORMATION:

1. Add a **BOXED WARNING** regarding what is now a **CONTRAINDICATION** for patients with myasthenia gravis;
2. Include a **WARNING** concerning visual disturbances and loss of consciousness, including information previously listed in the **PRECAUTIONS** section;
3. Include a Medication Guide for patients that replaces the Patient Information section

IMPORTANT PRESCRIBING INFORMATION:

1. **Remove** from the labeling recommendations for the use of Ketek in the treatment of acute exacerbations of chronic bronchitis (AECB) and acute bacterial sinusitis (ABS) in the **INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION and CLINICAL STUDIES** sections.

These changes have been approved by the US Food and Drug Administration.

The most important changes in the prescribing information relating to the above are as follows:

MYASTHENIA GRAVIS

Clinicians are advised to review carefully the Boxed Warning shown below, which has been added to the prescribing information.

Ketek is contraindicated in patients with myasthenia gravis. There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of Ketek. (See **CONTRAINDICATIONS**.)

CONTRAINDICATIONS

Added:

“KETEK is contraindicated in patients with myasthenia gravis. Exacerbations of myasthenia gravis have been reported in patients and sometimes occurred within a few hours of the first dose of telithromycin. Reports have included fatal and life-threatening acute respiratory failure with a rapid onset and progression.”

VISUAL DISTURBANCES AND SYNCOPE

WARNINGS

Added 2 new subsections:

“Visual disturbances*”

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.

“Loss of Consciousness*”

There have been post-marketing adverse event reports of transient loss of consciousness including some cases associated with vagal syndrome.

***Because of potential visual difficulties or loss of consciousness, patients should attempt to minimize activities such as driving a motor vehicle, operating heavy machinery or engaging in other hazardous activities during treatment with KETEK. If patients experience visual disorders or loss of consciousness while taking KETEK, patients should not drive a motor vehicle, operate heavy machinery or engage in other hazardous activities. (See PRECAUTIONS, Information for Patients.)”**

REMOVED: ACUTE EXACERBATION of CHRONIC BRONCHITIS (AECB) and ACUTE BACTERIAL SINUSITIS (ABS) INDICATIONS

INDICATIONS AND USAGE

Removed from the indications section acute exacerbation of chronic bronchitis (AECB) and acute bacterial sinusitis (ABS).

DOSAGE AND ADMINISTRATION

Revised the dosing information to delete references to infection type and to be specific for the community acquired-pneumonia indication as follows:

“The dose of KETEK tablets is 800 mg (2 tablets of 400 mg) taken orally once every 24 hours, for 7–10 days. KETEK tablets can be administered with or without food.”

We also remind healthcare professionals of the June 2006 labeling changes concerning hepatotoxicity. The current version of the warning follows.

“WARNINGS

“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.

“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.** If clinical hepatitis or transaminase elevations 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 macrolide antibiotic.

“In addition, less severe hepatic dysfunction associated with increased liver enzymes, hepatitis and in some cases jaundice was reported with the use of KETEK. These events associated with less severe forms of liver toxicity were reversible.”

At sanofi-aventis U.S., patient safety is our highest priority and we are committed to ensuring that healthcare professionals continue to have the information necessary to prescribe KETEK appropriately. Please carefully review this information and the revised labeling including the Medication Guide which are enclosed. Contact sanofi-aventis if you have any questions about this information or the safe and effective use of KETEK.

We also encourage you to report any adverse events experienced by your patients. Call sanofi-aventis U.S. at 1-800-633-1610 (option #2) to report adverse events occurring in connection with the use of KETEK. Alternatively, this information may be reported to FDA's MedWatch Reporting System by phone at 1-800-FDA-1088, by facsimile at 1-800-FDA-0178, or by mail using the Form 3500 at <http://www.fda.gov/medwatch/index.html>.

The revised product information including the Medication Guide will be included in Ketek® (telithromycin) packages manufactured after February 12, 2007, and is available on the company and product websites (www.sanofi-aventis.us and www.ketek.com) or by contacting Medical Information Services at 1-800-633-1610 (option #1) from 9 am to 5 pm (EST) Monday–Friday.

Sincerely,



Douglas A. Greene

Douglas Greene, MD

Senior Vice President US Medical Affairs & Chief Medical Officer
Sanofi-aventis U.S.

Enclosures: KETEK® (telithromycin) Full Prescribing Information

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About Ketek

Ketek is contraindicated in patients with myasthenia gravis. There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of Ketek.

KETEK tablets are indicated for the treatment of community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including multi-drug resistant isolates [MDRSP*]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydomphila pneumoniae*, or *Mycoplasma pneumoniae*, for patients 18 years old and above.

*MDRSP, Multi-drug resistant *Streptococcus pneumoniae* includes isolates known as PRSP (penicillin-resistant *Streptococcus pneumoniae*), and are isolates resistant to two or more of the following antibiotics: penicillin, 2nd generation cephalosporins, e.g., cefuroxime, macrolides, tetracyclines and trimethoprim/sulfamethoxazole.

To reduce the development of drug-resistant bacteria and maintain the effectiveness of KETEK and other antibacterial drugs, KETEK should be used only to treat infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

KETEK is contraindicated in patients with myasthenia gravis. Exacerbations of myasthenia gravis have been reported in patients and sometimes occurred within a few hours of the first dose of telithromycin. Reports have included fatal and life-threatening acute respiratory failure with a rapid onset and progression.

KETEK is contraindicated in patients with previous history of hepatitis and/or jaundice associated with the use of KETEK tablets, or any macrolide antibiotic.

KETEK is contraindicated in patients with a history of hypersensitivity to telithromycin and/or any components of KETEK tablets, or any macrolide antibiotic.

Concomitant administration of KETEK with cisapride or pimozide is contraindicated.

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.

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.** If clinical hepatitis or transaminase elevations 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 macrolide antibiotic.

In addition, less severe hepatic dysfunction associated with increased liver enzymes, hepatitis and in some cases jaundice was reported with the use of KETEK. These events associated with less severe forms of liver toxicity were reversible.

Telithromycin has the potential to prolong the QTc interval of the electrocardiogram in some patients. QTc prolongation may lead to an increased risk for ventricular arrhythmias, including torsades de pointes. Thus, telithromycin should be avoided in patients with congenital prolongation of the QTc interval, and in patients with ongoing proarrhythmic conditions such as uncorrected hypokalemia or hypomagnesemia, clinically significant bradycardia, and in patients receiving Class IA (e.g., quinidine and procainamide) or Class III (e.g., dofetilide) antiarrhythmic agents.

Cases of torsades de pointes have been reported post-marketing with KETEK. In clinical trials, no cardiovascular morbidity or mortality attributable to QTc prolongation occurred with telithromycin treatment in 4780 patients in clinical trials, including 204 patients having a prolonged QTc at baseline.

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 transient loss of consciousness including some cases associated with vagal syndrome.

Because of potential visual difficulties or loss of consciousness, patients should attempt to minimize activities such as driving a motor vehicle, operating heavy machinery or engaging in other hazardous activities during treatment with KETEK. If patients experience visual disorders or loss of consciousness while taking KETEK, patients should not drive a motor vehicle, operate heavy machinery or engage in other hazardous activities.

Clostridium difficile associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including KETEK, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

Therapy with simvastatin, lovastatin, or atorvastatin should be suspended during the course of KETEK treatment. Concomitant treatment of KETEK with rifampin, a CYP 3A4 inducer, should be avoided.

Most adverse events were mild to moderate and included diarrhea, nausea, headache, dizziness, and vomiting.