previous history of hepatitis/jaundice associated with the use of KETEK or macrolide antibiotics. (See **CONTRAINDICATIONS** and **WARNINGS.**)

- 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.*

- KETEK has the potential to produce changes in the electrocardiogram (QTc interval prolongation) and that they should report any fainting occurring during drug treatment.

- 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.

- diarrhea is a common problem caused by antibiotics which usually ends when the antibiotic is discontinued. Sometimes after starting treatment with antibiotics, patients can develop watery and bloody stools (with or without stomach cramps and fever) even as late as two or more months after having taken the last dose of the antibiotic. If this occurs, patients should contact their physician as soon as possible.

- 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.

- 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.

Drug interactions

Telithromycin is a strong inhibitor of the cytochrome P450 3A4 system. Co-administration of KETEK tablets and a drug primarily metabolized by the cytochrome P450 3A4 enzyme system may result in increased plasma concentration of the drug co-administered with telithromycin that could increase or prolong both the therapeutic and adverse effects. Therefore, appropriate dosage adjustments may be necessary for the drug co-administered with telithromycin.

The use of KETEK is contraindicated with cisapride. (See **CONTRAINDICATIONS** and **CLINICAL PHARMACOLOGY, *Drug-drug interactions.*)**

The use of KETEK is contraindicated with pimozide. Although there are no studies looking at the interaction between KETEK and pimozide, there is a potential risk of increased pimozide plasma levels by inhibition of CYP 3A4 pathways by KETEK as with macrolides. (See **CONTRAINDICATIONS.**)

In a pharmacokinetic study, simvastatin levels were increased due to CYP 3A4 inhibition by telithromycin. (See **CLINICAL PHARMACOLOGY, Other drug interactions.**) Similarly, an interaction may occur with lovastatin or *atorvastatin, but not with pravastatin or fluvastatin. High levels of HMG-CoA reductase inhibitors increase the* risk of myopathy. Use of simvastatin, lovastatin, or atorvastatin concomitantly with KETEK should be avoided. If KETEK is prescribed, therapy with simvastatin, lovastatin, or atorvastatin should be suspended during the course of treatment.

Monitoring of digoxin side effects or serum levels should be considered during concomitant administration of digoxin and KETEK. (See **CLINICAL PHARMACOLOGY, Drug-drug interactions.**)

Patients should be monitored with concomitant administration of midazolam and dosage adjustment of midazolam should be considered if necessary. Precaution should be used with other benzodiazepines, which are metabolized by CYP 3A4 and undergo a high first-pass effect (e.g., triazolam). (See **CLINICAL PHARMACOLOGY, Drug-drug interactions.**)

Concomitant treatment of KETEK with rifampin, a CYP 3A4 inducer, should be avoided. Concomitant administration of other CYP 3A4 inducers such as phenytoin, carbamazepine, or phenobarbital is likely to result in subtherapeutic levels of telithromycin and loss of effect. (See **CLINICAL PHARMACOLOGY, Other drug interactions.**)

In patients treated with metoprolol for heart failure, the increased exposure to metoprolol, a CYP 2D6 substrate, may be of clinical importance. Therefore, co-administration of KETEK and metoprolol in patients with heart failure should be considered with caution. (See **CLINICAL PHARMACOLOGY, Drug-drug interactions.**)

Spontaneous post-marketing reports suggest that administration of KETEK and oral anticoagulants concomitantly may potentiate the effects of the oral anticoagulants. Consideration should be given to monitoring *prothrombin times/INR while patients are receiving KETEK and oral anticoagulants simultaneously.*

No specific drug interaction studies have been performed to evaluate the following potential drug-drug interactions with KETEK. However, these drug interactions have been observed with macrolide products.
Drugs metabolized by the cytochrome P450 system such as carbamazepine, cyclosporine, tacrolimus, sirolimus, hexobarbital, and phenytoin: elevation of serum levels of these drugs may be observed when co-administered with telithromycin. As a result, increases or prolongation of the therapeutic and/or adverse effects of the concomitant drug may be observed.
Ergot alkaloid derivatives (such as ergotamine or dihydroergotamine): acute ergot toxicity characterized by severe peripheral vasospasm and dysesthesia has been reported when macrolide antibiotics were co-administered. *Without further data, the co-administration of KETEK and these drugs is not recommended.*

Laboratory test interactions

There are no reported laboratory test interactions.

Carcinogenesis, mutagenesis, impairment of fertility

Long-term studies in animals to determine the carcinogenic potential of KETEK have not been conducted.

Telithromycin showed no evidence of genotoxicity in four tests: gene mutation in bacterial cells, gene mutation in mammalian cells, chromosome aberration in human lymphocytes, and the micronucleus test in the mouse.

No evidence of impaired fertility in the rat was observed at doses estimated to be 0.61 times the human daily dose on a mg/m^2 basis. At doses of 1.8-3.6 times the human daily dose, at which signs of parental toxicity were observed, moderate reductions in fertility indices were noted in male and female animals treated with telithromycin.

Pregnancy

Teratogenic effects: Pregnancy Category C. Telithromycin was not teratogenic in the rat or rabbit. Reproduction studies have been performed in rats and rabbits, with effect on pre-post natal development studied in the rat. At doses estimated to be 1.8 times (900 mg/m^2) and 0.49 times (240 mg/m^2) the daily human dose of 800 mg (492 mg/m^2) in the rat and rabbit, respectively, no evidence of fetal terata was found. At doses higher than the 900 mg/m^2 and 240 mg/m^2 in rats and rabbits, respectively, maternal toxicity may have resulted in delayed fetal maturation. No adverse effects on prenatal and postnatal development of rat pups were observed at 1.5 times (750 mg/m^2/d) the daily human dose.

There are no adequate and well-controlled studies in pregnant women. Telithromycin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing mothers

Telithromycin is excreted in breast milk of rats. Telithromycin may also be excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when KETEK is administered to a nursing mother.

Pediatric use

The safety and effectiveness of KETEK in pediatric patients has not been established.

Geriatric use

In all Phase III clinical trials (n=4,780), KETEK was administered to 694 patients who were 65 years and older, *including 231 patients who were 75 years and older. Efficacy and safety in elderly patients ≥ 65 years were* generally similar to that observed in younger patients; however, greater sensitivity of some older individuals cannot be ruled out. No dosage adjustment is required based on age alone. (See **CLINICAL PHARMACOLOGY, Special populations, Geriatric** and ***DOSAGE AND ADMINISTRATION.***)

ADVERSE REACTIONS

In Phase III clinical trials, 4,780 patients (n=2702 in controlled trials) received daily oral doses of KETEK 800 mg once daily for 5 days or 7 to 10 days. Most adverse events were mild to moderate in severity. In the combined Phase III studies, discontinuation due to treatment-emergent adverse events occurred in 4.4% of KETEK-treated patients and 4.3% of combined comparator-treated patients. Most discontinuations in the KETEK group *were due to treatment-emergent adverse events in the gastrointestinal body system, primarily diarrhea (0.9% for* KETEK vs. 0.7% for comparators), nausea (0.7% for KETEK vs. 0.5% for comparators).

All and possibly related treatment-emergent adverse events (TEAEs) occurring in controlled clinical studies in ≥ 2.0% of all patients are included below:

Table 5

All and Possibly Related Treatment-Emergent Adverse Events Reported in Controlled Phase III Clinical Studies (Percent Incidence)

Adverse Event*	All TEAEs		Possibly-Related TEAEs	
	KETEK n= 2702	Comparator† n= 2139	KETEK n= 2702	Comparator† n= 2139
Diarrhea	10.8%	8.6%	10.0%	8.0%
Nausea	7.9%	4.6%	7.0%	4.1%
Headache	5.5%	5.8%	2.0%	2.5%
Dizziness (excl. vertigo)	3.7%	2.7%	2.8%	1.5%
Vomiting	2.9%	2.2%	2.4%	1.4%
Loose Stools	2.3%	1.5%	2.1%	1.4%
Dysgeusia	1.6%	3.6%	1.5%	3.6%

*Based on a frequency of all and possibly related treatment-emergent adverse events of ≥ 2% in KETEK or comparator groups.
† Includes comparators from all controlled Phase III studies.

The following events judged by investigators to be at least possibly drug related were observed infrequently (≥ 0.2% and < 2%), in KETEK-treated patients in the controlled Phase III studies.

Gastrointestinal system: abdominal distension, dyspepsia, gastrointestinal upset, flatulence, constipation, gastroenteritis, gastritis, anorexia, oral candidiasis, glossitis, stomatitis, watery stools.

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.**)

Nervous system: dry mouth, somnolence, insomnia, vertigo, increased sweating

Body as a whole: abdominal pain, upper abdominal pain, fatigue

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 **WARNINGS** and **PRECAUTIONS, Information for patients.**)

Females and patients under 40 years old experienced a higher incidence of telithromycin-associated visual adverse events. (See **CLINICAL STUDIES.**)

Urogenital system: vaginal candidiasis, vaginitis, vaginosis fungal

Skin: rash

Hematologic: increased platelet count

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.
Allergic: face edema, rare reports of severe allergic reactions, including angioedema and anaphylaxis.
Cardiovascular: atrial arrhythmias, palpitations
Gastrointestinal system: pancreatitis
Liver and biliary system: Hepatic dysfunction has been reported.
Severe 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. (See **CONTRAINDICATIONS** and **WARNINGS.**) Severe reactions, in some but not all cases, have been associated with serious underlying diseases or concomitant medications.
Data from post-marketing reports and clinical trials show that most cases of hepatic dysfunction were mild to moderate. (See **PRECAUTIONS, General.**)

Musculoskeletal: muscle cramps, rare reports of exacerbation of myasthenia gravis. (See **CONTRAINDICATIONS.**)
Nervous system: loss of consciousness, in some cases associated with vagal syndrome.

OVERDOSAGE

In the event of acute overdosage, the stomach should be emptied by gastric lavage. The patient should be carefully monitored (e.g., ECG, electrolytes) and given symptomatic and supportive treatment. Adequate hydration should be maintained. The effectiveness of hemodialysis in an overdose situation with KETEK is unknown.

DOSAGE AND ADMINISTRATION

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.

KETEK may be administered without dosage adjustment in the presence of hepatic impairment.

In the presence of severe renal impairment (CL_{CR} < 30 mL/min), including patients who need dialysis, the dose should be reduced to KETEK 600 mg once daily. In patients undergoing hemodialysis, KETEK should be given after the dialysis session on dialysis days. (See **CLINICAL PHARMACOLOGY, Renal insufficiency.**)

In the presence of severe renal impairment (CL_{CR} < 30 mL/min), with coexisting hepatic impairment, the dose should be reduced to KETEK 400 mg once daily. (See **CLINICAL PHARMACOLOGY, Multiple insufficiency.**)

HOW SUPPLIED

KETEK® 400 mg tablets are supplied as light-orange, oval, film-coated tablets, imprinted "H3647" on one side and "400" on the other side. These are packaged in bottles and blister cards (Ketek Pak™ and unit dose) as follows:

Bottles of 60	(NDC 0088-2225-41)
Ketek Pak™, 10-tablet cards (2 tablets per blister cavity)	(NDC 0088-2225-07)
Unit dose package of 100 (blister pack)	(NDC 0088-2225-49)

KETEK® 300 mg tablets are supplied as light-orange, oval, film-coated tablets, imprinted "38AV" on one side and blank on the other side. These are packaged in bottles as follows:

Bottles of 20	(NDC 0088-2223-20)

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature].

CLINICAL STUDIES

Community-acquired pneumonia (CAP)

KETEK was studied in four randomized, double-blind, controlled studies and four open-label studies for the treatment of community-acquired pneumonia. Patients with mild to moderate CAP who were considered appropriate for oral outpatient treatment were enrolled in these trials. Patients with severe pneumonia were excluded based on any one of the following: ICU admission, need for parenteral antibiotics, respiratory rate > 30/minute, hypotension, altered mental status, < 90% oxygen saturation by pulse oximetry, or white blood cell count < 4000/mm^3. Total number of clinically evaluable patients in the telithromycin group included 2016 patients.

Table 6. CAP: Clinical cure rate at post-therapy follow-up (17-24 days)

	Patients (n)		Clinical cure rate	
Controlled Studies	*KETEK*	*Comparator*	*KETEK*	*Comparator*
KETEK vs. clarithromycin 500 mg BID for 10 days	162	156	88.3%	88.5%
KETEK vs. trovafloxacin* 200 mg QD for 7 to 10 days	80	86	90.0%	94.2%
KETEK vs. amoxicillin 1000 mg TID for 10 days	149	152	94.6%	90.1%
KETEK for 7 days vs. clarithromycin 500 mg BID for 10 days	161	146	88.8%	91.8%

*This study was stopped prematurely after trovafloxacin was restricted for use in hospitalized patients with severe infection.

Clinical cure rates by pathogen from the four CAP controlled clinical trials in microbiologically evaluable patients given KETEK for 7-10 days or a comparator are displayed in Table 7.

Table 7. CAP: Clinical cure rate by pathogen at post-therapy follow-up (17-24 days)

Pathogen	KETEK	Comparator
Streptococcus pneumoniae	73/78 (93.6%)	63/70 (90.0%)
Haemophilus influenzae	39/47 (83.0%)	42/44 (95.5%)
Moraxella catarrhalis	12/14 (85.7%)	7/9 (77.8%)
Chlamydophila (Chlamydia) pneumoniae	23/25 (92.0%)	18/19 (94.7%)
Mycoplasma pneumoniae	22/23 (95.7%)	20/22 (90.9%)

Clinical cure rates for patients with CAP due to *Streptococcus pneumoniae* were determined from patients in controlled and uncontrolled trials. Of 333 evaluable patients with CAP due to *Streptococcus pneumoniae*, 312 (93.7%) achieved clinical success. Only patients considered appropriate for oral outpatient therapy were included in these trials. More severely ill patients were not enrolled. Blood cultures were obtained in all patients participating in the clinical trials of mild to moderate community-acquired pneumonia. In a limited number of outpatients with incidental pneumococcal bacteremia treated with KETEK, a clinical cure rate of 88% (67/76) has been observed. KETEK is not indicated for the treatment of severe community-acquired pneumonia or suspected pneumococcal bacteremia.

Clinical cure rates for patients with CAP due to multi-drug resistant *Streptococcus pneumoniae* (MDRSP*) were determined from patients in controlled and uncontrolled trials. Of 36 evaluable patients with CAP due to MDRSP, 33 (91.7%) achieved clinical success.

*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.

Table 8. Clinical cure rate for 36 evaluable patients with MDRSP treated with KETEK in studies of community-acquired pneumonia

Screening Susceptibility	*Clinical Success in Evaluable MDRSP* Patients	
	n/N[a]	%
Penicillin-resistant	20/23	86.9
2nd generation cephalosporin-resistant	20/22	90.9
Macrolide-resistant	25/28	89.3
Trimethoprim/ sulfamethoxazole-resistant	24/27	88.9
Tetracycline-resistant[b]	11/13	84.6

[a] n = the number of patients successfully treated; N = the number with resistance to the listed drug of the 36 evaluable patients with CAP due to MDRSP.
[b] Includes isolates tested for resistance to either tetracycline or doxycycline.

Visual Adverse Events

Table 9 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.

Table 9. Incidence of All Treatment-Emergent Visual Adverse Events in Controlled Phase III Studies

Gender/Age	Telithromycin	Comparators*
Female ≤ 40	2.1% (14/682)	0.0% (0/534)
Female > 40	1.0% (7/703)	0.35% (2/574)
Male ≤ 40	1.2% (7/563)	0.48% (2/417)
Male > 40	0.27% (2/754)	0.33% (2/614)
Total	1.1% (30/2702)	0.28% (6/2139)

* Includes all comparators combined

ANIMAL PHARMACOLOGY

Repeated dose toxicity studies of 1, 3, and 6 months' duration with telithromycin conducted in rat, dog and monkey showed that the liver was the principal target for toxicity with elevations of liver enzymes and histological evidence of damage. There was evidence of reversibility after cessation of treatment. Plasma exposures based on free fraction of drug at the no observed adverse effect levels ranged from 1 to 10 times the expected clinical exposure.

Phospholipidosis (intracellular phospholipid accumulation) affecting a number of organs and tissues (e.g., liver, kidney, lung, thymus, spleen, gall bladder, mesenteric lymph nodes, GI-tract) has been observed with the administration of telithromycin in rats at repeated doses of 900 mg/m^2/day (1.8x the human dose) or more for 1 month, and 300 mg/m^2/day (0.61x the human dose) or more for 3-6 months. Similarly, phospholipidosis has been observed in dogs with telithromycin at repeated doses of 3000 mg/m^2/day (6.1x the human dose) or more for 1 month and 1000 mg/m^2/day (2.0x the human dose) or more for 3 months. The significance of these findings for humans is unknown.

Pharmacology/toxicology studies showed an effect both in prolonging QTc interval in dogs *in vivo* and *in vitro* action potential duration (APD) in rabbit Purkinje fibers. These effects were observed at concentrations of free drug at least 8.8 (in dogs) times those circulating in clinical use. *In vitro* electrophysiological studies (hERG assays) suggested an inhibition of the rapid activating component of the delayed rectifier potassium current (I_{Kr}) as an underlying mechanism.

Rev. February 2007

Rx only

References

1. National Committee for Clinical Laboratory Standards. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically – Sixth Edition; Approved Standard, NCCLS Document M7-A6, Vol. 23, No. 2, NCCLS, Wayne, PA, January, 2003.

2. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Disk Susceptibility Tests - Eighth Edition; Approved Standard, NCCLS Document M2-A8, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2003.

3. National Committee for Clinical Laboratory Standards. Performance Standards for Antimicrobial Susceptibility Testing: Twelfth Informational Supplement; Approved Standard, NCCLS Document M2-A8 and M7-A6, Vol. 23, No. 1, NCCLS, Wayne, PA, January, 2004.

MEDICATION GUIDE
KETEK® (*KEE tek*) Tablets
(telithromycin)

READ THE MEDICATION GUIDE THAT COMES WITH KETEK BEFORE YOU START TAKING IT. TALK TO YOUR DOCTOR IF YOU HAVE ANY QUESTIONS ABOUT KETEK. THIS MEDICATION GUIDE DOES NOT TAKE THE PLACE OF TALKING WITH YOUR DOCTOR ABOUT YOUR MEDICAL CONDITION OR TREATMENT.

WHAT IS THE MOST IMPORTANT INFORMATION I SHOULD KNOW ABOUT KETEK?

1. **Do not take KETEK if you have Myasthenia Gravis (a rare disease which causes muscle weakness). Worsening of myasthenia gravis symptoms including life-threatening breathing problems have happened in patients with myasthenia gravis after taking KETEK in some cases leading to death.**

KETEK can cause other serious side effects, including:

2. SEVERE LIVER DAMAGE (HEPATOXICITY). **SEVERE LIVER DAMAGE, IN SOME CASES LEADING TO A LIVER TRANSPLANT OR DEATH HAS HAPPENED IN PATIENTS TREATED WITH KETEK. SEVERE LIVER DAMAGE HAS HAPPENED DURING TREATMENT, EVEN AFTER A FEW DOSES, OR RIGHT AFTER TREATMENT WITH KETEK HAS ENDED.**

Stop KETEK and call your doctor right away if you have signs of liver problems. Do not take another dose of KETEK unless your doctor tells you to do so.

Signs of liver problems include:
- increased tiredness
- *loss of appetite*
- yellowing of the skin and/or eyes
- right upper belly pain
- light-colored stools
- *dark urine*
- itchy skin

Do not take KETEK if you have ever had side effects of the liver while taking KETEK or macrolide antibiotics. Macrolide antibiotics include erythromycin, azithromycin (Zithromax®), clarithromycin (Biaxin®) or dirithromycin (Dynabac®).

3. **Vision problems.** KETEK may cause blurred vision, trouble focusing, and double vision. You may notice vision problems if you look quickly from near objects to far objects.

4. **Fainting.** You may faint especially if you are also having nausea, vomiting, and lightheadedness.

- BE AWARE THAT VISION PROBLEMS AND FAINTING WHILE TAKING KETEK MAY AFFECT YOUR ABILITY TO DRIVE OR DO DANGEROUS ACTIVITIES. LIMIT DRIVING AND OTHER DANGEROUS ACTIVITIES.
- IF YOU HAVE VISION PROBLEMS OR FAINT WHILE TAKING KETEK
  - DO NOT DRIVE, OPERATE HEAVY MACHINES, OR DO DANGEROUS ACTIVITIES.
  - CALL YOUR DOCTOR BEFORE TAKING ANOTHER DOSE OF KETEK IF YOU HAVE VISION PROBLEMS OR FAINT.

See "What are the possible side effects of KETEK? for other side effects of KETEK.

WHAT IS KETEK?

KETEK is an antibiotic. KETEK is used to treat adults 18 years of age and older with a lung infection called "community acquired pneumonia" that is caused by certain bacteria germs.

- KETEK is not for other types of infections caused by bacteria
- KETEK, like other antibiotics, does not kill viruses.

WHO SHOULD NOT TAKE KETEK?

Do not take KETEK if you:
- have myasthenia gravis
- have had side effects on the liver while taking KETEK or macrolide antibiotics.
- have ever had an allergic reaction to KETEK or macrolide antibiotics.
- take cisapride (Propulsid®) or pimozide (Orap®).

KETEK may not be right for you. Before taking KETEK, tell your doctor about all of your medical conditions, including if you:

- have myasthenia gravis
- have liver problems
- have (or have a family history of) a heart problem called "QTc prolongation"
- have other heart problems
- are pregnant or breastfeeding

Tell your doctor about all of the medicines you take, including prescription and nonprescription medicines, vitamins, and herbal supplements. KETEK and other medicines may affect or interact with each other, sometimes causing serious side effects.

You should not take the following cholesterol lowering medicines while taking KETEK:
- simvastatin (Zocor®, Vytorin®)
- lovastatin (Mevacor®)
- atorvastation (Lipitor®)

Know the medicines you take. Keep a list of your medicines with you to show your doctor or pharmacist.

Do not take other medicines with KETEK without first checking with your doctor. Your doctor will tell you if you can take other medicines with KETEK.

HOW SHOULD I TAKE KETEK?

- Take KETEK exactly as your doctor tells you. Skipping doses or not taking all of an antibiotic may:
  - make the treatment not work as well
  - increase the chance that the bacteria will develop resistance to the antibiotic
- The usual dose is two 400 mg KETEK Tablets taken at the same time once a day for 7 to 10 days. If you have kidney disease, your doctor may prescribe a lower dose for you.
- Take KETEK with or without food.
- Swallow KETEK tablets whole.
- Call your doctor if you took too much KETEK.

WHAT ARE THE POSSIBLE SIDE EFFECTS OF KETEK?

See "What is the most important information I should know about KETEK?" for worsening of myasthenia gravis symptoms, and serious liver, vision, and fainting side effects.

Other serious side effects include:
- **Pseudomembranous colitis** (an intestine infection). Pseudomembranous colitis can happen with most antibiotics, including KETEK. Call your doctor if you get watery diarrhea, diarrhea that does not go away, or bloody stools. You may also have stomach cramps and a fever. Pseudomembranous colitis can happen up to 2 months after you have finished your antibiotic.

The most common side effects of KETEK are nausea, headache, dizziness, vomiting, and diarrhea.

These are not all of the side effects of KETEK. Ask your doctor or pharmacist for more information.

HOW SHOULD I STORE KETEK?

- Store KETEK tablets at room temperature, 59° to 86°F (15° to 30°C).
- **Keep KETEK and all medicines out of the reach of children.**

GENERAL INFORMATION ABOUT KETEK

- Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide.
- Do not use KETEK for a condition for which it was not prescribed.
- Do not share KETEK with other people, even if they have the same symptoms that you have. It may harm them.

This Medication Guide summarizes the most important information about KETEK. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about KETEK that was written for healthcare professional. This information is also available on the KETEK website at www.KETEK.com.

What are the ingredients in KETEK?

Active Ingredient: telithromycin
Inactive Ingredients: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, red ferric oxide, talc, titanium dioxide, and yellow ferric oxide

Rx Only

Medication Guide as of February 2007

This Medication Guide has been approved by the U.S. Food and Drug Administration.

sanofi-aventis U.S. LLC
Bridgewater, NJ 08807

BIAXIN® (clarithromycin) is a registered trademark of Abbott Laboratories.
ZITHROMAX® (azithromycin) is a registered trademark of Pfizer Inc.
DYNABAC® (dirithromycin) is a registered trademark of Eli Lilly and Company.
PROPULSID® (cisapride) is a registered trademark of Johnson & Johnson.
ORAP® (pimozide) is a registered trademark of Teva Pharmaceuticals USA, Inc.
LIPITOR® (atorvastatin) is a registered trademark of Pfizer Inc.
ZOCOR® (simvastatin) is a registered trademark of Merck & Co Inc.
VYTORIN® (simvastatin and ezetimibe) is a registered trademark of Merck/Schering Plough Pharmaceuticals.
MEVACOR® (lovastatin) is a registered trademark of Merck & Co Inc..

（様式第６）

医薬品　外国における製造等の中止、回収、廃棄等の措置　調査報告書

識別番号・報告回数	G-07000028	第2報	報告日 2007年04月24日	第一報入手日 2007年03月30日	新医薬品等の区分 該当なし	機構処理欄
一般的名称	01：テリスロマイシン		外国における措置の公表状況	EMEAホームページ	公表国 イギリス	
販売名（企業名）	01：ケテック （サノフィ・アベンティス（株））					

外国における措置の概要	使用上の注意記載状況・その他参考事項等
□製造・輸入の中止 □販売中止 □回収・廃棄 ■その他問題点（ケテックの適応症に関するEMEAの勧告、意識消失及び視覚障害に関する注意喚起） ケテックの４つの適応症のうち３つについて、使用を制限するよう勧告することが3月30日付でEMEAのホームページに掲載された。 その内容は下記のとおり。 ケテックは、気管支炎および副鼻腔炎、扁桃炎/咽頭炎の治療には、その原因菌がマクロライド系もしくはβ-ラクタム系抗菌剤の耐性菌、もしくは耐性菌が疑わしい場合、あるいはこれらの抗菌剤が使用できない感染症にのみ使用すること。 もう１つの適応症である、市中肺炎の治療には上記の使用制限は勧告されていない。 EMEAの医薬品委員会（CHMP：Committee for Medicinal Products for Human Use）は、重症筋無力症患者へのケテックの使用を禁忌とすること、一過性の意識消失および視覚への影響に関する注意喚起を強めることをあわせて勧告した。 CHMPが承認した添付文書（案）の主な改訂点は下記のとおり。 ・慢性気管支炎の急性増悪及び急性副鼻腔炎：原因菌がβ-ラクタムまたはマクロライドに耐性株あるいはその疑いのある場合に限定。 ・扁桃炎/咽頭炎：原因菌が化膿レンサ球菌で、βラクタム系の抗菌薬での治療が不適切な場合で、「マクロライド耐性率が高い国・地域において、その耐性が特定の遺伝子（ermTRまたはmefA）によるもの」（「 」部分追加）。 ・重症筋無力症患者への投与は禁忌 ・視覚障害の詳細追記（視調節障害、霧視、複視） ・視覚障害及び意識消失による障害を避けるため、ケテックを睡眠時に服用することを推奨。 ・視覚障害、意識消失が起こることから、自動車の運転、重機の操作及び危険を伴う機械の操作を行わないこと。また、ケテック服用中に視覚障害または意識消失が発現した場合は、このような操作を行わないこと。	【効能・効果】 〈適応菌種〉 本剤に感性のブドウ球菌属，レンサ球菌属，肺炎球菌，モラクセラ（ブランハメラ）・カタラーリス，インフルエンザ菌，レジオネラ属，ペプトストレプトコッカス属，プレボテラ属，肺炎クラミジア（クラミジア・ニューモニエ），肺炎マイコプラズマ（マイコプラズマ・ニューモニエ） 〈適応症〉 咽頭・喉頭炎，扁桃炎，急性気管支炎，肺炎，慢性呼吸器病変の二次感染，副鼻腔炎，歯周組織炎，歯冠周囲炎，顎炎 【使用上の注意】 「重要な基本的注意」 重症筋無力症の患者に投与した場合、症状が悪化することが報告されている。 呼吸器感染症の治療目的で本剤を投与した場合、初回投与後、数時間以内に急性呼吸不全を起こすことがあり、致死的な例も報告されているので、他の治療がない場合を除き、本剤の使用は避けることが望ましい。 他に治療法がなく、本剤の投与が必要な場合、観察を十分に行い、異常があらわれた場合には直ちに投与を中止し、適切な処置を行うこと。 なお、当該措置は2007年4月2日にFAX報告済みである。 また、当該措置は「治験外国措置報告」においても審査部に報告済みである。

報告企業の意見	今後の対応
海外における適応症の制限の情報を入手したので措置報告を行う。 企業としては、禁忌に「重症筋無力症患者」を追加する方向で検討中である。その他の変更箇所については、現行の使用上の注意の記載で注意喚起できていると考える。	国内「使用上の注意」改訂について検討中である。なお、USPI、SmPCの改訂に対する国内の対応は、厚生労働省等と協議中である。本内容も含めて検討を行う。

7-0700028(ケトライド系300mg

European Medicines Agency
Press office

London, 30 March 2007
Doc. Ref. EMEA/129901/2007

PRESS RELEASE

European Medicines Agency recommends restricted use and strengthened warnings for Ketek

The European Medicines Agency (EMEA) has recommended restrictions on the use of Ketek (telithromycin) in three of its four approved indications. For the treatment of bronchitis, sinusitis and tonsillitis/pharyngitis, Ketek should only be used for infections caused by bacterial strains that are suspected or proven to be resistant to or cannot be treated with macrolide or beta-lactam antibiotics.

No such restrictions are recommended for the remaining indication, the treatment of community-acquired pneumonia.

The Agency's Committee for Medicinal Products for Human Use (CHMP) also recommended the contraindication of the use of Ketek in patients with myasthenia gravis and strengthened warnings on transient loss of consciousness and effects on vision.

The CHMP has been carrying out a comprehensive review of the safety and effectiveness of Ketek since January 2006, following reports of severe liver injuries in patients taking telithromycin. As part of this review several updates relating to the safety of Ketek were made to the Product Information during 2006. These included strengthening the warnings on serious liver reactions and contraindicating the use of the medicine in patients with a previous history of serious liver disorders. In January 2007, the Committee requested updated information from the marketing authorisation holder for Ketek, to allow a comprehensive assessment of the benefits and risks in each of the medicine's approved indications.

Finalising the review at its 19-22 March 2007 meeting, the Committee concluded that the effectiveness of Ketek has been demonstrated in the approved indications. However, its use is associated with a greater risk of certain side effects, some of which may be serious. These include a worsening of myasthenia gravis (which can be life-threatening), transient loss of consciousness, and temporary visual disturbances. Severe problems with the liver have been reported rarely, but do not occur more frequently than with other relevant antibiotic medicines.

The Committee concluded that the benefits of Ketek continue to outweigh its risks in the treatment for bronchitis, sinusitis and tonsillitis/pharyngitis, if used in accordance with the updated product information.

Prescribers are advised to consider the official guidance on the appropriate use of the antibiotics and the local prevalence of resistance.

--ENDS--

NOTES

1. More information about the recommendations for Ketek is available in a separate question and answer document.
2. The European Commission is currently conducting the procedures laid down in Community legislation with a view to issuing a decision to update the product information for Ketek.
3. The updated product information, for which the Commission decision is pending, is available here.

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 84 09
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

4. In the European Union, telithromycin is authorised as Ketek and Levviax. The marketing authorisation holder is Aventis Pharma S.A. It is marketed only as Ketek. The European public assessment report for Ketek is published on the EMEA website and can be found here.
5. Ketek is marketed in the European Union/European Economic Area in Austria, Belgium, Cyprus, Finland, France, Germany, Greece, Ireland, Italy, Luxembourg, Malta, Norway, Portugal, Slovenia, Spain, Sweden and the United Kingdom.
6. The EMEA's statement on the safety of Ketek from January 2006 can be found here.
7. This press release, together with other information about the work of the EMEA, may be found on the EMEA website: http://www.emea.europa.eu.

Media enquiries only please contact:
Martin Harvey Allchurch or Monika Benstetter
Tel. (44-20) 74 18 84 27, E-mail: press@emea.europa.eu

SUMMARY OF PRODUCT CHARACTERISTICS

This SPC was approved by the CHMP on 22 March 2007 and is pending for endorsement by the European Commission

1. NAME OF THE MEDICINAL PRODUCT

Ketek 400 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg of telithromycin.
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.
Light orange, oblong, biconvex tablet, imprinted with H3647 on one side and 400 on the other.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

When prescribing Ketek, consideration should be given to official guidance on the appropriate use of antibacterial agents and the local prevalence of resistance (Ssee also sections 4.4 and 5.1).

Ketek is indicated for the treatment of the following infections:

In patients of 18 years and older:

- *Community-acquired pneumonia, mild or moderate (see section 4.4).*

- **When treating infections caused by known or suspected beta-lactam and/or macrolide resistant strains (according to history of patients or national and/or regional resistance data) covered by the antibacterial spectrum of telithromycin (see sections 4.4 and 5.1):**
  - Acute exacerbation of chronic bronchitis,
  - Acute sinusitis

~~-Tonsillitis/pharyngitis caused by *Streptococcus pyogenes*, as an alternative when beta-lactam antibiotics are not appropriate.~~

In patients of 12 years and older~~to 18 years old:~~

- **Tonsillitis/pharyngitis caused by *Streptococcus pyogenes*, as an alternative when beta lactam antibiotics are not appropriate in countries/regions with a significant prevalence of macrolide resistant S. pyogenes, when mediated by ermTR or mefA (see sections 4.4 and 5.1).**

4.2 Posology and method of administration

The recommended dose is 800 mg once a day i.e. two 400 mg tablets once a day. The tablets should be swallowed whole with a sufficient amount of water. The tablets may be taken with or without food. **Consideration may be given to taking Ketek at bedtime, to reduce the potential impact of visual disturbances and loss of consciousness (see section 4.4).**

In patients of 18 years and older, according to the indication, the treatment regimen will be:

- Community-acquired pneumonia: 800 mg once a day for 7 to 10 days,
- Acute exacerbation of chronic bronchitis: 800 mg once a day for 5 days,
- Acute sinusitis: 800 mg once a day for 5 days,
- Tonsillitis/pharyngitis caused by *Streptococcus pyogenes:* 800 mg once a day for 5 days.