CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-144/S012

Trade Name: Ketek

Generic Name: (Telithromycin)

Sponsor: Sanofi Aventis US.

Approval Date: 2/12/2007

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-144/S012

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-144/S012

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-144/S-012

sanofi aventis
Attention: Kathleen O'Donnell
Assistant Director, Regulatory Development.
Anti-Infectives, Oncology, and Bone
Mail Code BX4-212A Box 6890
200 Crossing Boulevard
Bridgewater, NJ 08807

Dear Ms. O'Donnell :

Please refer to your supplemental new drug application dated February 9, 2007, received February 9, 2007, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Ketek (telithromycin) 400mg and 300 mg Tablets.

This supplemental new drug application provides for the addition of a boxed warning for myasthenia gravis patients, updates to the **Microbiology**, **INDICATIONS AND USAGE**, **CONDRAINDICATIONS, WARNINGS**, **PRECAUTIONS** and **ADVERSE REACTIONS** sections of the label. It also provides for a Medication Guide for patients.

We completed our review of this application. This application is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text.

The final printed labeling (FPL) must be identical to the enclosed labeling and Medication Guide, dated February 9, 2007.

Submit content of labeling [21CFR 314.50(1)] in structured product labeling (SPL) format, as described at http://www.fda.gov/oc/datacouncil/spl.html, that is identical to the submitted labeling text dated February 9, 2007. Upon receipt and verification, we will transmit that version to the National Library of Medicine for posting on the DailyMed website.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-144/S-012**." Approval of this submission by FDA is not required before the labeling is used.

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
5515 Security Lane
HFD-001, Suite 5100
Rockville, MD 20852

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, call Carmen DeBellas, Regulatory Project Manager, at (301) 796-1203.

Sincerely,

{See appended electronic signature page}

Janice M. Soreth, M.D.
Director
Division of Anti-Infective and Ophthalmology Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research

Enclosure:

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Janice Soreth
2/12/2007 09:01:53 AM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-144/S012

LABELING

Rev February 2007
KETEK®
(telithromycin) Tablets

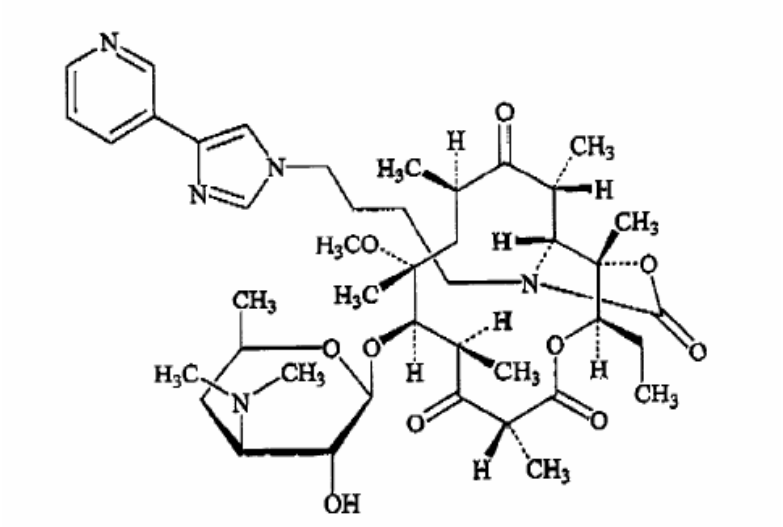
Ketek is contraindicated in patients with myasthenia gravis. There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of Ketek. (See **CONTRAINDICATIONS**.)

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 bacteria.

DESCRIPTION

KETEK® tablets contain telithromycin, a semisynthetic antibacterial in the ketolide class for oral administration. Chemically, telithromycin is designated as Erythromycin, 3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]-.

Telithromycin, a ketolide, differs chemically from the macrolide group of antibacterials by the lack of α-L-cladinose at position 3 of the erythronolide A ring, resulting in a 3-keto function. It is further characterized by a C11-12 carbamate substituted by an imidazolyl and pyridyl ring through a butyl chain. Its empirical formula is $C_{43}H_{65}N_5O_{10}$ and its molecular weight is 812.03. Telithromycin is a white to off-white crystalline powder. The following represents the chemical structure of telithromycin.



KETEK tablets are available as light-orange, oval, film-coated tablets, each containing 400 mg or 300 mg of telithromycin, and the following inactive ingredients: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, red ferric oxide, talc, titanium dioxide, and yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: Following oral administration, telithromycin reached maximal concentration at about 1 hour (0.5 - 4 hours).

It has an absolute bioavailability of 57% in both young and elderly subjects.

The rate and extent of absorption are unaffected by food intake, thus KETEK tablets can be given without regard to food.

In healthy adult subjects, peak plasma telithromycin concentrations of approximately 2 μg/mL are attained at a median of 1 hour after an 800-mg oral dose.

Steady-state plasma concentrations are reached within 2 to 3 days of once daily dosing with telithromycin 800 mg.

Following oral dosing, the mean terminal elimination half-life of telithromycin is 10 hours.

The pharmacokinetics of telithromycin after administration of single and multiple (7 days) once daily 800-mg doses to healthy adult subjects are shown in Table 1.

Table 1

	Mean (SD)	
Parameter	**Single dose (n=18)**	**Multiple dose (n=18)**
C_{max} (μg/mL)	1.9 (0.80)	2.27 (0.71)
T_{max} (h)*	1.0 (0.5-4.0)	1.0 (0.5-3.0)
$AUC_{(0-24)}$ (μg·h/mL)	8.25 (2.6)	12.5 (5.4)
Terminal $t_{1/2}$ (h)	7.16 (1.3)	9.81 (1.9)
C_{24h} (μg/mL)	0.03 (0.013)	0.07 (0.051)

* Median (min-max) values
SD=Standard deviation
C_{max}=Maximum plasma concentration
T_{max}=Time to C_{max}
AUC=Area under concentration vs. time curve
$t_{1/2}$=Terminal plasma half-life
C_{24h} =Plasma concentration at 24 hours post-dose

In a patient population, mean peak and trough plasma concentrations were 2.9 μg/mL (±1.55), (n=219) and 0.2 μg/mL (±0.22), (n=204), respectively, after 3 to 5 days of KETEK 800 mg once daily.

Distribution: Total *in vitro* protein binding is approximately 60% to 70% and is primarily due to human serum albumin.

Protein binding is not modified in elderly subjects and in patients with hepatic impairment.

The volume of distribution of telithromycin after intravenous infusion is 2.9 L/kg.

Telithromycin concentrations in bronchial mucosa, epithelial lining fluid, and alveolar macrophages after 800 mg once daily dosing for 5 days in patients are displayed in Table 2.

Table 2

	Hours post-dose	Mean concentration (μg/mL) Tissue or fluid	Plasma	Tissue/ Plasma Ratio
Bronchial mucosa	2	3.88*	1.86	2.11
	12	1.41*	0.23	6.33
	24	0.78*	0.08	12.11
Epithelial lining fluid	2	14.89	1.86	8.57
	12	3.27	0.23	13.8
	24	0.84	0.08	14.41
Alveolar macrophages	2	65	1.07	55
	8	100	0.605	180
	24	41	0.073	540

*Units in mg/kg

Telithromycin concentration in white blood cells exceeds the concentration in plasma and is eliminated more slowly from white blood cells than from plasma. Mean white blood cell concentrations of telithromycin peaked at 72.1 μg/mL at 6 hours, and remained at 14.1 μg/mL 24 hours after 5 days of repeated dosing of 600 mg once daily. After 10 days, repeated dosing of 600 mg once daily, white blood cell concentrations remained at 8.9 μg/mL 48 hours after the last dose.

Metabolism: In total, metabolism accounts for approximately 70% of the dose. In plasma, the main circulating compound after administration of an 800-mg radiolabeled dose was parent compound, representing 56.7% of the total radioactivity. The main metabolite represented 12.6% of the AUC of telithromycin. Three other plasma metabolites were quantified, each representing 3% or less of the AUC of telithromycin.

It is estimated that approximately 50% of its metabolism is mediated by CYP 450 3A4 and the remaining 50% is CYP 450-independent.

Elimination: The systemically available telithromycin is eliminated by multiple pathways as follows: 7% of the dose is excreted unchanged in feces by biliary and/or intestinal secretion; 13% of the dose is excreted unchanged in urine by renal excretion; and 37% of the dose is metabolized by the liver.

Special populations

Gender: There was no significant difference between males and females in mean AUC, C_{max}, and elimination half-life in two studies; one in 18 healthy young volunteers (18 to 40 years of age) and the other in 14 healthy elderly volunteers (65 to 92 years of age), given single and multiple once daily doses of 800 mg of KETEK.

Hepatic insufficiency: In a single-dose study (800 mg) in 12 patients and a multiple-dose study (800 mg) in 13 patients with mild to severe hepatic insufficiency (Child Pugh Class A, B and C), the C_{max}, AUC and $t_{1/2}$ of telithromycin were similar to those obtained in age- and sex-matched healthy subjects. In both studies, an increase in renal elimination was observed in hepatically impaired patients indicating that this pathway may compensate for some of the decrease in metabolic clearance. No dosage adjustment is recommended due to hepatic impairment. (See **PRECAUTIONS**, **General** and **DOSAGE AND ADMINISTRATION**.)

Renal insufficiency: In a multiple-dose study, 36 subjects with varying degrees of renal impairment received 400 mg, 600 mg, or 800 mg KETEK once daily for 5 days. There was a 1.4-fold increase in $C_{max,ss,}$ and a 1.9-fold increase in AUC $(0\text{-}24)_{ss}$ at 800 mg multiple doses in the severely renally impaired group (CL_{CR} < 30 mL/min) compared to healthy volunteers. Renal excretion may serve as a compensatory elimination pathway for telithromycin in situations where metabolic clearance is impaired. Patients with severe renal impairment are prone to conditions that may impair their metabolic clearance. Therefore, in the presence of severe renal

impairment (CL_{CR} < 30 mL/min), a reduced dosage of KETEK is recommended. (See **DOSAGE AND ADMINISTRATION**.)

In a single-dose study in patients with end-stage renal failure on hemodialysis (n=10), the mean C_{max} and AUC values were similar to normal healthy subjects when KETEK was administered 2 hours post-dialysis. However, the effect of dialysis on removing telithromycin from the body has not been studied.

Multiple insufficiency: The effects of co-administration of ketoconazole in 12 subjects (age ≥ 60 years), with impaired renal function were studied (CL_{CR}= 24 to 80 mL/min). In this study, when severe renal insufficiency (CL_{CR} < 30 mL/min, n=2) and concomitant impairment of CYP 3A4 metabolism pathway were present, telithromycin exposure (AUC (0-24)) was increased by approximately 4- to 5-fold compared with the exposure in healthy subjects with normal renal function receiving telithromycin alone. In the presence of severe renal impairment (CL_{CR} < 30 mL/min), with coexisting hepatic impairment, a reduced dosage of KETEK is recommended. (**See PRECAUTIONS, General** and **DOSAGE AND ADMINISTRATION**.)

Geriatric: Pharmacokinetic data show that there is an increase of 1.4-fold in exposure (AUC) in 20 patients ≥ 65 years of age with community acquired pneumonia in a Phase III study, and a 2.0-fold increase in exposure (AUC) in 14 subjects ≥ 65 years of age as compared with subjects less than 65 years of age in a Phase I study. No dosage adjustment is required based on age alone.

Drug-drug interactions

Studies were performed to evaluate the effect of CYP 3A4 inhibitors on telithromycin and the effect of telithromycin on drugs that are substrates of CYP 3A4 and CYP 2D6. In addition, drug interaction studies were conducted with several other concomitantly prescribed drugs.

CYP 3A4 inhibitors:

Itraconazole: A multiple-dose interaction study with itraconazole showed that C_{max} of telithromycin was increased by 22% and AUC by 54%.

Ketoconazole: A multiple-dose interaction study with ketoconazole showed that C_{max} of telithromycin was increased by 51% and AUC by 95%.

Grapefruit juice: When telithromycin was given with 240 mL of grapefruit juice after an overnight fast to healthy subjects, the pharmacokinetics of telithromycin were not affected.

CYP 3A4 substrates:

Cisapride: Steady-state peak plasma concentrations of cisapride (an agent with the potential to increase QT interval) were increased by 95% when co-administered with repeated doses of telithromycin, resulting in significant increases in QTc. (See **CONTRAINDICATIONS**.)

Simvastatin: When simvastatin was co-administered with telithromycin, there was a 5.3-fold increase in simvastatin C_{max}, an 8.9-fold increase in simvastatin AUC, a 15-fold increase in the simvastatin active metabolite C_{max}, and a 12-fold increase in the simvastatin active metabolite AUC. (See **PRECAUTIONS**.)

In another study, when simvastatin and telithromycin were administered 12 hours apart, there was a 3.4-fold increase in simvastatin C_{max}, a 4.0-fold increase in simvastatin AUC, a 3.2-fold increase in the active metabolite C_{max}, and a 4.3-fold increase in the active metabolite AUC. (See **PRECAUTIONS**.)

Midazolam: Concomitant administration of telithromycin with intravenous or oral midazolam resulted in 2- and 6-fold increases, respectively, in the AUC of midazolam due to inhibition of CYP 3A4-dependent metabolism of midazolam. (See **PRECAUTIONS**.)

CYP 2D6 substrates:

Paroxetine: There was no pharmacokinetic effect on paroxetine when telithromycin was co-administered.

Metoprolol: When metoprolol was co-administered with telithromycin, there was an increase of approximately 38% on the C_{max} and AUC of metoprolol, however, there was no effect on the elimination half-life of metoprolol. Telithromycin exposure is not modified with concomitant single-dose administration of metoprolol. (See **PRECAUTIONS**, **Drug interactions**.)

Other drug interactions:

Digoxin: The plasma peak and trough levels of digoxin were increased by 73% and 21%, respectively, in healthy volunteers when co-administered with telithromycin. However, trough plasma concentrations of digoxin (when equilibrium between plasma and tissue concentrations has been achieved) ranged from 0.74 to 2.17 ng/mL. There were no significant changes in ECG parameters and no signs of digoxin toxicity. (See **PRECAUTIONS**.)

Theophylline: When theophylline was co-administered with repeated doses of telithromycin, there was an increase of approximately 16% and 17% on the steady-state C_{max} and AUC of theophylline. Co-administration of theophylline may worsen gastrointestinal side effects such as nausea and vomiting, especially in female patients. It is recommended that telithromycin should be taken with theophylline 1 hour apart to decrease the likelihood of gastrointestinal side effects.

Sotalol: Telithromycin has been shown to decrease the C_{max} and AUC of sotalol by 34% and 20%, respectively, due to decreased absorption.

Warfarin: When co-administered with telithromycin in healthy subjects, there were no pharmacodynamic or pharmacokinetic effects on racemic warfarin.

Oral contraceptives: When oral contraceptives containing ethinyl estradiol and levonorgestrel were co-administered with telithromycin, the steady-state AUC of ethinyl estradiol did not change and the steady-state AUC of levonorgestrel was increased by 50%. The pharmacokinetic/pharmacodynamic study showed that telithromycin did not interfere with the antiovulatory effect of oral contraceptives containing ethinyl estradiol and levonorgestrel.

Ranitidine, antacid: There was no clinically relevant pharmacokinetic interaction of ranitidine or antacids containing aluminum and magnesium hydroxide on telithromycin.

Rifampin: During concomitant administration of rifampin and KETEK in repeated doses, C_{max} and AUC of telithromycin were dereased by 79%, and 86%, respectively. (See **PRECAUTIONS, Drug Interactions**.)

Microbiology

Telithromycin belongs to the ketolide class of antibacterials and is structurally related to the macrolide family of antibiotics. Telithromycin concentrates in phagocytes where it exhibits activity against intracellular respiratory pathogens. *In vitro*, telithromycin has been shown to demonstrate concentration-dependent bactericidal activity against isolates of *Streptococcus pneumoniae* (including multi-drug resistant isolates [MDRSP*]).

*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 antimicrobials: penicillin, 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Mechanism of action

Telithromycin blocks protein synthesis by binding to domains II and V of 23S rRNA of the 50S ribosomal subunit. By binding at domain II, telithromycin retains activity against gram-positive cocci (e.g., *Streptococcus pneumoniae*) in the presence of resistance mediated by methylases (*erm* genes) that alter the domain V binding site of telithromycin. Telithromycin may also inhibit the assembly of nascent ribosomal units.

Mechanism of resistance

Staphylococcus aureus and *Streptococcus pyogenes* with the constitutive macrolide-lincosamide-streptogramin B ($cMLS_B$) phenotype are resistant to telithromycin.

Mutants of *Streptococcus pneumoniae* derived in the laboratory by serial passage in subinhibitory concentrations of telithromycin have demonstrated resistance based on L22 riboprotein mutations (telithromycin MICs are elevated but still within the susceptible range), one of two reported mutations affecting the L4 riboprotein, and production of K-peptide. The clinical significance of these laboratory mutants is not known.

Cross resistance

Telithromycin does not induce resistance through methylase gene expression in erythromycin-inducibly resistant bacteria, a function of its 3-keto moiety. Telithromycin has not been shown to induce resistance to itself.

List of Microorganisms

Telithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical settings as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP*])

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

Aerobic gram-negative microorganisms

Haemophilus influenzae

Moraxella catarrhalis

Other microorganisms

Chlamydophila (Chlamydia) pneumoniae

Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown**.

At least 90% of the following microorganisms exhibit *in vitro* minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoint for telithromycin. However, the safety and efficacy of telithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

Staphylococcus aureus (methicillin and erythromycin susceptible isolates only)

Streptococcus pyogenes (erythromycin susceptible isolates only)

Streptococci (Lancefield groups C and G)

Other microorganisms

Legionella pneumophila

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods (broth or agar dilution)[1,3] or equivalent with standardized inoculum and concentrations of telithromycin powder. The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antibiotics. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 μg telithromycin to test the susceptibility of microorganisms to telithromycin. Disc diffusion zone sizes should be interpreted according to criteria in Table 3.

Table 3. Susceptibility Test Result Interpretive Criteria for Telithromycin

	Minimal Inhibitory Concentrations (μg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	S	I	R	S	I	R
Streptococcus pneumoniae	≤ 1	2	≥ 4	≥ 19	16-18	≤ 15
Haemophilus influenzae	≤ 4	8	≥ 16	≥ 15	12-14	≤ 11

A report of “Susceptible” indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antibacterial compound in the blood reaches the concentrations usually achievable. A report of “Intermediate” indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors

from causing major discrepancies in interpretation. A report of “Resistant” indicates that the antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality control:

Standardized susceptibility test procedures require the use of quality control microorganisms to determine the performance of the test procedures[1,2,3]. Standard telithromycin powder should provide the MIC ranges for the quality control organisms in Table 4. For the disk diffusion technique, the 15-µg telithromycin disk should provide the zone diameter ranges for the quality control organisms in Table 4.

Table 4. Acceptable Quality Control Ranges for Telithromycin

QC Strain	Minimum Inhibitory Concentrations (µg/mL)	Disk Diffusion (Zone diameter in mm)
Streptococcus pneumoniae ATCC 49619	0.004-0.03	27-33
Haemophilus influenzae ATCC 49247	1.0-4.0	17-23

ATCC = American Type Culture Collection

INDICATIONS AND USAGE

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*, *Chlamydophila 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.

CONTRAINDICATIONS

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. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions** and **PRECAUTIONS**.)

WARNINGS

Hepatotoxicity
Acute hepatic failure and severe liver injury, in some cases fatal, have been reported in patients treated with KETEK. These hepatic reactions included fulminant hepatitis and hepatic necrosis leading to liver transplant, and were observed during or immediately after treatment. In some of these cases, liver injury progressed rapidly and occurred after administration of a few doses of KETEK**.** (See **ADVERSE REACTIONS**.) Physicians and patients should monitor for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. **Patients with signs or symptoms of hepatitis must be advised to discontinue KETEK and immediately seek medical evaluation, which should include liver function tests**. (See **ADVERSE REACTIONS, PRECAUTIONS**, Information to Patients.) If clinical hepatitis or transaminase 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. (See **CONTRAINDICATIONS**.)

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.

QTc prolongation
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.

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.**)

PSEUDOMEMBRANOUS COLITIS
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.

PRECAUTIONS

General

Prescribing KETEK in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

Telithromycin is principally excreted via the liver and kidney. Telithromycin may be administered without dosage adjustment in the presence of hepatic impairment. In the presence of severe renal impairment (CL_{CR} < 30 mL/min), a reduced dosage of KETEK is recommended. (See **DOSAGE AND ADMINISTRATION.**)

Information for patients

A Medication Guide is provided to patients when Ketek is dispensed. Patients should be instructed to read the MedGuide when Ketek is received. In addition, the complete text of the MedGuide is reprinted at the end of this document.

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 **WARNINGS** and **ADVERSE REACTIONS.**)

  Patients should be advised that avoiding quick changes in viewing between objects in the distance and objects nearby may help to decrease the effects of these visual difficulties.

- **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 difficulties or loss of consciousness / fainting
- patients should seek advice from their physician before taking another dose
- patients should not drive a motor vehicle, operate heavy machinery, or engage in otherwise hazardous activities.

Patients should also be advised:
- **Ketek is contraindicated in patients with myasthenia gravis.** (See **CONTRAINDICATIONS.**)

- of the possibility of liver injury, associated with KETEK, which in rare cases may be severe. **Patients developing signs or symptoms of liver injury should be instructed to discontinue KETEK and seek medical attention immediately.** Symptoms of liver injury may include nausea, fatigue, anorexia, jaundice, dark urine, light-colored stools, pruritus, or tender abdomen. Ketek must not be taken by patients with a

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

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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

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-144/S012

MEDICAL REVIEW(S)

Medical Officer Review of the Labeling Supplement

Application Type:	NDA 21-144
Submission Number:	S-012
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Reviewer Name:	Tatiana Oussova, M.D., M.P.H.
Established Name:	Telithromycin
Trade Name:	Ketek
Therapeutic Class:	Ketolide Antibiotic
Applicant:	Sanofi Aventis Pharmaceuticals
Formulation:	400 mg Tablets and 300 mg Tablets
Dosing Regimen:	2 tablets (800 mg) once daily for 7-10 days
Indication:	Community-acquired pneumonia
Intended Population:	Adults

Background:

Telithromycin is a ketolide antimicrobial, chemically related to macrolides, but with *in vitro* activity against macrolide-resistant strains of *S. pneumoniae*. In April of 2004, Ketek was approved for the treatment of:

- Acute bacterial exacerbation of chronic bronchitis (ABECB)
- Acute bacterial sinusitis (ABS)
- Community acquired pneumonia (CAP) including MDRSP

Review of the original NDA raised safety concerns, including liver toxicity, cardiac toxicity, visual disturbances and potential drug-drug interactions. All safety issues identified during the NDA review were communicated properly in the label.
The **WARNINGS** section of the label included information on QT prolongation, myasthenia gravis exacerbation, and *C. difficile* colitis. The **PRECAUTIONS** section of the label included information on hepatic dysfunction and visual disturbances.

Following the initial approval, FDA and the sponsor continued monitoring of adverse events reports and subsequently, several revisions to the label were made incorporating newly available data.

Labeling supplements provided for changes to the **PRECAUTIONS** section of the labeling concerning the occurrence of syncope usually associated with vagal syndrome and the addition of palpitations, pancreatitis and syncope to the post-marketing reports in the **ADVERSE EVENTS** section.

Additional revisions to the **CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** and **PATIENT PACKAGE INSERT** sections of the labeling were made on June 29, 2006 based on post-marketing reports of liver toxicity and OSE analysis of those cases. OSE analysis was provided in a consult dated May 16, 2006. Additional analyses were provided on myasthenia gravis and visual adverse events/loss of consciousness in a consult dated October 10, 2006.

In light of newly accumulated post-marketing data, a joint meeting of the Drug Safety and Risk Management (DSaRM) Advisory Committee (AC) and the Anti-Infective Drugs Advisory Committee (AIDAC) was held on December 14-15, 2006 to re-evaluate available evidence of Ketek efficacy and safety for approved indications. This labeling supplement incorporates changes to the package insert for Ketek, based largely on OSE and Advisory Committee recommendations.

Discussion:

The following changes to the label were proposed and agreed upon:

1. Incorporate a boxed warning emphasizing that Ketek is contraindicated in patients with myasthenia gravis to increase physicians' awareness about possible life-threatening or fatal exacerbation of the disease associated with the use of Ketek.

In the original label, the WARNINGS section contained a statement that "Telithromycin should not be used in patients with myasthenia gravis unless no other therapeutic alternatives available". Despite this warning, several cases of life-threatening complications and deaths due to exacerbation of the disease were reported post-marketing. The joint AC felt that a stronger message emphasizing possible complications due to the drug use would be appropriate for myasthenia gravis.

2. Remove the following indications: acute bacterial sinusitis and acute exacerbation of chronic bronchitis.

The joint AC re-evaluated the available evidence of Ketek efficacy and safety for each of the approved indications. The Committee felt that the efficacy data derived from non-inferiority trials of Ketek make it difficult to establish its efficacy with certainty, and until it is proven in superiority trials, the safety profile of the drug outweighs the available evidence of efficacy. However, the indication of community-acquired pneumonia is retained since the consensus is that placebo-controlled trials are not ethical in this disease and the risks of possible adverse events associated with the drug use are justified given the potentially life-threatening natural disease course and its possible complications.

3. Other changes

The Patient Package Insert is removed to be replaced by a Medication Guide that will inform patients about possible adverse events and what to look for while taking Ketek.
Revisions were made to Microbiology section to be consistent with the revised indications for Ketek.
The CONTRAINDICATIONS section was revised to include myasthenia gravis patients.
The WARNINGS section was revised to strengthen issues related to liver toxicity and add language related to visual disturbances and loss of consciousness (moved from PRECAUTUIONS).
The warning for Pseudomembranous colitis was updated to be consistent with new wording recommended for all systemic antibiotics.
Revisions were made to Information for patients section to be consistent with the rest of the label.
Post-marketing Adverse Events reports and DOSAGE AND ADMINISTRATION sections were revised to be consistent with the rest of the label.
The descriptions of AECB and ABS studies were removed from the CLINICAL STUDIES section, since these indications were removed from the label.

Medical Officer Conclusions:

This reviewer recommends an approval of proposed changes. Those changes reflect the recommendations provided by the joint Advisory Committee and summarize a thorough discussion between the Division and OSE. It appears that proposed labeling changes adequately communicate the currently available data on efficacy and safety profile of Ketek and inform both health care professionals and patients about the risks and benefits associated with the drug when used as directed in the label.

The following pages show the changes to the last approved label of June 29, 2006, incorporating revisions as agreed to by the sponsor and FDA. Marked-up text shows the new additions and deletions to the label.

Rev. ~~June 2006~~ February 2007
KETEK®
(telithromycin) Tablets

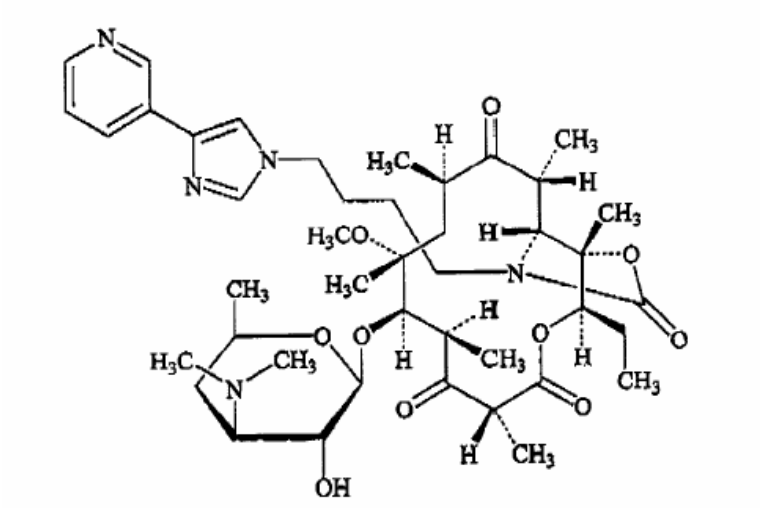
Ketek is contraindicated in patients with myasthenia gravis. There have been reports of fatal and life-threatening respiratory failure in patients with myasthenia gravis associated with the use of Ketek. (See **CONTRAINDICATIONS**.)

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 bacteria.

DESCRIPTION

KETEK® tablets contain telithromycin, a semisynthetic antibacterial in the ketolide class for oral administration. Chemically, telithromycin is designated as Erythromycin, 3-de[(2,6-dideoxy-3-C-methyl-3-O-methyl-α-L-ribo-hexopyranosyl)oxy]-11,12-dideoxy-6-O-methyl-3-oxo-12,11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]-.

Telithromycin, a ketolide, differs chemically from the macrolide group of antibacterials by the lack of α-L-cladinose at position 3 of the erythronolide A ring, resulting in a 3-keto function. It is further characterized by a C11-12 carbamate substituted by an imidazolyl and pyridyl ring through a butyl chain. Its empirical formula is $C_{43}H_{65}N_5O_{10}$ and its molecular weight is 812.03. Telithromycin is a white to off-white crystalline powder. The following represents the chemical structure of telithromycin.



KETEK tablets are available as light-orange, oval, film-coated tablets, each containing 400 mg or 300 mg of telithromycin, and the following inactive ingredients: croscarmellose sodium, hypromellose, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, red ferric oxide, talc, titanium dioxide, and yellow ferric oxide.

CLINICAL PHARMACOLOGY

Pharmacokinetics

Absorption: Following oral administration, telithromycin reached maximal concentration at about 1 hour (0.5 - 4 hours).

It has an absolute bioavailability of 57% in both young and elderly subjects.

The rate and extent of absorption are unaffected by food intake, thus KETEK tablets can be given without regard to food.

In healthy adult subjects, peak plasma telithromycin concentrations of approximately 2 μg/mL are attained at a median of 1 hour after an 800-mg oral dose.

Steady-state plasma concentrations are reached within 2 to 3 days of once daily dosing with telithromycin 800 mg.

Following oral dosing, the mean terminal elimination half-life of telithromycin is 10 hours.

The pharmacokinetics of telithromycin after administration of single and multiple (7 days) once daily 800-mg doses to healthy adult subjects are shown in Table 1.

Table 1

	Mean (SD)	
Parameter	**Single dose (n=18)**	**Multiple dose (n=18)**
C_{max} (μg/mL)	1.9 (0.80)	2.27 (0.71)
T_{max} (h)*	1.0 (0.5-4.0)	1.0 (0.5-3.0)
$AUC_{(0-24)}$ (μg·h/mL)	8.25 (2.6)	12.5 (5.4)
Terminal $t_{1/2}$ (h)	7.16 (1.3)	9.81 (1.9)
C_{24h} (μg/mL)	0.03 (0.013)	0.07 (0.051)

* Median (min-max) values
SD=Standard deviation
C_{max}=Maximum plasma concentration
T_{max}=Time to C_{max}
AUC=Area under concentration vs. time curve
$t_{1/2}$=Terminal plasma half-life
C_{24h} =Plasma concentration at 24 hours post-dose

In a patient population, mean peak and trough plasma concentrations were 2.9 μg/mL (±1.55), (n=219) and 0.2 μg/mL (±0.22), (n=204), respectively, after 3 to 5 days of KETEK 800 mg once daily.

Distribution: Total *in vitro* protein binding is approximately 60% to 70% and is primarily due to human serum albumin.

Protein binding is not modified in elderly subjects and in patients with hepatic impairment.

The volume of distribution of telithromycin after intravenous infusion is 2.9 L/kg.

Telithromycin concentrations in bronchial mucosa, epithelial lining fluid, and alveolar macrophages after 800 mg once daily dosing for 5 days in patients are displayed in Table 2.

Table 2

	Hours post-dose	Mean concentration (μg/mL) Tissue or fluid	Plasma	Tissue/ Plasma Ratio
Bronchial mucosa	2	3.88*	1.86	2.11
	12	1.41*	0.23	6.33
	24	0.78*	0.08	12.11
Epithelial lining fluid	2	14.89	1.86	8.57
	12	3.27	0.23	13.8
	24	0.84	0.08	14.41
Alveolar macrophages	2	65	1.07	55
	8	100	0.605	180
	24	41	0.073	540

*Units in mg/kg

Telithromycin concentration in white blood cells exceeds the concentration in plasma and is eliminated more slowly from white blood cells than from plasma. Mean white blood cell concentrations of telithromycin peaked at 72.1 μg/mL at 6 hours, and remained at 14.1 μg/mL 24 hours after 5 days of repeated dosing of 600 mg once daily. After 10 days, repeated dosing of 600 mg once daily, white blood cell concentrations remained at 8.9 μg/mL 48 hours after the last dose.

Metabolism: In total, metabolism accounts for approximately 70% of the dose. In plasma, the main circulating compound after administration of an 800-mg radiolabeled dose was parent compound, representing 56.7% of the total radioactivity. The main metabolite represented 12.6% of the AUC of telithromycin. Three other plasma metabolites were quantified, each representing 3% or less of the AUC of telithromycin.

It is estimated that approximately 50% of its metabolism is mediated by CYP 450 3A4 and the remaining 50% is CYP 450-independent.

Elimination: The systemically available telithromycin is eliminated by multiple pathways as follows: 7% of the dose is excreted unchanged in feces by biliary and/or intestinal secretion;

13% of the dose is excreted unchanged in urine by renal excretion; and 37% of the dose is metabolized by the liver.

Special populations

Gender: There was no significant difference between males and females in mean AUC, C_{max}, and elimination half-life in two studies; one in 18 healthy young volunteers (18 to 40 years of age) and the other in 14 healthy elderly volunteers (65 to 92 years of age), given single and multiple once daily doses of 800 mg of KETEK.

Hepatic insufficiency: In a single-dose study (800 mg) in 12 patients and a multiple-dose study (800 mg) in 13 patients with mild to severe hepatic insufficiency (Child Pugh Class A, B and C), the C_{max}, AUC and $t_{1/2}$ of telithromycin were similar to those obtained in age- and sex-matched healthy subjects. In both studies, an increase in renal elimination was observed in hepatically impaired patients indicating that this pathway may compensate for some of the decrease in metabolic clearance. No dosage adjustment is recommended due to hepatic impairment. (See **PRECAUTIONS**, **General** and **DOSAGE AND ADMINISTRATION**.)

Renal insufficiency: In a multiple-dose study, 36 subjects with varying degrees of renal impairment received 400 mg, 600 mg, or 800 mg KETEK once daily for 5 days. There was a 1.4-fold increase in $C_{max,ss,}$ and a 1.9-fold increase in AUC $(0\text{-}24)_{ss}$ at 800 mg multiple doses in the severely renally impaired group (CL_{CR} < 30 mL/min) compared to healthy volunteers. Renal excretion may serve as a compensatory elimination pathway for telithromycin in situations where metabolic clearance is impaired. Patients with severe renal impairment are prone to conditions that may impair their metabolic clearance. Therefore, in the presence of severe renal impairment (CL_{CR} < 30 mL/min), a reduced dosage of KETEK is recommended. (See **DOSAGE AND ADMINISTRATION**.)

In a single-dose study in patients with end-stage renal failure on hemodialysis (n=10), the mean C_{max} and AUC values were similar to normal healthy subjects when KETEK was administered 2 hours post-dialysis. However, the effect of dialysis on removing telithromycin from the body has not been studied.

Multiple insufficiency: The effects of co-administration of ketoconazole in 12 subjects (age ≥ 60 years), with impaired renal function were studied (CL_{CR}= 24 to 80 mL/min). In this study, when severe renal insufficiency (CL_{CR} < 30 mL/min, n=2) and concomitant impairment of CYP 3A4 metabolism pathway were present, telithromycin exposure (AUC (0-24)) was increased by approximately 4- to 5-fold compared with the exposure in healthy subjects with normal renal function receiving telithromycin alone. In the presence of severe renal impairment (CL_{CR} < 30 mL/min), with coexisting hepatic impairment, a reduced dosage of KETEK is recommended. (**See PRECAUTIONS, General** and **DOSAGE AND ADMINISTRATION**.)

Geriatric: Pharmacokinetic data show that there is an increase of 1.4-fold in exposure (AUC) in 20 patients ≥ 65 years of age with community acquired pneumonia in a Phase III study, and a 2.0-fold increase in exposure (AUC) in 14 subjects ≥ 65 years of age as compared with subjects

less than 65 years of age in a Phase I study. No dosage adjustment is required based on age alone.

Drug-drug interactions

Studies were performed to evaluate the effect of CYP 3A4 inhibitors on telithromycin and the effect of telithromycin on drugs that are substrates of CYP 3A4 and CYP 2D6. In addition, drug interaction studies were conducted with several other concomitantly prescribed drugs.

CYP 3A4 inhibitors:

Itraconazole: A multiple-dose interaction study with itraconazole showed that C_{max} of telithromycin was increased by 22% and AUC by 54%.

Ketoconazole: A multiple-dose interaction study with ketoconazole showed that C_{max} of telithromycin was increased by 51% and AUC by 95%.

Grapefruit juice: When telithromycin was given with 240 mL of grapefruit juice after an overnight fast to healthy subjects, the pharmacokinetics of telithromycin were not affected.

CYP 3A4 substrates:

Cisapride: Steady-state peak plasma concentrations of cisapride (an agent with the potential to increase QT interval) were increased by 95% when co-administered with repeated doses of telithromycin, resulting in significant increases in QTc. (See **CONTRAINDICATIONS**.)

Simvastatin: When simvastatin was co-administered with telithromycin, there was a 5.3-fold increase in simvastatin C_{max}, an 8.9-fold increase in simvastatin AUC, a 15-fold increase in the simvastatin active metabolite C_{max}, and a 12-fold increase in the simvastatin active metabolite AUC. (See **PRECAUTIONS**.)

In another study, when simvastatin and telithromycin were administered 12 hours apart, there was a 3.4-fold increase in simvastatin C_{max}, a 4.0-fold increase in simvastatin AUC, a 3.2-fold increase in the active metabolite C_{max}, and a 4.3-fold increase in the active metabolite AUC. (See **PRECAUTIONS**.)

Midazolam: Concomitant administration of telithromycin with intravenous or oral midazolam resulted in 2- and 6-fold increases, respectively, in the AUC of midazolam due to inhibition of CYP 3A4-dependent metabolism of midazolam. (See **PRECAUTIONS**.)

CYP 2D6 substrates:

Paroxetine: There was no pharmacokinetic effect on paroxetine when telithromycin was co-administered.

Metoprolol: When metoprolol was co-administered with telithromycin, there was an increase of approximately 38% on the C_{max} and AUC of metoprolol, however, there was no effect on the elimination half-life of metoprolol. Telithromycin exposure is not modified with concomitant single-dose administration of metoprolol. (See **PRECAUTIONS**, **Drug interactions**.)

Other drug interactions:

Digoxin: The plasma peak and trough levels of digoxin were increased by 73% and 21%, respectively, in healthy volunteers when co-administered with telithromycin. However, trough plasma concentrations of digoxin (when equilibrium between plasma and tissue concentrations has been achieved) ranged from 0.74 to 2.17 ng/mL. There were no significant changes in ECG parameters and no signs of digoxin toxicity. (See **PRECAUTIONS**.)

Theophylline: When theophylline was co-administered with repeated doses of telithromycin, there was an increase of approximately 16% and 17% on the steady-state C_{max} and AUC of theophylline. Co-administration of theophylline may worsen gastrointestinal side effects such as nausea and vomiting, especially in female patients. It is recommended that telithromycin should be taken with theophylline 1 hour apart to decrease the likelihood of gastrointestinal side effects.

Sotalol: Telithromycin has been shown to decrease the C_{max} and AUC of sotalol by 34% and 20%, respectively, due to decreased absorption.

Warfarin: When co-administered with telithromycin in healthy subjects, there were no pharmacodynamic or pharmacokinetic effects on racemic warfarin.

Oral contraceptives: When oral contraceptives containing ethinyl estradiol and levonorgestrel were co-administered with telithromycin, the steady-state AUC of ethinyl estradiol did not change and the steady-state AUC of levonorgestrel was increased by 50%. The pharmacokinetic/pharmacodynamic study showed that telithromycin did not interfere with the antiovulatory effect of oral contraceptives containing ethinyl estradiol and levonorgestrel.

Ranitidine, antacid: There was no clinically relevant pharmacokinetic interaction of ranitidine or antacids containing aluminum and magnesium hydroxide on telithromycin.

Rifampin: During concomitant administration of rifampin and KETEK in repeated doses, C_{max} and AUC of telithromycin were decreased by 79%, and 86%, respectively. (See **PRECAUTIONS, Drug Interactions**.)

Microbiology

Telithromycin belongs to the ketolide class of antibacterials and is structurally related to the macrolide family of antibiotics. Telithromycin concentrates in phagocytes where it exhibits activity against intracellular respiratory pathogens. *In vitro*, telithromycin has been shown to demonstrate concentration-dependent bactericidal activity against isolates of *Streptococcus pneumoniae* (including multi-drug resistant isolates [MDRSP*]).

*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 antimicrobials: penicillin, 2nd generation cephalosporins (e.g., cefuroxime), macrolides, tetracyclines, and trimethoprim/sulfamethoxazole.

Mechanism of action

Telithromycin blocks protein synthesis by binding to domains II and V of 23S rRNA of the 50S ribosomal subunit. By binding at domain II, telithromycin retains activity against gram-positive cocci (e.g., *Streptococcus pneumoniae*) in the presence of resistance mediated by methylases (*erm* genes) that alter the domain V binding site of telithromycin. Telithromycin may also inhibit the assembly of nascent ribosomal units.

Mechanism of resistance

Staphylococcus aureus and *Streptococcus pyogenes* with the constitutive macrolide-lincosamide-streptogramin B ($cMLS_B$) phenotype are resistant to telithromycin.

Mutants of *Streptococcus pneumoniae* derived in the laboratory by serial passage in subinhibitory concentrations of telithromycin have demonstrated resistance based on L22 riboprotein mutations (telithromycin MICs are elevated but still within the susceptible range), one of two reported mutations affecting the L4 riboprotein, and production of K-peptide. The clinical significance of these laboratory mutants is not known.

Cross resistance

Telithromycin does not induce resistance through methylase gene expression in erythromycin-inducibly resistant bacteria, a function of its 3-keto moiety. Telithromycin has not been shown to induce resistance to itself.

List of Microorganisms

Telithromycin has been shown to be active against most strains of the following microorganisms, both *in vitro* and in clinical settings as described in the **INDICATIONS AND USAGE** section.

Aerobic gram-positive microorganisms

~~*Staphylococcus aureus* (methicillin and erythromycin susceptible isolates only)~~

Streptococcus pneumoniae (including multi-drug resistant isolates [MDRSP*])

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

Aerobic gram-negative microorganisms

Haemophilus influenzae

Moraxella catarrhalis

Other microorganisms

Chlamydophila (Chlamydia) pneumoniae

Mycoplasma pneumoniae

The following *in vitro* data are available, **but their clinical significance is unknown**.

At least 90% of the following microorganisms exhibit *in vitro* minimum inhibitory concentrations (MICs) less than or equal to the susceptible breakpoint for telithromycin. However, the safety and efficacy of telithromycin in treating clinical infections due to these microorganisms have not been established in adequate and well-controlled clinical trials.

Aerobic gram-positive microorganisms

Staphylococcus aureus (methicillin and erythromycin susceptible isolates only)

Streptococcus pyogenes (erythromycin susceptible isolates only)

Streptococci (Lancefield groups C and G)

~~Viridans group streptococci~~

~~*Anaerobic bacteria*~~

~~*Prevotella bivia*~~

~~*Prevotella intermedia*~~

~~*Peptostreptococcus* spp.~~

Other microorganisms

Legionella pneumophila

Susceptibility Test Methods

When available, the clinical microbiology laboratory should provide cumulative results of *in vitro* susceptibility test results for antimicrobial drugs used in local hospitals and practice areas to the physician as periodic reports that describe the susceptibility profile of nosocomial and community-acquired pathogens. These reports should aid the physician in selecting the most effective antimicrobial.

Dilution techniques:

Quantitative methods are used to determine antimicrobial minimum inhibitory concentrations (MICs). These MICs provide estimates of the susceptibility of bacteria to antibacterial compounds. The MICs should be determined using a standardized procedure. Standardized procedures are based on dilution methods (broth or agar dilution)[1,3] or equivalent with standardized inoculum and concentrations of telithromycin powder. The MIC values should be interpreted according to criteria provided in Table 3.

Diffusion techniques:

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antibiotics. One such standardized procedure[2,3] requires the use of standardized inoculum concentrations. This procedure uses paper disks impregnated with 15 µg telithromycin to test the susceptibility of microorganisms to telithromycin. Disc diffusion zone sizes should be interpreted according to criteria in Table 3.

Table 3. Susceptibility Test Result Interpretive Criteria for Telithromycin

	Minimal Inhibitory Concentrations (µg/mL)			Disk Diffusion (zone diameters in mm)		
Pathogen	S	I	R[a]	S	I	R[a]
~~*Staphylococcus aureus*~~	~~≤ 0.25~~			~~≥ 22~~		
Streptococcus pneumoniae	≤ 1	2	≥ 4	≥ 19	16-18	≤ 15
Haemophilus influenzae	≤ 4	8	≥ 16	≥ 15	12-14	≤ 11

[a] ~~The current absence of data on resistant isolates precludes defining any category other than "Susceptible". If strains yield MIC results other than susceptible, they should be submitted to a reference laboratory for further testing.~~

A report of "Susceptible" indicates that the antimicrobial is likely to inhibit growth of the pathogen if the antibacterial compound in the blood reaches the concentrations usually achievable. A report of "Intermediate" indicates that the result should be considered equivocal, and, if the microorganism is not fully susceptible to alternative, clinically feasible drugs, the test should be repeated. This category implies possible clinical applicability in body sites where the drug is physiologically concentrated or in situations where high dosage of drug can be used. This category also provides a buffer zone that prevents small uncontrolled technical factors from causing major discrepancies in interpretation. A report of "Resistant" indicates that the

antimicrobial is not likely to inhibit growth of the pathogen if the antimicrobial compound in the blood reaches the concentrations usually achievable; other therapy should be selected.

Quality control:

Standardized susceptibility test procedures require the use of quality control microorganisms to determine the performance of the test procedures[1,2,3]. Standard telithromycin powder should provide the MIC ranges for the quality control organisms in Table 4. For the disk diffusion technique, the 15-µg telithromycin disk should provide the zone diameter ranges for the quality control organisms in Table 4.

Table 4. Acceptable Quality Control Ranges for Telithromycin

QC Strain	Minimum Inhibitory Concentrations (µg/mL)	Disk Diffusion (Zone diameter in mm)
~~*Staphylococcus aureus* ATCC® 29213~~	~~0.06-0.25~~	~~Not Applicable~~
~~*Staphylococcus aureus* ATCC 25923~~	~~Not Applicable~~	~~24-30~~
Streptococcus pneumoniae ATCC 49619	0.004-0.03	27-33
Haemophilus influenzae ATCC 49247	1.0-4.0	17-23

ATCC = American Type Culture Collection

INDICATIONS AND USAGE

KETEK tablets are indicated for the treatment of ~~infections caused by susceptible strains of the designated microorganisms in the conditions listed below~~ community-acquired pneumonia (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including multi-drug resistant isolates [MDRSP*]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, or *Mycoplasma pneumoniae*, for patients 18 years old and above.

~~**Acute bacterial exacerbation of chronic bronchitis** due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, or *Moraxella catarrhalis*.~~

~~**Acute bacterial sinusitis** due to *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, or *Staphylococcus aureus*.~~

~~**Community acquired pneumonia** (of mild to moderate severity) due to *Streptococcus pneumoniae*, (including multi drug resistant isolates [MDRSP*]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydophila pneumoniae*, or *Mycoplasma pneumoniae*.~~

*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.

CONTRAINDICATIONS

KETEK is contraindicated in patients with ~~a history of hypersensitivity to telithromycin and/or any components of KETEK tablets, or any macrolide antibiotic~~**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. (See **CLINICAL PHARMACOLOGY, Drug-drug Interactions** and **PRECAUTIONS**.)

WARNINGS

Hepatotoxicity

Acute hepatic failure and severe liver injury, in some cases fatal, have been reported in patients treated with KETEK. These hepatic reactions included fulminant hepatitis and hepatic necrosis leading to liver transplant, and were observed during or immediately after treatment. In some of these cases, liver injury progressed rapidly and occurred after administration of a few doses of KETEK**.** (See **ADVERSE REACTIONS**.)

Physicians and patients should monitor for the appearance of signs or symptoms of hepatitis, such as fatigue, malaise, anorexia, nausea, jaundice, bilirubinuria, acholic stools, liver tenderness or hepatomegaly. **Patients with signs or symptoms of hepatitis must be advised to**

discontinue KETEK and immediately seek medical evaluation, which should include liver function tests. (See **ADVERSE REACTIONS, PRECAUTIONS**, Information to Patients.) If clinical hepatitis or transaminase 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. (See **CONTRAINDICATIONS**.)

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

QTc prolongation

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.

~~No~~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 ~~efficacy~~ trials, including 204 patients having a prolonged QTc at baseline.

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.)**

Pseudomembranous colitis

~~Pseudomembranous colitis~~*Clostridium difficile* associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including ~~telithromycin~~KETEK, and may range in severity from mild diarrhea to ~~life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of any antibacterial agents~~fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of *C. difficile*.

~~Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that toxin~~

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of *C~~lostridium difficile~~* ~~are the primary cause of "antibiotic associated colitis".~~ *. 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.

~~After the diagnosis of pseudomembranous colitis has been established, therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *C. difficile* colitis. (See **ADVERSE REACTIONS.**)~~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.

PRECAUTIONS

General

Prescribing KETEK in the absence of a proven or strongly suspected bacterial infection or a prophylactic indication is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria.

~~**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.**)~~

~~Hepatic dysfunction, including increased liver enzymes and hepatitis, with or without jaundice, has been reported with the use of KETEK. These events were generally reversible, though acute hepatic failure and severe liver injury, in some cases fatal, have been reported..~~

~~(See **WARNINGS, ADVERSE REACTIONS, Liver and biliary system.**)~~

Telithromycin is principally excreted via the liver and kidney. Telithromycin may be administered without dosage adjustment in the presence of hepatic impairment. In the presence of severe renal impairment (CL_{CR} < 30 mL/min), a reduced dosage of KETEK is recommended. (See **DOSAGE AND ADMINISTRATION.**)

Information for patients

A Medication Guide is provided to patients when Ketek is dispensed. Patients should be instructed to read the MedGuide when Ketek is received. In addition, the complete text of the MedGuide is reprinted at the end of this document.

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**~~**WARNINGS** and **ADVERSE REACTIONS.**)

~~If visual difficulties occur:~~

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

Patients should be advised that 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~~**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.

~~Patients should be aware of the possibility of experiencing syncope (fainting), and its impact on the ability to~~

If patients experience visual difficulties or loss of consciousness / fainting

- patients should seek advice from their physician before taking another dose
- patients should not 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~~operate heavy machinery, or ~~engaging~~engage in otherwise hazardous activities.

Patients should also be advised:

- **Ketek is contraindicated in patients with myasthenia gravis.** (See **CONTRAINDICATIONS.**)

- of the possibility of liver injury, associated with KETEK, which in rare cases may be severe. **Patients developing signs or symptoms of liver injury should be instructed to discontinue KETEK and seek medical attention immediately.** Symptoms of liver injury may include nausea, fatigue, anorexia, jaundice, dark urine, light-colored stools, pruritus, or tender abdomen. Ketek must not be taken by patients with a previous history of hepatitis/jaundice associated with the use of KETEK or macrolide antibiotics. (See **CONTRAINDICATIONS** and **WARNINGS**.)

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

- ~~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~~ 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.

- ~~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.

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 ~~**PRECAUTIONS, General**~~**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 ~~**WARNINGS**~~**CONTRAINDICATIONS.**)
Nervous system: ~~syncope usually~~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~~.~~ ~~The duration of therapy depends on the infection type and is described below.~~ , for 7–10 days. KETEK tablets can be administered with or without food.

~~**Table 6**~~

~~**Infection**~~	~~**Daily dose and route of administration**~~	~~**Frequency of administration**~~	~~**Duration of treatment**~~
~~Acute bacterial exacerbation of chronic bronchitis~~	~~800 mg oral (2 tablets of 400 mg)~~	~~once daily~~	~~5 days~~
~~Acute bacterial sinusitis~~	~~800 mg oral (2 tablets of 400 mg)~~	~~once daily~~	~~5 days~~
~~Community acquired pneumonia~~	~~800 mg oral (2 tablets of 400 mg)~~	~~once daily~~	~~7–10 days~~

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 ~~7.~~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 ~~8~~7.

Table ~~8.~~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 ~~9.~~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.

~~**Acute bacterial sinusitis**~~

~~**KETEK was studied in two randomized, double blind, comparative studies for the treatment of acute sinusitis. Clinical cure rates with KETEK given for 5 days and comparator drug are shown in**~~ **Visual Adverse Events**

~~Table 10.~~

Table 10. Acute Sinusitis: Clinical cure rate at post-therapy follow-up (17-24 days)

	Patients (n)		Clinical cure rate	
Controlled Studies	**KETEK (5 day treatment)**	**Comparator (10 day treatment)**	**KETEK (5 day treatment)**	**Comparator (10 day treatment)**
KETEK vs. amoxicillin/clavulanic acid 500/125 mg TID	146	137	75.3%	74.5%
KETEK vs. cefuroxime axetil 250 mg BID	189	89	85.2%	82.0%

A third study compared 5 days with 10 days of KETEK for the treatment of acute bacterial sinusitis, clinical cure rates for the two treatments were similar (91.1% vs. 91.0% respectively).

Clinical cure rates in microbiologically evaluable patients for KETEK against the most common pathogens from the two acute sinusitis controlled clinical trials are displayed in Table 11.

Table 11. Acute Sinusitis: Clinical cure rate by pathogen

Pathogen	**KETEK 5 days**	**Comparator 10 days**
Streptococcus pneumoniae	27/31 (87.1%)	14/16 (87.5%)
Haemophilus influenzae	28/34 (82.4%)	13/15 (86.7%)
Moraxella catarrhalis	7/7 (100%)	7/7 (100%)
Staphylococcus aureus	8/8 (100%)	2/3 (66.7%)

Acute bacterial exacerbation of chronic bronchitis (AECB)

KETEK was studied in three randomized, double-blind, controlled studies for the treatment of acute exacerbation of chronic bronchitis. Clinical cure rates are displayed in Table 12.

Table 12. AECB: Clinical cure rate at post-therapy follow-up (17-24 days)

Controlled Studies	**Patients (n)**		**Clinical cure rate**	
	KETEK	**Comparator**	**KETEK**	**Comparator**
KETEK (5 day therapy) vs. cefuroxime axetil 500mg BID (10 day therapy)	140	142	86.4%	83.1%
KETEK (5 day therapy) vs. amoxicillin/clavulanic acid 500/125 mg TID (10 day therapy)	115	112	86.1%	82.1%
KETEK (5 day therapy) vs. clarithromycin 500mg BID (10 day therapy)	225	231	85.8%	89.2%

Clinical cure rates in microbiologically evaluable patients treated with KETEK against the most common pathogens from the three acute exacerbation of chronic bronchitis clinical trials are displayed in Table 13.

~~Table 13. AECB: Clinical cure rate by pathogen at post therapy follow-up (17-24 days)~~

~~Pathogen~~	~~KETEK~~	~~Comparator~~
~~*Streptococcus pneumoniae*~~	~~22/27 (81.5%)~~	~~15/19 (78.9%)~~
~~*Haemophilus influenzae*~~	~~44/60 (73.3%)~~	~~45/53 (84.9%)~~
~~*Moraxella catarrhalis*~~	~~27/29 (93.1%)~~	~~29/34 (85.3%)~~

~~Visual Adverse Events~~

Table ~~14~~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 14. Incidence of All Treatment-Emergent Visual Adverse Events in Controlled Phase III Studies~~

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. ~~June 2006~~February 2007

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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.

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PATIENT INFORMATION ABOUT:
KETEK®
(telithromycin)

Before beginning your treatment, please read this section to learn important information about KETEK® (telithromycin). Although the information presented here will be useful during your therapy, not all the benefits and risks of treatment with KETEK are discussed in this document. This section is not intended to take the place of conversations with your doctor or healthcare provider about your treatment or medical condition. The medicine described here can only be prescribed by a licensed healthcare provider. With this in mind, be sure to talk to your healthcare provider if you have any questions. It's important to note that only a doctor or healthcare provider can determine if KETEK is right for you.

What is KETEK?

KETEK (*KEE tek*) is an antibiotic used to treat adults 18 years of age and older with certain respiratory (lung and sinus) infections caused by certain germs called bacteria. KETEK kills many of the types of bacteria that can infect the lungs and sinuses, and has been found to treat these infections safely and effectively in clinical trials.

Not all respiratory infections are caused by bacteria. For example, common colds are caused by viruses. KETEK, like other antibiotics, does not kill viruses.

KETEK Tablets are light orange, oval, film coated tablets each containing 400 mg or 300 mg of the active drug. The 400 mg tablet is imprinted with "H3647" on one side and "400" on the other side.
The 300 mg tablet is imprinted with "38AV" on one side and is blank on the other side.

How and when should I take KETEK?

The usual dose is two 400 mg KETEK Tablets taken at the same time once daily for 5 to 10 days. If you have kidney disease, with or without liver disease, your healthcare provider may change the dose prescribed for you.
KETEK tablets should be swallowed whole and may be taken with or without food. Try to take your tablets at the same time every day, unless your healthcare provider tells you otherwise.

Follow the dosing instructions carefully, and do not take more than the prescribed amount. If you miss a dose, take it as soon as you remember. Do not take more than one dose (e.g., two tablets) of KETEK in a 24 hour period. If you have any questions, talk to your healthcare provider.

To make sure that all bacteria are killed, take all of the medicine that was prescribed for you even if you begin to feel better, unless instructed otherwise. You should contact your healthcare provider if your condition is not improving while taking KETEK.

Who should not take KETEK?

You must not take KETEK if:

- You have ever had a severe allergic reaction to KETEK or to any of the group of antibiotics known as "macrolides" such as erythromycin, azithromycin (Zithromax®), clarithromycin (Biaxin®) or dirithromycin (Dynabac®).
- You are currently taking cisapride (Propulsid®) or pimozide (Orap®).
- You have ever experienced side effects on the liver while taking KETEK.

You should be sure to talk to your healthcare provider before taking KETEK if any of the following are true, so he/she can determine if KETEK is right for you:

- If you have, or if a relative has, a rare heart condition known as congenital prolongation of the QT interval.
- If you are being treated for heart rhythm disturbances with certain medicines known as antiarrhythmics (such as quinidine, procainamide, or dofetilide) or if you have low blood potassium (hypokalemia), or low blood magnesium (hypomagnesemia).
- If you have a disease known as myasthenia gravis.
- If you are pregnant, planning to become pregnant, or are nursing.
- If you have ever experienced jaundice (yellow color of the skin and/or eyes) while taking KETEK.
- If you have any other serious medical conditions, including heart, liver, or kidney disease.

What about other medications I am taking?

It is important to let your healthcare provider know about all of the medicines you are taking, including those obtained without a prescription. Also see section "**Who should not take KETEK?**"

It is important to tell your healthcare provider if you are taking:

- Simvastatin, lovastatin, or atorvastatin (used for lowering cholesterol). You should stop treatment with these medications while you are taking KETEK.
- Medicines that correct heart rhythm called "antiarrhythmics" (such as quinidine, procainamide, or dofetilide).
- Any of the following medicines: itraconazole, ketoconazole, midazolam, digoxin, ergot alkaloid derivatives, cyclosporine, carbamazepine, hexobarbital, phenytoin, tacrolimus, sirolimus, metoprolol, theophylline, rifampin or warfarin and other oral anticoagulants (sometimes called blood thinners).
- Medicines called diuretics (also sometimes called water pills) such as furosemide or hydrochlorothiazide.

What are the possible side effects of KETEK?

~~KETEK is generally well tolerated. Most side effects are mild to moderate.~~

~~The most common side effects are nausea, headache, dizziness, vomiting, and diarrhea. If diarrhea persists call your healthcare provider.~~

~~There have been reports of side effects on the liver, including severe liver disease. In some cases, liver damage worsened rapidly and happened after just a few doses of KETEK. If you develop signs or symptoms of hepatitis (liver disease), such as tiredness, body aches, loss of appetite, nausea, jaundice (yellow color of the skin and/or eyes), dark urine, light colored stools, itchy skin, or belly pains, stop your medication and immediately contact your healthcare provider.~~

~~Worsening of myasthenia gravis has been reported in patients treated with KETEK. This has sometimes occurred within a few hours after taking the first dose . Reports have included death and life threatening breathing trouble that happens fast in myasthenia gravis patients. If you have myasthenia gravis, you should talk with your doctor before 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 sometimes came back with the next dose.~~

~~If visual difficulties occur:~~

- ~~You should avoid driving a motor vehicle, operating heavy machinery, or engaging in otherwise hazardous activities.~~
- ~~Avoiding quickly looking between objects in the distance and objects nearby may help you to decrease these visual difficulties.~~
- ~~You should contact your physician if these visual difficulties interfere with your daily activities.~~
-

~~You should be aware of the possibility of experiencing syncope (fainting), and its impact on the ability to drive, especially if you are experiencing vagal symptoms (severe nausea, vomiting, and/or lightheadedness).~~
~~If you experience these symptoms, you should avoid driving a motor vehicle, operating heavy machinery, or engaging in otherwise hazardous activities.~~

~~KETEK has the potential to affect the heart, as seen on an electrocardiogram (EKG) test. In very rare cases, this condition may result in a serious abnormal heartbeat. Contact your healthcare provider if you have a fainting spell.~~

~~If you have other side effects not mentioned in this section or have concerns about side effects, be sure to talk to your healthcare provider.~~

How can I find out more about KETEK?

This is a summary of selected key points about KETEK. If you'd like more information or if you have concerns, talk to your healthcare provider. You can also visit the KETEK website at www.KETEK.com. But remember, neither this Patient Information nor the website can replace discussions with your doctor or healthcare provider.

Other key points to remember:

- Take your prescribed dose of KETEK once a day at the same time each day.
- Complete the course of medication (take all the tablets prescribed), even if you start to feel better, unless instructed otherwise.
- As with all other medications, do not use KETEK for other conditions or give tablets to others.
- Store KETEK tablets at room temperature.
- Keep this medication out of the reach of children.
- Do not take your tablets after the expiration date noted.
- Talk to your healthcare provider if you have questions or concerns.

Patient Information as of June 2006

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.

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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

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Medication Guide as of February 2007

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

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/s/

Tatiana Oussova
2/9/2007 06:59:21 PM
MEDICAL OFFICER
John, if Janice needs to sign it off, please, include her name.

John Alexander
2/12/2007 08:36:09 AM
MEDICAL OFFICER
I concur with this review.

Janice Soreth
2/12/2007 08:56:59 AM
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