

APPENDIX G: LABELING

USPI June 2006

Dear Health Care Professional Letter

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Post approval labeling modifications, US and EU (01-Apr-04 to 15-Sep-06)

Post approval labeling modifications, EU (09-Jul-01 to 01-Apr-04)

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KETEK[®]

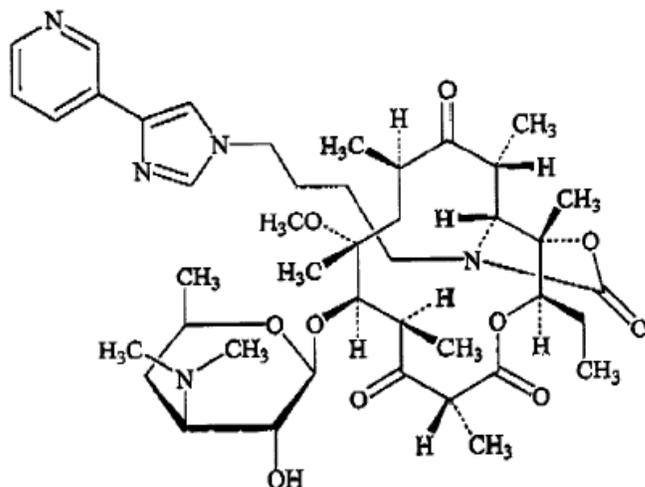
(telithromycin) Tablets

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

Parameter	Mean (SD)	
	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 ($\mu\text{g/mL}$)		Tissue/ Plasma Ratio
		Tissue or fluid	Plasma	
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 $\mu\text{g/mL}$ at 6 hours, and remained at 14.1 $\mu\text{g/mL}$ 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 $\mu\text{g/mL}$ 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 (0-24)_{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 antiovolatory 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

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

Pathogen	Minimal Inhibitory Concentrations (µg/mL)			Disk Diffusion (zone diameters in mm)		
	S	I	R ^a	S	I	R ^a
<i>Staphylococcus aureus</i>	≤ 0.25			≥ 22		
<i>Streptococcus pneumoniae</i>	≤ 1	2	≥ 4	≥ 19	16-18	≤ 15
<i>Haemophilus influenzae</i>	≤ 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- μ g 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 (μ g/mL)	Disk Diffusion (Zone diameter in mm)
<i>Staphylococcus aureus</i> ATCC [®] 29213	0.06-0.25	Not Applicable
<i>Staphylococcus aureus</i> ATCC 25923	Not Applicable	24-30
<i>Streptococcus pneumoniae</i> ATCC 49619	0.004-0.03	27-33
<i>Haemophilus influenzae</i> 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 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*, *Chlamydomphila 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.

KETEK is contraindicated in patients with previous history of hepatitis and/or jaundice associated with the use 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.

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 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.

Pseudomembranous colitis

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including telithromycin, and may range in severity from mild 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.

Treatment with antibacterial agents alters the flora of the colon and may permit overgrowth of clostridia. Studies indicate that toxin-producing strains of *Clostridium difficile* are the primary cause of “antibiotic-associated colitis”.

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.**)

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

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

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

If visual difficulties occur:

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

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

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

Patients should also be advised:

- 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. (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 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 ($900 \text{ mg}/\text{m}^2$) and 0.49 times ($240 \text{ mg}/\text{m}^2$) the daily human dose of 800 mg ($492 \text{ mg}/\text{m}^2$) in the rat and rabbit, respectively, no evidence of fetal terata was found. At doses higher than the $900 \text{ mg}/\text{m}^2$ and $240 \text{ mg}/\text{m}^2$ 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 ($750 \text{ mg}/\text{m}^2/\text{d}$) 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 \geq 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 \geq 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 \geq 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 ($\geq 0.2\%$ 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** 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**.)

Nervous system: syncope usually associated with vagal syndrome.

OVERDOSAGE

In the event of acute overdose, 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 taken orally once every 24 hours. The duration of therapy depends on the infection type and is described below. 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)
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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/mm³. Total number of clinically evaluable patients in the telithromycin group included 2016 patients.

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

Controlled Studies	Patients (n)		Clinical cure rate	
	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%
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*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.

Table 8. CAP: Clinical cure rate by pathogen at post-therapy follow-up (17-24 days)

Pathogen	KETEK	Comparator
<i>Streptococcus pneumoniae</i>	73/78 (93.6%)	63/70 (90.0%)
<i>Haemophilus influenzae</i>	39/47 (83.0%)	42/44 (95.5%)
<i>Moraxella catarrhalis</i>	12/14 (85.7%)	7/9 (77.8%)
<i>Chlamydomphila (Chlamydia) pneumoniae</i>	23/25 (92.0%)	18/19 (94.7%)
<i>Mycoplasma pneumoniae</i>	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. 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
2 nd 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 Table 10.

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

Controlled Studies	Patients (n)		Clinical cure rate	
	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
<i>Streptococcus pneumoniae</i>	27/31 (87.1%)	14/16 (87.5%)
<i>Haemophilus influenzae</i>	28/34 (82.4%)	13/15 (86.7%)
<i>Moraxella catarrhalis</i>	7/7 (100%)	7/7 (100%)
<i>Staphylococcus aureus</i>	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
<i>Streptococcus pneumoniae</i>	22/27 (81.5%)	15/19 (78.9%)
<i>Haemophilus influenzae</i>	44/60 (73.3%)	45/53 (84.9%)
<i>Moraxella catarrhalis</i>	27/29 (93.1%)	29/34 (85.3%)

Visual Adverse Events

Table 14 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		
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/m²/day (1.8x the human dose) or more for 1 month, and 300 mg/m²/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/m²/day (6.1x the human dose) or more for 1 month and 1000 mg/m²/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.

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Rx only**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 pimozone (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.

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sanofi-aventis U.S. LLC

Bridgewater, NJ 08807

Rx only

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June 2006

Dear Healthcare Professional:

Sanofi-aventis U.S. would like to inform you of important updated safety information regarding KETEK® (telithromycin) Tablets. The prescribing information has been revised to provide additional information about adverse hepatic events reported in patients taking Ketek. The prescribing information also includes revised recommendations regarding the use of Ketek in patients with myasthenia gravis. These changes have been reviewed and agreed to by the US Food and Drug Administration.

The KETEK Prescribing Information has been updated to:

1. Include a **CONTRAINDICATION** for patients with a previous history of hepatitis and/or jaundice associated with the use of KETEK tablets or any macrolide antibiotics;
2. Update the **WARNINGS, PRECAUTIONS, ADVERSE REACTIONS** and **PATIENT PACKAGE INSERT** sections to describe the nature and characterization of hepatic events reported in connection with the use of KETEK; and
3. Update the **WARNINGS, PRECAUTIONS,** and **PATIENT PACKAGE INSERT** sections to provide revised recommendations regarding use of the drug in patients with myasthenia gravis.

The changes in the prescribing information relating to hepatic events and myasthenia gravis are provided below.

Hepatic Events

CONTRAINDICATIONS

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

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

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**, and **Information for 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**.)

PRECAUTIONS

General

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.)

Information for patients

Patients should also be advised:

- 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. (See **CONTRAINDICATIONS** and **WARNINGS**.)

ADVERSE EVENTS

Post-Marketing Adverse Event Reports

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**.)

Myasthenia Gravis

WARNINGS

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.

PRECAUTIONS

Information for patients

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

In addition, the Patient Package Insert has been revised to state as follows:

PATIENT PACKAGE INSERT

Who should not take KETEK?

You must not take KETEK if:

- o 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®).
- o You are currently taking cisapride (Propulsid®) or pimozide (Orap®).
- o You have ever experienced side effects on the liver while taking KETEK.

What are the possible side effects of KETEK?

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.

ABOUT KETEK

KETEK tablets are indicated for the treatment of infections caused by susceptible strains of the designated microorganisms in the conditions listed below 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^[1]]), *Haemophilus influenzae*, *Moraxella catarrhalis*, *Chlamydomphila pneumoniae*, or *Mycoplasma pneumoniae*.

Please refer to the accompanying **Important Safety Information** and the enclosed **FULL PRESCRIBING INFORMATION**, including patient information, for a complete discussion of **INDICATIONS, CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, ADVERSE REACTIONS, and DOSAGE and ADMINISTRATION**.

Patient safety is our highest priority at sanofi-aventis U.S., and we are committed to ensuring that healthcare professionals continue to have the information necessary to prescribe KETEK appropriately. Please carefully review this information and contact sanofi-aventis if you should have any questions about this information or the safe and effective use of KETEK.

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

The revised product information will be included in Ketek® (telithromycin) packages manufactured after June 2006, and is available on the company and product websites (www.sanofi-aventis.us and www.ketek.com) or by calling Customer Information at 1-800-633-1610.

If you have further questions or require additional information, please contact our Medical Information Department at 1-800-633-1610 (option #1) from 9am to 5pm (EST) Monday–Friday.

Sincerely,

Jerome Premmreur, MD
Vice President
US Medical Affairs & Acting Chief Medical Officer
Sanofi-aventis U.S.

(1) 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

Enclosures: KETEK® (telithromycin) Full Prescribing Information
KETEK® (telithromycin) Important Safety Information



Important Safety Information

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

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

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

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

KETEK must not be re-administered to patients with a previous history of hepatitis and/or jaundice associated with the use of KETEK tablets, or any macrolide antibiotic.

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. 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.

Concomitant administration of KETEK with cisapride or pimozide is contraindicated.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including telithromycin, and may range in severity from mild to life-threatening.

KETEK 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, KETEK 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 (eg, quinidine and procainamide) or Class III (e.g., dofetilide) antiarrhythmic agents.

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.

There have been post marketing adverse event reports of syncope. Patients should be cautioned about the potential effects of visual disturbance and syncope on driving or engaging in potentially hazardous activities.

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. Concomitant treatment of KETEK with rifampin, a CYP 3A4 inducer, should be avoided

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

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Ketek 400 mg film-coated tablets.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 400 mg of telithromycin.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Ketek is indicated for the treatment of the following infections:

In patients of 18 years and older:

- Community-acquired pneumonia, mild or moderate (see section 4.4).
- Acute exacerbation of chronic bronchitis,
- Acute sinusitis
- Tonsillitis/pharyngitis caused by Group A *beta streptococci*, as an alternative when beta lactam antibiotics are not appropriate.

In patients of 12 to 18 years old:

- Tonsillitis/pharyngitis caused by Group A *beta streptococci*, as an alternative when beta lactam antibiotics are not appropriate.

4.2 Posology and method of administration

The recommended dose is 800 mg once a day i.e. two 400 mg tablets once a day. The tablets should be swallowed whole with a sufficient amount of water. The tablets may be taken with or without food.

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

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

In patients of 12 to 18 years old, the treatment regimen will be:

- Tonsillitis/pharyngitis caused by Group A *beta streptococci*: 800 mg once a day for 5 days.

In the elderly:

No dosage adjustment is required in elderly patients based on age alone.

In children:

Ketek is not recommended for use in children below 12 years of age due to lack of data on safety and efficacy (see section 5.2).

Impaired renal function:

No dosage adjustment is necessary in patients with mild or moderate renal impairment. Ketek is not recommended as first choice in patients with severe renal impairment (creatinine clearance <30ml/min) or patients with both severe renal impairment and co-existing hepatic impairment, as an optimal dosage format (600 mg) is not available. If telithromycin treatment is deemed necessary, these patients may be treated with alternating daily doses of 800 mg and 400 mg, starting with the 800 mg dose.

In haemodialysed patients, the posology should be adjusted so that Ketek 800 mg is given after the dialysis session (see also section 5.2)..

Impaired hepatic function:

No dosage adjustment is necessary in patients with mild, moderate, or severe hepatic impairment, unless renal function is severely impaired, however the experience in patients with impaired hepatic function is limited. Hence, Ketek should be used with caution (see also section 4.4 and 5.2).

4.3 Contraindications

Hypersensitivity to the active substance, to any of the macrolide antibacterial agents, or to any of the excipients.

Concomitant administration of Ketek and any of the following substances is contraindicated: cisapride, ergot alkaloid derivatives (such as ergotamine and dihydroergotamine), pimozone, astemizole and terfenadine (see section 4.5).

Ketek should not be used concomitantly with simvastatin, atorvastatin and lovastatin. Treatment with these agents should be interrupted during Ketek treatment (see section 4.5).

Ketek is contraindicated in patients with a history of congenital or a family history of long QT syndrome (if not excluded by ECG) and in patients with known acquired QT interval prolongation.

In patients with severely impaired renal and/or hepatic function, concomitant administration of Ketek and strong CYP3A4 inhibitors, such as protease inhibitors or ketoconazole, is contraindicated.

4.4 Special warnings and precautions for use

As with macrolides, due to a potential to increase QT interval, Ketek should be used with care in patients with coronary heart disease, a history of ventricular arrhythmias, uncorrected hypokalaemia and or hypomagnesaemia, bradycardia (<50 bpm), or during concomitant administration of Ketek with QT interval prolonging agents or potent CYP 3A4 inhibitors such as protease inhibitors and ketoconazole.

As with nearly all antibacterial agents, diarrhoea, particularly if severe, persistent and /or bloody, during or after treatment with Ketek may be caused by *pseudomembranous colitis*. If *pseudomembranous colitis* is suspected, the treatment must be stopped immediately and patients should be treated with supportive measures and/or specific therapy.

Exacerbation of myasthenia gravis has been reported in patients with myasthenia gravis treated with telithromycin. This usually occurred within one to three hours after intake of first dose of telithromycin.

Reports have included potentially life threatening acute respiratory failure with a rapid onset in myasthenic patients treated for respiratory tract infections with telithromycin. Telithromycin is not recommended in patients with myasthenia gravis unless other therapeutic alternatives are not available.

Patients with myasthenia gravis taking telithromycin should be advised to immediately seek medical attention if they experience exacerbation of their symptoms. Ketek must then be discontinued and supportive care administered as medically indicated (see section 4.8).

Alterations in hepatic enzymes have been commonly observed in clinical studies with telithromycin. Post-marketing cases of severe hepatitis and liver failure have been reported (see section 4.8). These hepatic reactions were observed during or immediately after treatment, and in most cases were reversible after discontinuation of telithromycin.

Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop such as anorexia, jaundice, dark urine, pruritus or tender abdomen.

Due to limited experience, Ketek should be used with caution in patients with liver impairment (see section 5.2).

Ketek should not be used during and 2 weeks after treatment with CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort). Concomitant treatment with these medicinal products is likely to result in subtherapeutic levels of telithromycin and therefore encompass a risk of treatment failure (see section 4.5).

Ketek is an inhibitor of CYP3A4 and should only be used under specific circumstances during treatment with other medicinal products that are metabolised by CYP3A4.

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to telithromycin and other antibiotics.

In community acquired pneumonia, efficacy has been demonstrated in a limited number of patients with risk factors such as *pneumococcal bacteraemia* or age higher than 65 years.

Experience of treatment of infections caused by penicillin/or erythromycin resistant *S. pneumoniae* is limited, but so far, clinical efficacy and eradication rates have been similar compared with the treatment of susceptible *S. pneumoniae*. Caution should be taken when *S. aureus* is the suspected pathogen and there is a likelihood of erythromycin resistance based on local epidemiology.

L. pneumophila is highly susceptible to telithromycin *in vitro*, however, the clinical experience of the treatment of pneumonia caused by *legionella* is limited.

As for macrolides, *H. influenzae* is classified as intermediately susceptible. This should be taken into account when treating infections caused by *H. influenzae*.

4.5 Interaction with other medicinal products and other forms of interaction

Interaction studies have only been performed in adults.

- Effect of Ketek on other medicinal product

Telithromycin is an inhibitor of CYP3A4 and a weak inhibitor of CYP2D6. *In vivo* studies with simvastatin, midazolam and cisapride have demonstrated a potent inhibition of intestinal CYP3A4 and a moderate inhibition of hepatic CYP3A4. The degree of inhibition with different CYP3A4 substrates is difficult to predict. Hence, Ketek should not be used during treatment with medicinal products that are CYP3A4 substrates, unless plasma concentrations of the CYP3A4 substrate, efficacy or adverse events can be closely monitored. Alternatively, interruption in the treatment with the CYP3A4 substrate should be made during treatment with Ketek.

Medicinal products with a potential to prolong QT interval

Ketek is expected to increase the plasma levels of cisapride, pimozone, astemizole and terfenadine. This could result in QT interval prolongation and cardiac arrhythmias including ventricular

tachycardia, ventricular fibrillation and torsades de pointes. Concomitant administration of Ketek and any of these medicinal products is contraindicated (see section 4.3).

Caution is warranted when Ketek is administered to patients taking other medicinal products with the potential to prolong QT interval (see section 4.4).

Ergot alkaloid derivatives (such as ergotamine and dihydroergotamine)

By extrapolation from erythromycin A and josamycin, concomitant medication of Ketek and alkaloid derivatives could lead to severe vasoconstriction (“ergotism”) with possibly necrosis of the extremities. The combination is contraindicated (see section 4.3).

Statins

When simvastatin was coadministered with Ketek, there was a 5.3 fold increase in simvastatin C_{max} , an 8.9 fold increase in simvastatin AUC, a 15-fold increase in simvastatin acid C_{max} and an 11-fold increase in simvastatin acid AUC. In vivo interaction studies with other statins have not been performed, but Ketek may produce a similar interaction with lovastatin and atorvastatin, a lesser interaction with cerivastatin and little or no interaction with pravastatin and fluvastatin. Ketek should not be used concomitantly with simvastatin, atorvastatin and lovastatin. Treatment with these agents should be interrupted during Ketek treatment. Cerivastatin should be used with caution and patients should be carefully monitored for signs and symptoms of myopathy.

Benzodiazepins

When midazolam was coadministered with Ketek, midazolam AUC was increased 2.2-fold after intravenous administration of midazolam and 6.1-fold after oral administration. The midazolam half-life was increased about 2.5-fold. Oral administration of midazolam concomitantly with Ketek should be avoided. Intravenous dosage of midazolam should be adjusted as necessary and monitoring of the patient be undertaken. The same precautions should also apply to the other benzodiazepins which are metabolized by CYP3A4, (especially triazolam but also to a lesser extent alprazolam). For those benzodiazepins which are not metabolized by CYP3A4 (temazepam, nitrazepam, lorazepam) an interaction with Ketek is unlikely.

Cyclosporin, tacrolimus, sirolimus

Due to its CYP3A4 inhibitory potential, telithromycin can increase blood concentrations of these CYP3A4 substrates. Thus, when initiating telithromycin in patients already receiving any of these immunosuppressive agents, cyclosporin, tacrolimus or sirolimus levels must be carefully monitored and their doses decreased as necessary. When telithromycin is discontinued, cyclosporin, tacrolimus or sirolimus levels must be again carefully monitored and their dose increased as necessary.

Metoprolol

When metoprolol (a CYP2D6 substrate) was coadministered with Ketek, metoprolol C_{max} and AUC were increased by approximately 38%, however, there was no effect on the elimination half-life of metoprolol. The increase exposure to metoprolol may be of clinical importance in patients with heart failure treated with metoprolol. In these patients, co-administration of Ketek and metoprolol, a CYP2D6 substrate, should be considered with caution.

Digoxin

Ketek has been shown to increase the plasma concentrations of digoxin. The plasma trough levels, C_{max} , AUC and renal clearance were increased by 20 %, 73 %, 37 % and 27% respectively, in healthy volunteers. There were no significant changes in ECG parameters and no signs of digoxin toxicity were observed. Nevertheless, monitoring of serum digoxin level should be considered during concomitant administration of digoxin and Ketek.

Theophylline

There is no clinically relevant pharmacokinetic interaction of Ketek and theophylline administered as extended release formulation. However, the co-administration of both medicinal products should be separated by one hour in order to avoid possible digestive side effects such as nausea and vomiting.

Oral anticoagulants

Increased anticoagulant activity has been reported in patients simultaneously treated with anticoagulants and antibiotics, including telithromycin. The mechanisms are incompletely known. Although Ketek has no clinically relevant pharmacokinetic or pharmacodynamic interaction with warfarin after single dose administration, more frequent monitoring of prothrombin time/INR (International Normalised Ratio) values should be considered during concomitant treatment.

Oral contraceptives

There is no pharmacodynamic or clinically relevant pharmacokinetic interaction with low-dose triphasic oral contraceptives in healthy subjects.

- Effect of other medicinal products on Ketek

During concomitant administration of rifampicin and telithromycin in repeated doses, C_{max} and AUC of telithromycin were on average decreased by 79% and 86% respectively. Therefore, concomitant administration of CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) is likely to result in subtherapeutic levels of telithromycin and loss of effect. The induction gradually decreases during 2 weeks after cessation of treatment with CYP3A4 inducers. Ketek should not be used during and 2 weeks after treatment with CYP3A4 inducers.

Interaction studies with itraconazole and ketoconazole, two CYP3A4 inhibitors, showed that maximum plasma concentrations of telithromycin were increased respectively by 1.22 and 1.51 fold and AUC by respectively 1.54 fold and 2.0 fold. These changes in the pharmacokinetics of telithromycin do not necessitate dosage adjustment as telithromycin exposure remains within a well tolerated range. The effect of ritonavir on telithromycin has not been studied and could lead to larger increase in telithromycin exposure. The combination should be used with caution.

Ranitidine (taken 1 hour before Ketek) and antacid containing aluminium and magnesium hydroxide has no clinically relevant influence on telithromycin pharmacokinetics.

4.6 Pregnancy and lactation

There are no adequate data from the use of Ketek in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Ketek should not be used during pregnancy unless clearly necessary.

Telithromycin is excreted in the milk of lactating animals, at concentrations about 5 times those of maternal plasma. Corresponding data for humans is not available. Ketek should not be used by breast-feeding women.

4.7 Effects on ability to drive and use machines

Ketek may cause undesirable effects such as visual disturbances which may reduce the capacity for the completion of certain tasks. In addition, rare cases of transient loss of consciousness, which may be preceded by vagal symptoms, have been reported (see section 4.8). Patients should be informed that these undesirable effects may occur as early as after the first dose of medication. Patients should be cautioned about the potential effects of these events on the ability to drive or operate machinery.

4.8 Undesirable effects

In 2461 patients treated by Ketek in phase III clinical trials, the following undesirable effects possibly or probably related to telithromycin have been reported. This is shown below.

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System organ class	Very common (≥ 1/10)	Common (≥1/100 to <1/10)	Uncommon (≥1/1,000 to <1/100)	Rare (≥1/10,000 to <1/1,000)	Very rare (< 1/10,000)
Blood and the lymphatic system disorders			Eosinophilia		
Nervous system disorders		Dizziness, headache, disturbance of taste	Vertigo somnolence, nervousness, insomnia,	Transient loss of consciousness, paraesthesia	Parosmia
Eye disorders			Blurred vision	Diplopia	
Cardiovascular disorders			Flush Palpitations	Atrial arrhythmia, hypotension, bradycardia	
Gastro-intestinal disorders	Diarrhoea	Nausea, vomiting, gastrointestinal pain, flatulence	Oral moniliasis, stomatitis anorexia, constipation, ,		Pseudomembranous colitis
Hepato-biliary disorders		Increase in liver enzymes (AST, ALT, alkaline phosphatase)	Hepatitis	Cholestatic jaundice	
Skin and subcutaneous tissue disorders			Rash, urticaria, pruritus	Eczema	Erythema multiforme
Musculoskeletal, connective tissue					Muscle cramps
Reproductive system disorders		Vaginal moniliasis			

Visual disturbances (<1%) associated with the use of Ketek, including blurred vision, difficulty focusing and diplopia, were mostly mild to moderate. They typically occurred within a few hours after the first or second dose, recurred upon subsequent dosing, lasted several hours and were fully reversible either during therapy or following the end of treatment. These events have not been associated with signs of ocular abnormality.

In clinical trials the effect on QTc was small (mean of approximately 1 msec). In comparative trials, similar effects to those observed with clarithromycin were seen with an on-therapy Δ QTc >30 msec in 7.6% and 7.0% of cases, respectively. No patient in either group developed a Δ QTc >60 msec. There were no reports of TdP or other serious ventricular arrhythmias or related syncope in the clinical program and no subgroups at risk were identified.

During post-marketing experience the following reactions have been reported (frequency unknown):

- Immune system disorders: Angioneurotic oedema, anaphylactic reactions including anaphylactic shock
- Cardiac disorders: QT/QTc interval prolongation
- Gastrointestinal disorders: Pancreatitis,
- Hepato-biliary disorders: Severe hepatitis and liver failure.
- Nervous system disorders: Cases of rapid onset of exacerbation of myasthenia gravis have been reported (see section 4.4).

4.9 Overdose

In the event of acute overdose the stomach should be emptied. The patients should be carefully observed and given symptomatic and supportive treatment. Adequate hydration should be maintained.

Blood electrolytes (especially potassium) must be controlled. Due to the potential for the prolongation of the QT interval and increased risk of arrhythmia, ECG monitoring must take place

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: macrolides, lincosamides and streptogramins, ATC Code: J01FA15.

Telithromycin is a semisynthetic derivative of erythromycin A belonging to the ketolides, a class of antibacterial agents related to macrolides.

Mode of action

Telithromycin inhibits protein synthesis by acting at the ribosome level.

The affinity of telithromycin for the 50S bacterial subunit of ribosome is 10 fold higher than that of erythromycin A when the strain is susceptible to erythromycin A. Against erythromycin A resistant strains, due to an MLS_B mechanism of resistance, telithromycin shows a more than 20 fold affinity compared to erythromycin A in the 50S bacterial subunit.

Telithromycin interferes with the ribosome translation at the 23S ribosomal RNA level, where it interacts with domain V and II. Furthermore, telithromycin is able to block the formation of the 50S and 30S ribosomal subunits.

Breakpoints

The recommended MIC breakpoints for telithromycin, separating susceptible organisms from intermediately susceptible organisms and intermediately susceptible organisms from resistant organisms, are: susceptible ≤ 0.5 mg/l, resistant > 2 mg/l.

Antibacterial spectrum

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

This information provides only an approximate guidance on probabilities as to whether microorganisms will be susceptible to telithromycin.

Commonly susceptible species

Aerobic Gram-positive bacteria

Staphylococcus aureus methicillin susceptible (MSSA)*

Lancefield group C and G (β haemolytic) streptococci

Streptococcus agalactiae

Streptococcus pneumoniae *

Viridans group streptococci

<p><u>Aerobic Gram- negative bacteria</u></p> <p><i>Legionella pneumophila</i> <i>Moraxella catarrhalis</i>*</p>
<p><u>Other</u></p> <p><i>Chlamydophila pneumoniae</i>* <i>Chlamydia psittaci</i> <i>Mycoplasma pneumoniae</i>*</p>
<p>Species for which acquired resistance may be a problem</p> <p><u>Aerobic Gram-positive bacteria</u> <i>Staphylococcus aureus</i> methicillin resistant (MRSA)+ <i>Streptococcus pyogenes</i>*</p> <p><u>Aerobic Gram- negative bacteria</u> <i>Haemophilus influenzae</i>\$* <i>Haemophilus parainfluenzae</i>\$</p>
<p>Inherantly resistant organisms</p> <p><u>Aerobic Gram- negative bacteria</u> <i>Acinetobacter</i> <i>Enterobacteriaceae</i> <i>Pseudomonas</i></p>

* Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.

\$ natural intermediate susceptibility

+Among MRSA the rate of MLS_{Bc} resistant strains is more than 80%, telithromycin is not active against MLS_{Bc}.

Resistance

Telithromycin does not induce MLS_B resistance in vitro to *S. aureus*, *S. pneumoniae*, and *S. pyogenes*, an attribute related to its 3 keto function. Development of in vitro resistance to telithromycin due to spontaneous mutation is rare. The majority of MRSA are resistant to erythromycin A by a constitutive MLS_B mechanism.

In vitro results have shown that telithromycin is affected by the erythromycin ermB or mefA related resistance mechanisms but to lesser extent than erythromycin. While exposure to telithromycin did select for pneumococcal mutants with increased MICs, the MICs remained within the proposed susceptibility range.

For *S. pneumoniae*, there is no cross- or co-resistance between telithromycin and other antibacterial classes including erythromycin A and/or penicillin resistance .

For *S. pyogenes*, cross-resistance occurs for high-level erythromycin A resistant strains.

Effect on oral and faecal flora

In a comparative study in healthy human volunteers, telithromycin 800 mg daily and clarithromycin 500 mg twice daily for 10 days showed a similar and reversible reduction of oral and faecal flora. However, in contrast to clarithromycin, no resistant strains of alpha streptococci emerged in saliva on treatment with telithromycin.

5.2 Pharmacokinetic properties

Absorption

Following oral administration, telithromycin is fairly rapidly absorbed. A mean maximum plasma concentration of about 2 mg/l is reached within 1-3 hour after dose with once-daily dosing of telithromycin 800 mg. The absolute bioavailability is about 57 % after a single dose of 800 mg. The rate and extent of absorption is unaffected by food intake, and thus Ketek tablets can be given without regard to food.

Mean steady-state trough plasma concentrations of between 0.04 and 0.07 mg/l are reached within 3 to 4 days with once-daily dosing of telithromycin 800 mg. At steady-state AUC is approximately 1.5 fold increased compared to the single dose.

Mean peak and trough plasma concentrations at steady state in patients were 2.9 ± 1.6 mg/l (range 0.02-7.6 mg/l) and 0.2 ± 0.2 mg/l (range 0.010 to 1.29 mg/l), during a therapeutic 800 mg once-daily dose regimen.

Distribution

The in vitro protein binding is approximately 60 % to 70 %. Telithromycin is widely distributed throughout the body. The volume of distribution is 2.9 ± 1.0 l/kg. Rapid distribution of telithromycin into tissues results in significantly higher telithromycin concentrations in most target tissues than in plasma. The maximum total tissue concentration in epithelial lining fluid, alveolar macrophages, bronchial mucosa, tonsils and sinus tissue were 14.9 ± 11.4 mg/l, 318.1 ± 231 mg/l, 3.88 ± 1.87 mg/kg, 3.95 ± 0.53 mg/kg and 6.96 ± 1.58 mg/kg, respectively. The total tissue concentration 24 h after dose in epithelial lining fluid, alveolar macrophages, bronchial mucosa, tonsils and sinus tissue were 0.84 ± 0.65 mg/l, 162 ± 96 mg/l, 0.78 ± 0.39 mg/kg, 0.72 ± 0.29 mg/kg and 1.58 ± 1.68 mg/kg, respectively. The mean maximum white blood cell concentration of telithromycin was 83 ± 25 mg/l.

Metabolism

Telithromycin is metabolized primarily by the liver. After oral administration, two-thirds of the dose is eliminated as metabolites and one-third unchanged. The main circulating compound in plasma is telithromycin. Its principal circulating metabolite represents approximately 13 % of telithromycin AUC, and has little antimicrobial activity compared with the parent medicinal product. Other metabolites were detected in plasma, urine and faeces and represent less or equal than 3 % of plasma AUC.

Telithromycin is metabolized both by CYP450 isoenzymes and non-CYP enzymes. The major CYP450 enzyme involved in the metabolism of telithromycin is CYP3A4. Telithromycin is an inhibitor of CYP3A4 and CYP2D6, but has no or limited effect on CYP1A, 2A6, 2B6, 2C8, 2C9, 2C19 and 2E1.

Elimination

After oral administration of radiolabelled telithromycin, 76 % of the radioactivity was recovered from faeces, and 17 % from the urine. Approximately one-third of telithromycin was eliminated unchanged; 20 % in faeces and 12 % in urine. Telithromycin displays moderate non-linear pharmacokinetics. The non-renal clearance is decreased as the dose is increased. The total clearance (mean \pm SD) is approximately 58 ± 5 l/h after an intravenous administration with renal clearance accounting for about 22 % of this. Telithromycin displays a tri-exponential decay from plasma, with a rapid distribution half-life of 0.17 h. The main elimination half-life of telithromycin is 2-3 h and the terminal, less important, half-life is about 10 h at the dose 800 mg once daily.

Special populations

-Renal impairment

In a multiple-dose study, 36 subjects with varying degrees of renal impairment, a 1.4-fold increase in $C_{max,ss}$, and a 2-fold increase in $AUC(0-24)_{ss}$ at 800 mg multiple doses in the severe renally impaired group ($CLCR < 30$ mL/min) compared to healthy volunteers were observed and a reduced dosage of Ketek is recommended (See Section 4.2.). Based on observed data, a 600 mg daily dose is approximately equivalent with the target exposure observed in healthy subjects. Based on simulation data, an alternating daily dosing regimen of 800 mg and 400 mg in patients with severe renal impairment can approximate the $AUC(0-48h)$ in healthy subjects receiving 800 mg once daily.

The effect of dialysis on the elimination of telithromycin has not been assessed.

-Hepatic impairment

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 compared to those obtained in age- and sex-matched healthy subjects. In both studies, higher renal elimination was observed in the hepatically impaired patients. Due to limited experience in patients with decreased metabolic capacity of the liver, Ketek should be used with caution in patients with hepatic impairment (see also section 4.4).

-Elderly subjects: In subjects over 65 (median 75 years), the maximum plasma concentration and AUC of telithromycin were increased approximately 2 fold compared with those achieved in young healthy adults. These changes in pharmacokinetics do not necessitate dosage adjustment.

-Paediatric patients: The pharmacokinetics of telithromycin in paediatric population less than 12 years old have not yet been studied. Limited data, obtained in paediatric patients 13 to 17 years of age, showed that telithromycin concentrations in this age group were similar to the concentrations in patients 18 to 40 years of age.

-Gender

The pharmacokinetics of telithromycin are similar between males and females.

5.3 Preclinical safety data

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. These effects showed a tendency to regress after cessation of treatment. Plasma exposures based on free fraction of active substance, at the no observed adverse effect levels ranged from 1.6 to 13 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 in rats and dogs administered telithromycin at repeated doses of 150 mg/kg/day or more for 1 month and 20 mg/kg/day or more for 3-6 months. This administration corresponds to free active substance systemic exposure levels of at least 9 times the expected levels in human after 1 month and less than the expected level in humans after 6 months, respectively. There was evidence of reversibility upon cessation of treatment. The significance of these findings for humans is unknown.

In similarity to some macrolides, telithromycin caused a prolongation of Qtc interval in dogs and on action potential duration in rabbit Purkinje fibers in vitro. Effects were evident at plasma levels of free drug 8 to 13 times the expected clinical level. Hypokalaemia and quinidine had additive/supra-additive effects in vitro while potentiation was evident with sotalolol. Telithromycin, but not its major human metabolites, had inhibitory activity on HERG and $Kv1.5$ channels.

Reproduction toxicity studies showed reduced gamete maturation in rat and adverse effects on fertilization. At high doses embryotoxicity was apparent and an increase in incomplete ossification and in skeletal anomalies was seen. Studies in rats and rabbits were inconclusive with respect to potential

for teratogenicity, there was equivocal evidence of adverse effects on foetal development at high doses.

Telithromycin, and its principal human metabolites, were negative in tests on genotoxic potential *in vitro* and *in vivo*. No carcinogenicity studies have been conducted with telithromycin.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline cellulose
Povidone K25
Croscarmellose sodium
Magnesium stearate

Tablet coating:

Talc
Macrogol 8000
Hypromellose 6 cp
Titanium dioxide E171
Yellow iron oxide E172
Red iron oxide E172

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

No special precautions for storage.

6.5 Nature and contents of container

Two tablets are contained in each blister cavity.

Available as packs of 10, 14, 20 and 100 tablets.
Opaque PVC/Aluminium blisters

Available as pack of 5 x 2 tablets.
Opaque PVC/Aluminium perforated unit dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Aventis Pharma S.A.
20, Avenue Raymond Aron
F-92160 ANTONY
France

8. MARKETING AUTHORISATION NUMBERS

EU/1/01/191/001-005

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorizatoin: 9 July 2001

Date of first renewal: 9 July 2006

10. DATE OF REVISION OF THE TEXT

ANNEX II

- A. MANUFACTURING AUTHORISATION HOLDER
RESPONSIBLE FOR BATCH RELEASE**

- B. CONDITIONS OF THE MARKETING AUTHORISATION**

A MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release:

Aventis Pharma S.p.A.
Strada Statale No 17, km22
67019 Scoppito (L'Aquila)
Italy

B CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

Medicinal product subject to medical prescription

- **CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

The holder of this marketing Authorisation will have to submit PSURs on a yearly basis.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING**Carton****1. NAME OF THE MEDICINAL PRODUCT**

Ketek 400 mg film-coated tablets
Telithromycin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 400 mg of telithromycin

3. LIST OF EXCIPIENTS**4. PHARMACEUTICAL FORM AND CONTENTS**

10 film-coated tablets
14 film-coated tablets
20 film-coated tablets
100 film-coated tablets
5 x 2 film-coated tablets

5. METHOD AND, ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children

7. OTHER SPECIAL WARNING(S), IF NECESSARY**8. EXPIRY DATE**

EXP {month/year}

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE**11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER**

Aventis Pharma S.A.
20, Avenue Raymond Aron
F-92160 ANTONY
France

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/191/001 10 tablets
EU/1/01/191/002 14 tablets
EU/1/01/191/003 20 tablets
EU/1/01/191/004 100 tablets
EU/1/01/191/005 5x2 tablets

13. BATCH NUMBER

Batch {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE**16. INFORMATION IN BRAILLE**

Ketek

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**1. NAME OF THE MEDICINAL PRODUCT**

Ketek 400 mg film-coated tablets
Telithromycin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Aventis Pharma S.A.

3. EXPIRY DATE

EXP {month/year}

4. BATCH NUMBER

Batch {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET : INFORMATION FOR THE USER**Ketek 400 mg film-coated tablets**
Telithromycin**Read all of this leaflet carefully before you start taking this medicine.**

- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor or your pharmacist.
- This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
- If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:

1. What Ketek is and what it is used for
2. Before you take Ketek.
3. How to take Ketek.
4. Possible side effects
5. How to store Ketek
6. Further Information

1. WHAT KETEK IS AND WHAT IT IS USED FOR

Ketek belongs to one of a group of medicines called ketolides, a new class of antibiotics related to macrolides. Antibiotics stop the growth of bacteria which cause infections.

Ketek is used in adults and adolescents of 12 years and older to treat infections due to bacteria against which the medicine is active. The infections which Ketek can be used to treat are: infections of throat, infections of the sinuses, chest infections in patients with long standing breathing difficulties and pneumonia.

2. BEFORE YOU TAKE KETEK**Do not take Ketek:**

- if you are allergic (hypersensitive) to telithromycin, to any of the macrolide antibiotics or to any of the other ingredients of Ketek . If in doubt, talk to your doctor or pharmacist.
- if you are taking certain medicinal products to control the blood level of cholesterol or other lipids.
- if you are known to have an abnormality of electrocardiogram (ECG) called “long QT syndrome”.
- while taking other medicines containing any of the following active substances:
 - ergotamine or dihydroergotamine (tablets or inhaler for migraine)
 - terfenadine or astemizole (allergic problems)
 - cisapride (digestive problems)
 - pimozone (psychiatric problems)

-if you have severely impaired renal function and/or severely impaired hepatic function, do not take Ketek while taking other medicines containing any of the following active substances:

- ketoconazole (anti fungal treatment)
- a medicine called protease inhibitor (HIV treatment)

Refer also to section “Taking other medicines”.

Take special care with Ketek:

- if you have had certain heart problems such as coronary heart disease, ventricular arrhythmias, bradycardia or if you have had certain abnormal blood tests due to medical conditions such as hypokalaemia, hypomagnesaemia.
- if you develop severe or prolonged or bloody diarrhoea during or after taking Ketek. tablets, consult your doctor immediately since it may be necessary to interrupt the treatment. This may be a sign of bowel inflammation (*pseudomembranous colitis*) which can occur following treatment with antibiotics.
- if you suffer from myasthenia gravis, a rare disease which causes muscle weakness.
- if you experience any worsening of your symptoms of myasthenia gravis during treatment with Ketek, you should interrupt treatment with Ketek and immediately seek medical attention
- if you have liver disease.
- Ketek tablets are not recommended for use in children and adolescents less than 12 years old.

Refer also to sections “Do not take Ketek” and “Taking other medicines”.

Taking other medicines

Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription, as some of them could have an interaction with Ketek.

Refer also to section “Do not take Ketek”.

Taking Ketek with food and drink

Ketek may be taken with or without food.

Pregnancy and Breast-feeding

If you are pregnant do not take Ketek tablets as the safety of Ketek in pregnancy is insufficiently established. If you are breast-feeding do not take Ketek tablets.

Driving and using machines

Taking Ketek tablets may cause side effects such as visual disturbances which may reduce the capacity to carry out certain tasks. Rare cases of transient loss of consciousness (fainting), which may be preceded by vagal symptoms (malaise, gastrointestinal distress), have been reported. These symptoms may appear as early as after the first dose of Ketek. You should be aware of the potential effect of these symptoms on your ability to drive or operate machinery.

3. HOW TO TAKE KETEK

Your doctor will tell you how many Ketek tablets to take, at what time and for how long.

The recommended dose of Ketek for adults and children of 12 years and older two tablets of 400 mg once daily (800 mg once daily).

If you have severe renal insufficiency you should take alternating daily doses of 800 mg (two tablets of 400 mg) and 400 mg (one tablet of 400 mg), starting with the 800 mg dose.

Swallow the tablets whole with a glass of water.

It is best to take tablets at the same time each day.

The length of time for which you have to take Ketek tablets is usually between 5 to 10 days.

If you take more Ketek than you should

If you accidentally take one tablet too many, nothing is likely to happen. If you accidentally take several tablets too many, contact your doctor or pharmacist. If possible, take your tablets or the box with you to show the doctor or pharmacist.

If you forget to take Ketek

If you forgot to take a dose, take it as soon as possible. However, if it is nearly time for your next dose skip the missed dose and take the next tablet at the usual time.

If you stop taking Ketek

Take the complete course of tablets prescribed by your doctor, even if you begin to feel better before you have finished them all. If you stop taking the tablets too soon, the infection may return, or your condition may get worse.

If you stop taking the tablets too soon you may also create a bacterial resistance to the medicine. If you feel you are suffering from a side effect, tell a doctor immediately to get advice before taking the next dose.

If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines Ketek can cause side effects, although not everybody gets them. Most of them are mild and transient, but very rare cases, of serious adverse liver reactions and liver failure have been reported. So, if any of the following happens, stop taking Ketek and tell your doctor immediately:

- Allergic or skin reactions such as face swelling, general allergic reactions including allergic shock, or serious skin conditions associated with red spots, blisters.
- Severe, persistent or bloody diarrhoea associated with abdominal pain or fever, which can be a sign of serious bowel inflammation which may occur very rarely following treatment with antibiotics.
- Signs and symptoms of hepatitis (liver disease) such as yellowing of skin and eyes, dark urine, itching, loss of appetite or abdominal pain.
- Worsening of a condition called myasthenia gravis, a rare disease which causes muscle weakness.

The above serious side effects are rare (1 out of 10,000 to less than 1 out of 1000 patients) or very rare (less than 1/10,000 patients including isolated report), but may require urgent medical attention.

The other side effects listed below are given with an estimation of the frequency with which they may occur.

The most common side effect (10 or more out of 100 patients) which may occur with Ketek is diarrhoea, usually mild and temporary.

Other side effects which may commonly (1 to 10 out of 100 patients) occur with Ketek are:

- Nausea, vomiting, abdominal pain, flatulence (excess winds), dizziness, headaches, disturbance of taste, vaginal moniliasis (fungal infection associated with local itching, burning and white discharge), increase in liver enzymes (detected by blood test).

Uncommon or rare side effects (1 out of 10,000 to less than 1 out of 100 patients) which may occur with Ketek are:

- Constipation, anorexia (loss of appetite), stomatitis (inflammation or “thrush” in the throat), rash, urticaria (hives), pruritus (itching), eczema, somnolence, insomnia, nervousness, vertigo, paraesthesia (tingling of the hands or feet), muscle cramps, visual disturbances (blurred vision, difficulty in focusing, double vision), disturbance of smell, flushes, transient loss of consciousness (fainting), arrhythmia, bradycardia or palpitations (changes in heart rate or in ECG), hypotension (low blood pressure), eosinophilia (increase of certain white blood cells, detected by blood test).

If any of these undesirable effects are troublesome, severe, or do not wear off as treatment goes on, tell your doctor.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE KETEK .

Keep out of the reach and sight of children.

Do not use Ketek after the expiry date which is stated on the pack..

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Ketek contains

- The active substance is telithromycin
- The other ingredients are microcrystalline cellulose, povidone K25, croscarmellose sodium, magnesium stearate in the tablet core as well as talc, macrogol 8000 , hypromellose 6 cp, titanium dioxide E171, yellow iron oxide E172, red iron oxide E172 in the film-coating.

What Ketek looks like and contents of the pack

Ketek 400 mg tablets are light orange, oblong, biconvex, film-coated tablet imprinted with “H3647” on one side and “400” on the other.

Ketek tablets are presented in blister packs. Two tablets are contained in each blister cavity. They are available in packs of 10, 5x2, 14, 20 and 100 tablets. Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

The marketing authorisation holder of Ketek is:

Aventis Pharma S.A.
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F-92160 ANTONY
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The manufacturer of Ketek is:

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This leaflet was last approved in

US AND EU LABELING MODIFICATIONS

Postapproval labeling modifications, US and EU (01-Apr-04 to 15-Sep-06)

Reference number	Submission date(s)	Scope	Approval date(s)	Supporting document(s)
Dose adjustment for patients with severe renal impairment				
NDA 21-144 S-001	17-Jun-04	To add information re: dose reduction in patients with severe renal impairment and multiple insufficiencies (USPI sections CLINICAL PHARMACOLOGY, PRECAUTIONS, DOSAGE AND ADMINISTRATION)	09-Feb-05	CSR for PK Study A1062 (17-Jun-02) CSR for PK Study A1063 (06-Jun-02)
EMEA/H/C/354/II/37 EMEA/H/C/355/II/37	14-Feb-06	To add PK data re: patients with severe renal impairment (SPC sections sections 5.2 Pharmacokinetic properties, 4.2 Posology and method of administration) To add contraindication re: concomitant administration of TEL with CYP3A4 inhibitors for patients with severe renal or hepatic impairment (SPC section 4.3 Contraindications)	CHMP Opinion: 21-Sep-06 EC Decision: Pending	CSR for PK Study A1062 (17-Jun-02) CSR for PK Study A1063 (06-Jun-02)

Reduced size tablets (300 and 400 mg), removal of 2 excipients (lactose and corn starch)

Reference number	Submission date(s)	Scope	Approval date(s)	Supporting document(s)
NDA 21-144 S-001 NDA 21-144 S-005	17-Jun-04	To add CMC information re: reduced size tablets and 300 mg tablets (USPI sections DESCRIPTION and HOW SUPPLIED; PPI introductory text and section "What is Ketek?")	09-Feb-05 08-Apr-06	CMC data
EMEA/H/C/354/II/24 EMEA/H/C/355/II/24	10-Nov-04	To add CMC information re: reduced size tablets (SPC section 6.1 List of excipients; PIL section 2 BEFORE YOU TAKE KETEK) NB: 300 mg tablets are not registered in EU	CHMP Opinion: 20-Jan-05 EC Decision: 07-Mar-05	CMC data
Potential drug-drug interaction with oral anticoagulants				
NDA 21-144 S-003	05-Jan-05	To add precaution re: potential drug-drug interaction between TEL and oral anticoagulants (USPI section PRECAUTIONS; PPI section "What about other medications I am taking?")	09-Feb-05	Reasoned Statement: <i>Potential for Drug Interaction between Telithromycin and Oral Anticoagulants</i> (13-May-04)
EMEA/H/C/354/II/22 EMEA/H/C/355/II/22	10-Sep-04	To add precaution re: potential drug-drug interaction between TEL and oral anticoagulants (SPC section 4.5 Interaction with other medicinal products and other forms of interaction)	CHMP Opinion: 18-Nov-04 EC Decision: 11-Jan-05	Reasoned Statement: <i>Potential for Drug Interaction between Telithromycin and Oral Anticoagulants</i> (13-May-04)
Postmarketing reports of adverse events: pancreatitis, palpitations, transient loss of consciousness usually associated with vagal syndrome				
NDA 21-144 S-004	25-Oct-05	To add the following AEs: pancreatitis (USPI section	02-Nov-05	Reasoned Statement: <i>Safety Update: Report of Pancreatitis</i>

Reference number	Submission date(s)	Scope	Approval date(s)	Supporting document(s)
		Adverse reactions, subsection Post-Marketing Adverse Events); palpitations (USPI section Adverse reactions, subsection Post-Marketing Adverse Events); LOC (USPI sections PRECAUTIONS and ADVERSE REACTIONS and PPI section "What are the possible side effects of KETEK?")		<i>with Telithromycin Administration (02-Sep-04)</i> Reasoned Statement: <i>Cumulative Review of Syncope and Loss of Consciousness Associated with Telithromycin Use (02-Sep-04)</i> Reasoned Statement: <i>Review of Palpitations (02-Sep-04)</i>
EMEA/H/C/354/II/25 EMEA/H/C/355/II/25	09-Dec-04	To add the following AEs: pancreatitis (SPC section 4.8 Undesirable effects – frequency: very rare); palpitations (in initial SPC as uncommon); LOC (SPC sections 4.7 Effects on ability to drive and use machines and 4.8 Undesirable effects – frequency: rare; PIL sections 2 (BEFORE YOU TAKE KETEK and 4 POSSIBLE SIDE EFFECTS)	CHMP Opinion: 21-Apr-05 EC Decision: 03-Jun-05	Reasoned Statement: <i>Safety Update: Report of Pancreatitis with Telithromycin Administration (02-Sep-04)</i> Reasoned Statement: <i>Cumulative Review of Syncope and Loss of Consciousness Associated with Telithromycin Use (02-Sep-04)</i> Reasoned Statement: <i>Review of Palpitations (02-Sep-04)</i>
EMEA 5-year renewal of marketing authorization				
EMEA/H/C/354/II/34 EMEA/H/C/355/II/34	12-Jan-06	Renewal procedure Editorial changes (SPC, PIL)	CHMP Opinion: 23-Mar-06 EC Decision: 27-Apr-06	<i>Clinical Expert Statement, July 2001-November 2005</i>

Reference number	Submission date(s)	Scope	Approval date(s)	Supporting document(s)
Postmarketing reports of adverse events: additional information re hepatic adverse events				
EMEA/H/C/354/II/36 EMEA/H/C/355/II/36	01-Feb-06	To add postmarketing reports of severe hepatic AEs (SPC sections 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects)	CHMP Opinion: 24-Feb-06 EC Decision: 27-Apr-06	<i>Clinical Overview: An Updated Cumulative Review of Hepatic Adverse Events Reported with Telithromycin (01-Feb-06)</i>
Uncommon adverse event: vertigo				
Initial USPI		Vertigo listed as AE in initial USPI	01-Apr-04	
EMEA/H/C/354/II/35 EMEA/H/C/355/II/35	11-Jan-06	To add uncommon AE vertigo (SPC section 4.8 Undesirable effects; PIL section 4 Possible side effects)	CHMP Opinion: 23-Mar-06 EC Decision: 27-Apr-06	Clinical Overview: <i>Vertigo</i> (Dec-05)
Dose adjustment for patients with severe hepatic impairment				
Initial USPI		PK data re: patients with severe hepatic impairment	01-Apr-04	
EMEA/H/C/354/II/38 EMEA/H/C/355/II/38	17-Feb-06	To add PK data re: patients with severe hepatic impairment (SPC sections 4.2 Posology and method of administration and 5.2 PK properties)	CHMP Opinion: 28-Jun-06 EC Decision: 07-Aug-06	CSR for PK Study A1015 (30-Jul-99) CSR for PK Study A1060 (15-Oct-01)
Adverse event: potential for prolongation of QT/QTc interval				
Initial USPI		Potential for prolongation of QT/QTc interval	01-Apr-04	

Reference number	Submission date(s)	Scope	Approval date(s)	Supporting document(s)
EMEA/H/C/354/II/39 EMEA/H/C/355/II/39	20-Apr-06	To add potential for prolongation of QT/QTc interval (SPC section 4.8 Undesirable effects)	CHMP Opinion: 28-Jun-06 EC Decision: 07-Aug-06	Clinical Overview: <i>Assessment of QTc Prolongation with Telithromycin</i> (29-Mar-06)
Postmarketing reports of adverse events: severe hepatic adverse events and exacerbation of myasthenia gravis with fatal outcome				
NDA 21-144 S-011	29-Jun-06	To add severe hepatic AEs and exacerbation of myasthenia gravis with fatal outcome (USPI sections CONTRAINDICATIONS, WARNINGS, PRECAUTIONS, and ADVERSE REACTIONS; PPI sections "Who should not take KETEK?" and "What are the possible side effects of KETEK?")	29-Jun-06	Briefing Document for 06-Jun-06 DAIOP/OSE/sanofi-aventis Meeting (26-May-06 with erratum 15-Jun-06) <i>Response to Agency Request for Hepatic Expert Assessment of FDA-Defined Cases of Acute Liver Failure Dated June 6, 2006</i> (14-Jun-06) <i>Response to Agency Request for Information on Postmarketing Reports of Exacerbation of Myasthenia Gravis with KETEK® (Telithromycin) Dated June 23, 2006, including Clinical Overview re: Exacerbation of Myasthenia Gravis</i> (12-Jul-06) <i>Update to Telithromycin Risk Management Plan re: Epidemiology Studies of Severe Hepatic Injury</i> (15-Aug-06)

Reference number	Submission date(s)	Scope	Approval date(s)	Supporting document(s)
EMEA/H/C/354/III/40 EMEA/H/C/355/III/40	13-Jul-06	To add severe hepatic AEs and exacerbation of myasthenia gravis with fatal outcome (SPC sections 4.3 Contraindications, 4.4 Special warnings and precautions for use, and 4.8 Undesirable effects; PIL sections 2 Before you take Ketek and 4 Possible side effects)	CHMP Opinion: Pending	Clinical Overview: <i>Documentation in Support of Hepatic Labeling Changes for Telithromycin</i> (07-Jul-06) Addendum to Clinical Overview: Briefing Document for 06-Jun-06 DAIOP/OSE/sanofi-aventis Meeting (erratum 15-Jun-06) Clinical Overview: <i>Exacerbation of Myasthenia Gravis</i> (10-Jul-06)

All CHMP Opinions described above were positive.

USPI = US Prescribing Information; PPI = Patient Package Insert (US); SPC = Summary of Product Characteristics; PIL = Patient Information Leaflet (EU); CSR = clinical study report; PK = Pharmacokinetic; CHMP = Committee of Medicinal Products for Human Use; EC = European Commission; LOC = loss of consciousness; AE = adverse event; DAIOP = Division of Anti-infective and Ophthalmologic Products; OSE = Office of Surveillance and Epidemiology.

EU LABELING MODIFICATIONS

Postapproval labeling modifications, EU (09-Jul-01 to 01-Apr-04)

Reference number	Submission date(s)	Scope	Approval date(s)	Supporting document(s)
Potential drug-drug interaction with rifampicin				
EMEA/H/C/354/III/04 EMEA/H/C/355/III/04	18-Dec-01	To add potential drug-drug interaction with rifampicin (SPC sections 4.4 Special warnings and special precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction)	CHMP Opinion: 21-Mar-02 EC Decision: 07-Jun-02	CSR for PK Study A1058 (11-Apr-01)
Additional information re: visual adverse events				
EMEA/H/C/354/III/10 EMEA/H/C/355/III/10	29-Aug-02	To add information re visual AEs (blurred vision) (SPC section 4.8 Undesirable effects)	CHMP Opinion: 21-Nov-02 EC Decision: 04-Mar-03	CSR for Phase I visual safety Study A1064, (30-May-02) CSR for follow-up Phase I visual safety Study A1066 (23-Jul-02)
Pharmacokinetic data re: telithromycin concentration in sinus tissue				
EMEA/H/C/354/III/11 EMEA/H/C/355/III/11	29-Aug-02	To add PK data re: TEL concentration in sinus tissue (SPC section 5.2 Pharmacokinetic properties)	CHMP Opinion: 21-Nov-02 EC Decision: 04-Mar-03	CSR for PK Study A1501 (date)
Potential drug-drug interaction with metoprolol				
EMEA/H/C/354/III/12 EMEA/H/C/355/III/12	10-Jan-03	To add potential drug-drug interaction with metoprolol (SPC sections 4.4 Special warnings and special precautions for use and 4.5 Interaction with other medicinal products and other forms of interaction)	CHMP Opinion: 19-Mar-03 EC Decision: 09-Jul-03	CSR for PK Study A1061 (21-May-02)

Reference number	Submission date(s)	Scope	Approval date(s)	Supporting document(s)
Postmarketing reports of adverse events: exacerbation of myasthenia gravis				
EMEA/H/C/354/III/14 EMEA/H/C/355/III/14	18-Apr-03	To add postmarketing reports of exacerbation of myasthenia gravis (SPC sections 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects; PIL sections 2 Before you take Ketek and 4 Possible side effects)	CHMP Opinion: 24-Jun-03 EC Decision: 08-Oct-03	Reasoned Statement: <i>Reports of Myasthenia Gravis with Telithromycin Use</i>
Very rare adverse events: hepatitis, angioneurotic oedema, anaphylactic reactions				
Additional information re: visual adverse events				
EMEA/H/C/354/III/15 EMEA/H/C/355/III/15	18-Apr-03	To add very rare AEs hepatitis, angioneurotic oedema, and anaphylactic reactions including anaphylactic shock (SPC section 4.8 Undesirable effects) To add information re: visual AEs (SPC section 4.7 Effects on ability to drive and use machines; PIL section 4 Possible side effects)	CHMP Opinion: 22-Oct-03 EC Decision: 27-Jan-04	Reasoned Statement: <i>Anaphylactic Reactions and Angioedema (15-Oct-02)</i>
Additional information re: phospholipidosis				
EMEA/H/C/354/III/16 EMEA/H/C/355/III/16	18-Apr-03	To add information re: phospholipidosis (SPC section 5.3 Preclinical safety data)	CHMP Opinion: 24-Jun-03 EC Decision: 08-Oct-03	<i>Information on the histopathologic review of repeated-dose oral toxicity studies in rats and dogs (18-Oct-02)</i>

All CHMP Opinions described above were positive.

SPC = Summary of Product Characteristics; PIL = Patient Information Leaflet (EU); CSR = clinical study report; PK = Pharmacokinetic; CHMP = Committee of Medicinal Products for Human Use; EC = European Commission; LOC = loss of consciousness; AE = adverse event.