

# Data Sheet

## KETEK™

### Name of the Medicine

### Non-proprietary Name

Telithromycin

### CAS Number

The CAS number is 173838-31-8.

### Description

KETEK tablets contain telithromycin, a novel semisynthetic ketolide antibacterial with broad-spectrum activity.

Chemically, telithromycin is designated as 11,12-dideoxy-3-de [(2,6-dideoxy-3-C-methyl-3-O-methyl- $\alpha$ -L-ribo-hexopyranosyl) oxy]6-O-methyl-3-oxo-12, 11-[oxycarbonyl[[4-[4-(3-pyridinyl)-1H-imidazol-1-yl]butyl]imino]]erythromycin.

Telithromycin differs chemically from the macrolide-azalide group of antibacterials by the substitution of a keto function at position 3 of the macrolactone ring in place of a cladinose moiety. In addition, telithromycin also possesses a novel 11-12- carbamate extension.

The empirical formula of telithromycin is  $C_{43}H_{65}N_5O_{10}$  and its molecular weight is 812.03.

### Pharmacology

**Mechanism of Action** Telithromycin belongs to a new chemical family, the ketolides. Ketolides are recent additions to the macrolide-lincosamide streptogramin (MLSB) class. Telithromycin exerts its antimicrobial effects by inhibiting bacterial protein synthesis. This occurs not only by directly blocking translation of the bacterial 23S ribosomal RNA but also by inhibiting the assembly of new bacterial ribosomes. Telithromycin has been shown to bind more tightly to the bacterial ribosome than erythromycin, 10-fold more tightly in erythromycin-susceptible ribosomes and >20-fold more tightly in MLSB-resistant ribosomes (data from *Escherichia coli*).

This enhanced binding appears to be related to the presence of the C11-12 side chain, and correlates with the distinctly different modes of interaction that telithromycin and erythromycin exhibit in domain II of the 23S ribosomal RNA. It may also explain the high activity of telithromycin against common pathogens and its ability to overcome cross-resistance in gram-positive cocci. Telithromycin is highly concentrated in phagocytes and has good activity against atypical respiratory pathogens.

### Pharmacokinetics

#### Absorption

Following oral administration, telithromycin is rapidly absorbed. It has an absolute bioavailability of approximately 57%. The rate and extent of absorption are unaffected by food intake, and thus KETEK tablets can be given with or without food.

In fasting healthy adult subjects, peak plasma telithromycin concentrations of approximately 2 µg/mL are attained within 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 and are approximately 1.5 times the single-dose concentration after 7 days of dosing. After the last dose, the mean terminal elimination half-life of telithromycin is 10 hours.

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

Parameter	Single dose (n=18)	Multiple dose (n=18)
C <sub>max</sub> (µg/mL)	1.9	2.27
T <sub>max</sub> (h)*	1.0	1.0
AUC (0-24) (µg.h/mL)	8.25	12.5
Terminal t <sub>1/2</sub> (h)	7.16	9.81
C <sub>24h</sub> (µg/mL)	0.03	0.07

\* Median values

C<sub>24h</sub> =Plasma concentration at 24 hours postdose

In a patient population of 219 subjects, mean peak and trough plasma concentrations were 2.9 and 0.2 µg/mL after 3 to 5 days of KETEK 800 mg once daily.

### Distribution

Over a clinically relevant concentration range, total *in vitro* protein binding is approximately 60% to 70% and is primarily due to human serum albumin with some involvement of α1-acid glycoprotein and lipoproteins.

Telithromycin is widely distributed throughout the body. Rapid distribution of telithromycin into tissues results in significantly higher telithromycin concentrations in most target tissues than in plasma. Plasma, bronchial mucosa, epithelial lining fluid, and tonsil telithromycin concentrations after 800 mg once-daily dosing for 5 days are shown below.

	Hours- postdose	Concentration (µg/mL)			
		Tissue or fluid	Plasma	Ratio	
Bronchial mucosa	2	3.88	1.86	2.11	
	Epithelial lining fluid	2	5.4	1.07	4.8
		8	4.2	0.605	6.5
		24	1.17	0.073	14.3
Tonsils	3	3.95*	1.22	3.38	
	12	0.88*	0.23	7.1	
	24	0.72*	0.058	13.1	

\*Units in mg/kg

Telithromycin is rapidly concentrated by white blood cells and is eliminated more slowly from white blood cells than from plasma. Mean white blood cell concentrations of telithromycin peaked at 72.1 µg/mL and remained at 14.1 µg/mL 24 hours after 5 days of repeated dosing of 600 mg once daily. After 10 days, repeated dosing of 600 mg once daily, white blood cell concentrations remained at 8.9 µg/mL 48 hours after the last dose. Similarly, telithromycin is eliminated slowly from alveolar macrophages with concentrations of 41 µg/mL at 24 hours after repeated doses of 800 mg once daily. The mean concentration of telithromycin in white blood cells and alveolar macrophages is summarized in the table below.

Cell type	Hours postdose	Dose (mg)	n	Concentration (µg/mL)		
				Intracellular	Plasma	Ratio
White blood cells	2	600	5	64.6	0.775	87
	6	600	5	72.1	0.201	380
	12	600	5	39.4	0.049	1046
	24	600	5	14.1	0.014	1085
Alveolar macrophages	2	800	5	65	1.07	55
	8	800	6	100	0.605	180
	24	800	6	41	0.073	536

### Metabolism

Telithromycin is primarily metabolized in the liver by cytochrome P450 3A4 (CYP3A4) and to a lesser extent by cytochrome P450 1A (CYP1A) and displays a competitive inhibition of CYP3A4. Telithromycin is also a competitive inhibitor of CYP2D6. *In vitro* studies showed no formation of inhibitor complexes with CYP450. After oral administration, two thirds of the dose was eliminated as metabolites and one third remained unchanged. The main circulating compound in plasma is telithromycin. Its principle metabolite (resulting from the loss of aryl rings of the lateral chain) is present in concentrations of approximately 13% of telithromycin and has little antimicrobial activity compared with the parent drug. Other minor metabolites have been identified in plasma, all with concentrations less than 3% of telithromycin.

### Elimination

After administration of radiolabeled telithromycin, 76% of the radioactivity was recovered from faeces, with an additional 17% recovered from the urine. Approximately one third of telithromycin was eliminated unchanged, 20% in faeces and 12% in urine. The total clearance is approximately 71 L/hr with renal clearance accounting for 17% of this.

### **Microbiology**

Telithromycin shows a bactericidal activity against *Streptococcus pneumoniae* (including penicillin and erythromycin resistant strains), *Streptococcus pyogenes*, *Haemophilus influenzae*, and *Legionella pneumophila*.

Telithromycin exhibits activity against *S. pneumoniae* irrespective of the susceptibility of the isolates to other antibacterial classes, eg, penicillins, cephalosporins, macrolides, and fluoroquinolones.

Telithromycin also retains enhanced activity against *S. pneumoniae* resistant to macrolides regardless of mechanism of resistance.

In addition, telithromycin does not induce MLSB resistance *in vitro*, an attribute related to its novel 3 keto function. It has been shown *in vitro* that resistance to telithromycin due to spontaneous mutation is a rare occurrence.

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

**Aerobic gram-positive microorganisms**

*Staphylococcus aureus* (methicillin and erythromycin susceptible strains)

*S. pneumoniae* (penicillin- and erythromycin- susceptible and resistant strains)

*S. pyogenes*

Streptococci (Groups C and G)

**Aerobic gram-negative microorganisms**

*Haemophilus influenzae*

*H. parainfluenzae*

*Moraxella catarrhalis*

**Other microorganisms**

*Chlamydia pneumoniae*

*Legionella pneumophila*

*Mycoplasma pneumoniae*

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

Telithromycin exhibits *in vitro* minimum inhibitory concentrations (MICs) of 1 µg/mL or less against most (90%) strains of the following microorganisms; however the safety and effectiveness of telithromycin in treating clinical infections due to these microorganisms have not been established in clinical trials.

**Aerobic gram-positive microorganisms**

*Staphylococcus aureus* (methicillin- and erythromycin- resistant strains)

*Streptococcus agalactiae*

*Viridans streptococci*

Coagulase negative staphylococci (methicillin and erythromycin susceptible strains)

*Enterococcus faecalis*

*Enterococcus faecium*

*Listeria monocytogenes*

*Corynebacterium diphtheriae*

**Aerobic gram-negative microorganisms**

*Neisseria meningitidis*

*Bordetella pertussis*

**Anaerobic bacteria**

Porphyromonas spp.

Prevotella spp.

Peptostreptococcus spp.

**Other microorganisms**

*Chlamydia psittaci*

*Coxiella burnetti*

*Francisella tularensis*

Legionella spp.

**Susceptibility tests**

**Dilution techniques:**

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

For testing Staphylococci, Enterococci, and Streptococci including *Streptococcus pneumoniae*<sup>a</sup>:

<b>MIC (µg/mL)</b>	<b>Interpretation</b>
≤1.0	Susceptible (S)
2.0	Intermediate (I)
≥4.0	Resistant (R)

a This interpretive standard is applicable to test performed on Mueller-Hinton agar with 5% sheep blood and incubated in 6% CO<sub>2</sub>.

For testing *Haemophilus influenzae*<sup>b</sup>:

<b>MIC (µg/mL)</b>	<b>Interpretation</b>
≤2.0	Susceptible (S)
4.0	Intermediate (I)
≥8.0	Resistant (R)

b This interpretive standard is applicable to test performed on HTM agar and incubated in 6% CO<sub>2</sub>.

A report of “Susceptible” indicates that the pathogen is likely to be inhibited if the antimicrobial compound in blood reaches the concentrations usually attainable.

A report of “Intermediate” indicates that the result should be considered unclear and the test repeated if the microorganism is not completely susceptible to alternative drugs.

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 pathogen is not likely to be inhibited if the antimicrobial compound in the blood reaches the concentrations usually attainable and that other therapy should be selected. Standardized susceptibility test procedures require the use of laboratory control microorganisms to control the technical aspects of the laboratory procedures.

Standard telithromycin powder should provide the following MIC values:

<b>Microorganism</b>		<b>MIC (µg/mL)</b>
Staphylococcus aureus	ATCC 29213	0.06 – 0.25
S. aureus	ATCC 25923	NA
Enterococcus faecalis	ATCC 29212	0.015 – 0.12
Streptococcus pneumoniae	ATCC 49619 <sup>c</sup>	0.008 – 0.03
Haemophilus influenzae	ATCC 49247 <sup>d</sup>	1.0 – 4.0

<sup>c</sup> This quality control range is applicable to only S. pneumoniae ATCC 49619 tested on Mueller-Hinton agar with 5% sheep blood and incubated in 6% CO<sub>2</sub>.

<sup>d</sup> This quality control range is applicable to only H. influenzae ATCC 49247 tested on HTM agar and incubated in 6% CO<sub>2</sub>.

#### **Diffusion techniques:**

Quantitative methods that require measurement of zone diameters also provide reproducible estimates of the susceptibility of bacteria to antimicrobial compounds. One such standardized procedure 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. Reports from the laboratory providing results of the standard single-disk susceptibility test with a 15 µg telithromycin disk should be interpreted according to the following criteria:

The following zone diameter interpretive criteria should be used for testing Staphylococci and Enterococci species:

<b>Zone diameter (mm)</b>	<b>Interpretation</b>
≥22	Susceptible (S)
20-21	Intermediate (I)
≤19	Resistant (R)

For testing Streptococcus pneumoniae<sup>e</sup>:

<b>Zone diameter (mm)</b>	<b>Interpretation</b>
≥19	Susceptible (S)
16-18	Intermediate (I)
≤15	Resistant (R)

<sup>e</sup> This interpretive standard is applicable to test performed on Mueller-Hinton agar with 5% sheep blood and incubated in 6% CO<sub>2</sub>.

For testing *Haemophilus influenzae*:

Zone diameter (mm)	Interpretation
≥16	Susceptible (S)
14-15	Intermediate (I)
≤13	Resistant (R)

† This interpretive standard is applicable to test performed on HTM agar and incubated in 6% CO<sub>2</sub>.

Interpretation should be as stated above for results using dilution techniques. Interpretation involves correlation of the diameter obtained in the disk test with the MIC for telithromycin.

As with standardized dilution techniques, diffusion methods require the use of laboratory control microorganisms that are used to control the technical aspects of the laboratory procedures.

For the diffusion technique, the 15 µg telithromycin disk should provide the following zone diameters in these laboratory test quality control strains:

Microorganism		Zone diameter (mm)
Staphylococcus aureus	ATCC 29213	NA
S. aureus	ATCC 25923	24 – 30
Enterococcus faecalis	ATCC 29212	NA
Streptococcus pneumoniae	ATCC 49619 <sub>g</sub>	27 - 33
Haemophilus influenzae	ATCC 49247 <sub>h</sub>	17 - 23

g These quality control limits are applicable to only *S. pneumoniae* ATCC 49619 tested on Mueller-Hinton agar with 5% sheep blood and incubated in 6% CO<sub>2</sub>.

h These quality control limits are applicable to only *H. influenzae* ATCC 49247 tested on HTM agar and incubated in 6% CO<sub>2</sub>.

## Indications

KETEK tablets are indicated for the treatment of Community-Acquired Pneumoniae of mild to moderate severity, due to *S. pneumoniae*, including strains resistant to penicillin and erythromycin A, *H. influenzae*, *H. parainfluenzae*, *M. catarrhalis*, *C. pneumoniae*, *L. pneumophila*, *M. pneumoniae* and *S. aureus* in patients 18 years and older.

## 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 and ergot alkaloids derivatives must not be co-administered

Concomitant administration of KETEK and cisapride, astemizole or terfenadine is contraindicated.

KETEK is contraindicated in patients with myasthenia gravis

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

## Pimozide

When clarithromycin was co-administered with pimozide, there were postmarketing reports of fatal drug interactions involving cardiac arrhythmias (QT prolongation, ventricular tachycardia, ventricular fibrillation, and torsades de pointes). This was most likely due to inhibition of hepatic metabolism of pimozide by clarithromycin. Although there are no studies looking at the interaction between KETEK and pimozide, there is a potential risk for similar interactions between pimozide and drugs metabolized by the CYP3A pathway including KETEK. Therefore, concomitant administration of KETEK and pimozide is contraindicated.

## **Precautions**

### **General**

Pseudomembranous colitis has been reported with nearly all antibacterial agents and may range in severity from mild to life-threatening. Therefore it is important to consider this diagnosis in patients who present with diarrhoea 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 a toxin produced by *Clostridium difficile* is 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 Effects**).

### **Hepatic Effects**

Alterations in hepatic enzymes have been commonly observed in clinical studies with telithromycin.

Post-marketing cases of severe hepatitis and liver failure, in some cases fatal, which have generally been associated with serious underlying diseases or concomitant medications, have been reported. These hepatic reactions were observed during or shortly after treatment, and in most cases were reversible after discontinuation of telithromycin.

Physicians and patients should watch for signs and symptoms of hepatic disease, such as anorexia, jaundice, dark urine, pruritus or tender abdomen. In case of signs and symptoms of hepatitis, patients must be advised to stop treatment and contact their doctor.

### **QTc Interval Prolongation**

Telithromycin may have the potential to prolong the QTc interval of the electrocardiogram in some patients. Telithromycin should be avoided in patients with congenital prolongation of the QTc interval, with uncorrected hypokalemia ( $\leq 3$  mmol/L (mEq/L)), hypomagnesemia, bradycardia (<50 bpm) and/or in patients receiving Class IA (e.g. quinidine or procainamide) or Class III (e.g. dofetilide) antiarrhythmic agents.

## **Visual Disturbances**

KETEK may cause visual disturbances (<1%) particularly in slowing the ability to accommodate and the ability to release accommodation. Visual disturbances included blurred vision, difficulty focusing and diplopia. Most events were mild to moderate; however, severe cases have been reported.

## **Loss of Consciousness**

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

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

## **Statins**

The risk of myopathy and rhabdomyolysis may be increased with high statin plasma levels. Therefore, concomitant administration of KETEK with statins primarily metabolised by CYP3A4 should be avoided.

## **Effects on Fertility**

A study to investigate possible effects on fertility and early embryonic development was carried out in the rat at doses of 0, 50, 150, 300 mg/kg/day. No evidence of impaired fertility was observed at doses estimated to be 3.8 times (50 mg/kg/day) the daily human dose of 800 mg.

## **Use in Pregnancy (Category B)**

Telithromycin was not teratogenic in the rat or rabbit. Reproduction studies have been performed in the rat (doses of 0, 50, 150, 300 mg/kg/day) and rabbit (doses of 0, 20, 60, 180 mg/kg/day) with effects on pre/post natal development studied in the rat (doses of 0, 50, 125, 200 mg/kg/day). At doses estimated to be 11.5 times (150 mg/kg) and 1.5 times (20 mg/kg) the daily human dose of 800 mg in the rat and rabbit, respectively, no evidence of foetal harm was observed. At doses higher than 150 mg/kg and 20 mg/kg in rats and rabbits, respectively, maternal toxicity resulted in delayed foetal maturation. No adverse effects on prenatal and neonatal development of rat pups were observed at 9.6 times (125 mg/kg/day) the daily human dose.

There are no studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

## **Use in Lactation**

It is not known whether telithromycin is excreted in human milk, however, it is excreted in animal milk. Pre-weaned rats, exposed indirectly via consumption of milk from dams treated with 200 mg/kg/day for 3 weeks, were not adversely affected, despite data indicating higher drug levels in milk than in plasma. Because many drugs are excreted in human milk, caution should be exercised when KETEK is administered to a nursing mother.

## Paediatric Use

Clinical trials to establish safety and effectiveness of KETEK did not include paediatric patients 12 years and under.

## Use in the Elderly

In the 10 Phase III clinical trials (n=2461), KETEK was administered to 278 patients who were 65 years and older, including 77 patients who were 75 years and older. Efficacy and safety were similar to that observed in younger patients.

However greater sensitivity of some older individuals cannot be ruled out.

## Carcinogenicity and Mutagenicity

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

## Interactions with other Medicines

The potential for pharmacokinetic drug interactions between KETEK and cisapride, digoxin, theophylline, itraconazole, ketoconazole, warfarin, oral contraceptives, ranitidine, antacids (containing aluminium and magnesium hydroxide), and paroxetine has been studied. There was no clinically significant effect of KETEK on warfarin, oral contraceptives, and paroxetine. There was no effect of ranitidine and antacids on KETEK. KETEK did not have a clinically relevant pharmacokinetic interaction with theophylline. However, like macrolide antibiotics, KETEK was shown to interact with itraconazole, ketoconazole, digoxin, and cisapride. Further information is described below.

### CYP450 Inhibition

Telithromycin is primarily metabolised by cytochrome P450 3A4 (CYP3A4) and to a lesser extent by cytochrome P450 1A (CYP1A). *In vitro*, telithromycin is an inhibitor of CYP3A4. Caution should be exercised during concomitant administration of other drugs that are CYP3A4 substrates.

Treatment with KETEK should be avoided during and 2 weeks after treatment with CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine, St John's wort).

### Cisapride

Peak plasma concentrations of cisapride (an agent with the potential to increase QT interval) were increased by 100% when co-administered with repeated doses of KETEK, resulting in significant increases in the QTc interval. Therefore, the concomitant administration of KETEK and cisapride is contraindicated. (see **Contraindications**)

### Digoxin

KETEK has been shown to increase the plasma concentrations of digoxin. The plasma peak and trough levels were increased by 73% and 21%, respectively, in healthy volunteers. Nevertheless there were no significant changes in ECG parameters and no signs of digoxin toxicity were observed. Monitoring of serum digoxin level should be considered during concomitant administration of digoxin and KETEK.

### Metoprolol

In patients treated with metoprolol for heart failure, the increased exposure to metoprolol, a CYP2D6 substrate, may be of clinical importance. Therefore, co-administration of KETEK and metoprolol in patients with heart failure should be considered with caution.

### Statins

Patients concomitantly treated with statins should be carefully monitored for signs and symptoms of myopathy and rhabdomyolysis.

The risk of myopathy and rhabdomyolysis may be increased with high levels of simvastatin. Therefore, concomitant administration of KETEK with simvastatin or other statins primarily metabolised by CYP3A4 should be avoided. Telithromycin may be expected to produce a similar interaction with lovastatin and a lesser extent with atorvastatin. KETEK slightly inhibits the *in vitro* transporter uptake of pravastatin however the *in vivo* relevance of this finding has not been established. Fluvastatin is metabolised by CYP2C9 rather than CYP3A4, therefore no drug interaction is expected.

### Theophylline

There was no clinically relevant pharmacokinetic interaction between KETEK and theophylline extended release formulation. However, the administration of both drugs should be separated by 1 hour in order to avoid local digestive side effects.

### Itraconazole

A multiple-dose interaction study with itraconazole, a CYP3A4 inhibitor, and KETEK showed that maximum plasma concentrations of telithromycin were increased by 22% and AUC by 54% when co-administered with itraconazole. This interaction does not necessitate a dosage adjustment.

### Ketoconazole

A multiple-dose interaction study with ketoconazole, a CYP3A4 inhibitor, and KETEK showed that maximum plasma concentrations of telithromycin were increased by 51% and AUC by 95%. The maximum ketoconazole plasma concentrations and AUC were both decreased by 20% when co-administered with KETEK. This interaction does not necessitate a dosage adjustment.

### Warfarin

There was no pharmacodynamic or pharmacokinetic interaction of KETEK with racemic warfarin in healthy subjects.

### Oral Anticoagulants

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.

### Oral Contraceptives

Based on a pharmacokinetic interaction study, KETEK did not interfere with the antiovolatory effect of oral contraceptives.

### Ranitidine, Antacid

There was no clinically relevant interaction of ranitidine or antacids containing aluminium and magnesium hydroxide on KETEK.

### Paroxetine

There was no pharmacokinetic interaction of KETEK with paroxetine, a CYP2D6 substrate.

### Benzodiazepines

Concomitant administration of telithromycin with intravenous or oral midazolam resulted in 2- and 6-fold increases, respectively in the AUC of midazolam. 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 metabolised by CYP3A4.

### Sotalol

Telithromycin has been shown to decrease  $C_{max}$  by 34% and AUC of sotalol by 20% due to decreased absorption.

### Ergot Alkaloids

Reactions of ergotism with possible peripheral necrosis have been reported after concomitant therapy of macrolides with vasoconstrictive ergot alkaloids, particularly ergotamine and dihydroergotamine. Because a clinical interaction with telithromycin cannot be excluded, administration of telithromycin to patients taking ergot alkaloids is contraindicated.

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. Until further data are developed regarding drug interactions when KETEK and these drugs are used concomitantly, careful monitoring of patients is advised:

Drugs metabolized by the cytochrome P450 system such as: carbamazepine, cyclosporine, disopyramide, hexobarbital, phenytoin, quinidine, and triazolam.

Effect on Laboratory Tests There are no reported laboratory test interactions.

## **Adverse Effects**

Out of 2461 patients in all the Phase III trials (n=1889 in controlled trials) treated with KETEK 800 mg once daily for 5 days or 7 to 10 days, approximately 35% of patients experienced adverse reactions. Most of these events were mild to moderate in severity. In the controlled studies, discontinuation due to a possible related treatment-emergent adverse event occurred in 4.0% of KETEK-treated patients. Most discontinuations in the KETEK groups were due to treatment emergent adverse events in the gastrointestinal body system, primarily diarrhoea (1.0%), nausea (1.0%), and vomiting (1.0%).

Treatment-emergent adverse reactions judged by investigators to be at least possibly drug related and occurring in  $\geq 2.0\%$  of all KETEK-treated patients were: diarrhoea (12.9%), nausea (7.3%), dizziness (3.0%), vomiting (2.6%), and headache (2.1%).

Additional events, judged by investigators to be at least possibly drug related that occurred in  $\geq 0.1\%$  and  $< 2\%$  of KETEK-treated patients were:

### Gastrointestinal System

Dyspepsia, abdominal pain, flatulence, constipation, gastroenteritis, gastritis, abnormal stools, anorexia, oral moniliasis, glossitis, fullness, stomatitis, sore mouth.

### Liver and Biliary System

Increased liver enzymes (ALT, AST, alkaline phosphatase)

### Nervous System

Dry mouth, somnolence, insomnia, vertigo, nervousness, abnormal dreams

### Body as a Whole

Asthenia, allergic reaction

### Special Senses

Taste perversion, blurred vision, abnormal vision

### Urogenital System

Vaginal moniliasis, vaginitis, creatinine clearance decreased

### Skin

Rash, pruritus, dry skin, urticaria

### Haematologic

Thrombocytosis, eosinophilia, leukopenia, anaemia

### Metabolic

Hyperkalaemia

### Cardiovascular

Vasodilatation, QT interval prolonged

### Other Uncommon and Rare Events Included

Pseudomembranous colitis, esophagitis, tooth discoloration, cholestatic jaundice, hepatitis, hepatic dysfunction, face oedema, paresthesia, tremor, parosmia, erythema multiforme, eczema, severe allergic reactions (including angioedema and anaphylaxis), atrial arrhythmia, hypotension, bradycardia, palpitations, muscle cramps, exacerbation of myasthenia gravis, pancreatitis, transient loss of consciousness.

There have been reports of visual disturbances associated with the use of KETEK, including blurred vision, difficulty focusing and diplopia. Most events were mild to moderate. Typically visual events 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.

### Postmarketing experience

In addition, the following undesirable effects have been reported: QT/QTc interval prolongation, severe liver failure (which have generally been associated with serious underlying diseases or concomitant medications), hypersensitivity, erythema multiforme, face edema, pancreatitis, transient loss of consciousness/syncope which may be

preceded by vagal symptoms, confusion, hallucination, ageusia, anosmia, arthralgia and myalgia.

## Dosage and Administration

KETEK tablets can be taken with or without food.

<b>Infection</b>	<b>Daily dose and route of administration</b>	<b>Frequency of administration</b>	<b>Duration of treatment</b>
Community-acquired Pneumonia	800 mg oral (2 tablets)	once daily	7-10 days

Impaired renal function: No dosage adjustment for KETEK is necessary in patients with mild, moderate, or severe renal impairment. For haemodialysis patients, on dialysis days, KETEK tablets should be given after each dialysis session.

Impaired hepatic function: No dosage adjustment is required in patients with mild, moderate, or severe hepatic impairment.

## Special populations

### Gender

In 18 healthy young volunteers (20 to 34 years of age) and in 14 healthy elderly volunteers (65 to 92 years of age) given single and multiple doses of 800 mg KETEK™, there was no statistical difference between males and females in mean AUC, C<sub>max</sub> and elimination half-life.

### Hepatic Insufficiency

In 12 patients with mild to severe hepatic insufficiency, the maximum plasma concentration and AUC of telithromycin were not affected compared to normal healthy subjects. The terminal elimination half-life was increased by 40%; however, no special dosage adjustments of KETEK are required.

### Renal Insufficiency

In 20 patients with mild to severe renal impairment, C<sub>max</sub> and AUC values increased by an average of 37 to 38% and 41 to 52%, respectively, compared to normal healthy subjects. The increases are not clinically significant. Patients with end-stage renal failure (n=10) had mean C<sub>max</sub> and AUC values very similar to normal healthy subjects. No special dosage adjustments are required. For haemodialysis patients, on dialysis days, KETEK tablets should be given after each dialysis session.

### Geriatric

In subjects aged 65 to 92 years (n=14), plasma telithromycin C<sub>max</sub> and AUC were increased 100% and 120%, respectively, compared to healthy adults aged 19 to 29 (n=12) after multiple dosing. There was no statistically significant change in the elimination half-life. During Phase III trials, elderly subjects (n=278) received the same

telithromycin dose (800 mg) as younger subjects with no differences in safety and efficacy noted between the groups. No dosage adjustment is required.

### Paediatric

The pharmacokinetics of KETEK in paediatric populations 12 years of age and under have not been studied. In clinical trials, population pharmacokinetic analysis including limited data (n=20) 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 60 years of age (n=1329).

### **Overdosage**

In animal studies, telithromycin had low acute toxicity with a LD50 value in the range of 1500-2000 mg/kg in the mouse and a minimum lethal dose of greater than 2000 mg/kg in the rat. No clinical signs were observed in rats; in mice, hypotonia was seen at 1500 mg/kg and above, with tremors prior to death.

In the event of acute overdosage, the stomach should be emptied by inducing vomiting or gastric lavage. The patient should be carefully observed and given symptomatic and supportive treatment. Adequate hydration should be maintained.

The effectiveness of haemodialysis in an overdose situation with KETEK is unknown.

### **Presentation and Storage Conditions**

KETEK 400 mg tablets are light-orange, oval, film-coated tablets, imprinted with "H3647" on one side and "400" on the other side. The following inactive ingredients are present: maize starch, croscarmellose sodium, hydroxypropyl methylcellulose, lactose monohydrate, magnesium stearate, microcrystalline cellulose, polyethylene glycol, povidone, iron oxide red, talc, titanium dioxide, and iron oxide yellow.

Telithromycin is a white to off-white crystalline powder, very slightly soluble in water and freely soluble in methanol, ethanol and acetone.

The tablets are supplied in PVC/Alu blister packs of 2, 10 and 14 tablets. Each blister cavity contains 2 tablets.

Blister: Store in the original package. Store below 30 °C.

### **Medicine Classification**

Prescription Only Medicine

### **Name and Address of the Sponsor**

sanofi-aventis new zealand limited  
56 Cawley Street  
Ellerslie, Auckland, New Zealand

### **Date of Preparation**

4 March 2009