In patients of 12 to 18 years old, the treatment regimen will be:
- Tonsillitis/pharyngitis caused by *Streptococcus pyogenes:* 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

Ketek is contraindicated in patients with myasthenia gravis (see section 4.4).

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

Ketek must not be used in patients with previous history of hepatitis and/or jaundice associated with the use of telithromycin.

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

Ketek should not be used concomitantly with simvastatin, atorvastatin and lovastastin. -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.

Exacerbations of myasthenia gravis haves been reported in patients ~~with myasthenia gravis~~ treated with telithromycin and ~~sometimes. This usually~~ occurred within ~~one to three~~ 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 (see section 4.8).~~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, including fatal cases (which have generally been associated with serious underlying diseases or concomitant medications), 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 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. (see sections 4.7 and 4.8).

There have been post-marketing adverse event reports of transient loss of consciousness including some cases associated with vagal syndrome (see sections 4.7 and 4.8).

Consideration may be given to taking Ketek at bedtime, to reduce the potential impact of visual disturbances and loss of consciousness.

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, pimozide, 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 simvastatine 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, atorvastastin 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 CYP34A4 substrates. Thus, when initiating telithromycin in patients already receiving any of theses 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, metropolol Cmax 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). Because of potential visual difficulties or loss of consciousness, patients should attempt to minimize activities such as driving a motor vehicle, operating heavy machinery or engaging in other hazardous activities during treatment with Ketek. If patients experience visual disorders or loss of consciousness while taking Ketek, patients should not drive a motor vehicle, operate heavy machinery or engage in other hazardous activities (see sections 4.4 and 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 *Candida* infection, 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 *Candida* infection			

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 (see sections 4.4 and 4.7).
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 ΔQTc >30 msec in 7.6% and 7.0% of cases, respectively. No patient in either group developed a ΔQTc >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 (see section 4.4)
-Nervous system disorders: Cases of rapid onset of exacerbation of myasthenia gravis have been reported (see sections 4.43 and 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 >2mg/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 (ß haemolytic) streptococci
Streptococcus agalactiae
Streptococcus pneumoniae *
Viridans group streptococci

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

* Clinical efficacy has been demonstrated for susceptible isolates in the approved clinical indications.
$ natural intermediate susceptibility
+Among MRSA the rate of MLSBc resistant strains is more than 80%, telithromycin is not active against MLS_Bc.

Resistance

Telithromycin does not induce MLS_B resistance in vitro to *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus 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 *Streptococcus pneumoniae*, there is no cross- or co-resistance between telithromycin and other antibacterial classes including erythromycin A and/or penicillin resistance-.

For *Streptococcus 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 ±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 $(0\text{-}24)_{ss}$ 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 sotalol. 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 ~~authorizaton~~ authorisation: 9 July 2001
Date of first renewal: 9 July 2006

10. DATE OF REVISION OF THE TEXT

PACKAGE LEAFLET

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

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

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. In adolescents of 12 years and older, Ketek can be used to treat: infections of the throat. In adults, Ketek can be used to treat infections of the 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 suffer from myasthenia gravis, a rare disease which causes muscle weakness.
- 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 have had a hepatitis and/or jaundice while taking Ketek in the past.
- if you are taking certain medicinal products to control the blood level of cholesterol or other lipids.
- if you or someone in your family 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)
  - pimozide (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)