

**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

Medicinal product no longer authorised

## 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 the full list of excipients, see section 6.1.

## 3. PHARMACEUTICAL FORM

Film-coated tablet.

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

## 4. CLINICAL PARTICULARS

### 4.1 Therapeutic indications

When prescribing Ketek, consideration should be given to official guidance on the appropriate use of antibacterial agents and the local prevalence of resistance (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).
- When treating infections caused by known or suspected beta-lactam and/or macrolide resistant strains (according to history of patients or national and/or regional resistance data) covered by the antibacterial spectrum of telithromycin (see sections 4.4 and 5.1):
  - Acute exacerbation of chronic bronchitis,
  - Acute sinusitis.

*In patients of 12 years and older:*

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

### 4.2 Posology and method of administration

#### Posology

The recommended dose is 800 mg once a day i.e. two 400 mg tablets once a day.

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

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

*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.

### Elderly population

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

### Paediatric population:

The safety and efficacy of Ketek in children below 12 years of age have not been established (see section 5.2). Ketek is not recommended in this population.

### Renal impairment

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 <30 ml/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).

### Hepatic impairment

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

### Method of administration

The tablets should be swallowed whole with a sufficient amount of water. The tablets may be taken with or without food.

Consideration may be given to taking Ketek at bedtime, to reduce the potential impact of visual disturbances and loss of consciousness (see section 4.4).

## **4.3 Contraindications**

Hypersensitivity to the active substance, to any of the macrolide antibacterial agents, or to any of the excipients listed in section 6.1.

Myasthenia gravis (see section 4.4).

Previous history of hepatitis and/or jaundice associated with the use of telithromycin.

Concomitant administration with medicinal products that prolong the QT interval and are CYP3A4 substrates, such as cisapride, pimozide, astemizole, terfenadine, dronedarone, saquinavir (see section 4.5).

Concomitant administration with ergot alkaloid derivatives (such as ergotamine and dihydroergotamine) (see section 4.5).

Concomitant administration with simvastatin, atorvastatin, and lovastatin. Treatment with these agents should be interrupted during Ketek treatment (see section 4.5).

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 azole antifungals (e.g. ketoconazole, fluconazole), is contraindicated.

Concomitant administration of Ketek and colchicine in patients with renal and/or hepatic impairment (see section 4.5).

#### 4.4 Special warnings and precautions for use

##### QT interval prolongation

Due to a potential to increase the QT interval, Ketek should be used with care in patients with coronary heart disease, a history of ventricular arrhythmias, uncorrected hypokalaemia and/or hypomagnesaemia, or bradycardia (<50 bpm), during concomitant administration of Ketek with QT interval prolonging agents, or in patients concomitantly treated with potent CYP 3A4 inhibitors such as protease inhibitors or azole antifungals (e.g. ketoconazole, fluconazole) (see sections 4.3 and 4.5). Ventricular arrhythmias (including ventricular tachycardia, torsade de pointes) have been reported in patients treated with telithromycin and sometimes occurred within a few hours of the first dose (see section 4.8).

##### Clostridium difficile-associated disease

Diarrhoea, particularly if severe, persistent and /or bloody, during or after treatment with Ketek may be caused by pseudomembranous colitis (see section 4.8). If pseudomembranous colitis is suspected, the treatment must be stopped immediately and patients should be treated with supportive measures and/or specific therapy.

##### Myasthenia gravis

Exacerbations of myasthenia gravis have been reported in patients treated with telithromycin and sometimes occurred within a few hours of the first dose. Reports have included death and life threatening acute respiratory failure with rapid onset (see section 4.8).

##### Hepatobiliary disorders

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 medicinal products), 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).

##### Visual disturbances

Ketek may cause visual disturbances particularly in slowing the ability to accommodate and the ability to release accommodation. Visual disturbances included blurred vision, difficulty focusing, and diplopia. Most events were mild to moderate; however, severe cases have been reported. The onset of the visual reaction may be sudden. It is important that patients prescribed telithromycin should be informed that visual adverse reactions may occur during the treatment (see sections 4.7 and 4.8).

##### Loss of consciousness

There have been post-marketing adverse reaction 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.

##### CYP3A4 inducers

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).

### CYP3A4 substrates

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. Patients with concomitant treatment of pravastatin, rosuvastatin or fluvastatin should be carefully monitored for signs and symptoms of myopathy and rhabdomyolysis. (See sections 4.3 and 4.5).

### Resistance

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 products

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 reactions can be closely monitored. Alternatively, interruption in the treatment with the CYP3A4 substrate should be made during treatment with Ketek.

Telithromycin is also a P-glycoprotein inhibitor. Concomitant administration of Ketek with drugs that are substrates of P-glycoprotein might result in increased exposure to the P-glycoprotein substrates such as digoxin and dabigatran etexilate. If telithromycin is co-administered with dabigatran etexilate close clinical monitoring (looking for signs of bleeding or anaemia) should be exercised.

### 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.

#### Medicinal products with a potential to prolong QT interval

Ketek is expected to increase the plasma levels of cisapride, pimoziide, astemizole, terfenadine, dronedarone, saquinavir. 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 the QT interval (see section 4.4). These include Class IA (e.g. quinidine, procainamide, disopyramide) and Class III (e.g. dofetilide, amiodarone) antiarrhythmic agents, citalopram, tricyclic antidepressants, methadone, some antipsychotics (e.g. phenothiazines), fluoroquinolones (e.g. moxifloxacin), some antifungals (e.g. fluconazole, pentamidine), and some antiviral drugs (e.g. telaprevir).

#### 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. Ketek may produce a similar interaction with lovastatin and atorvastatin which are also mainly metabolised by CYP3A4. Ketek should therefore not be used concomitantly with simvastatin, atorvastatin, or lovastatin (see section 4.3). Treatment with these agents should be interrupted during Ketek treatment. The exposure of pravastatin, rosuvastatin and to a lesser extent fluvastatin, may be increased due to possible involvement of transporter proteins, but this increase is expected to be lesser than interactions involving CYP3A4 inhibition. However, patients should be carefully monitored for signs and symptoms of myopathy and rhabdomyolysis when co-treated with pravastatin, rosuvastatin and fluvastatin.

#### Benzodiazepines

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 should be undertaken. The same precautions should also apply to the other benzodiazepines which are metabolised by CYP3A4, (especially triazolam but also to a lesser extent alprazolam). For those benzodiazepines which are not metabolised by CYP3A4 (temazepam, nitrazepam, lorazepam) an interaction with Ketek is unlikely.

#### Digoxin

Ketek has been shown to increase the plasma concentrations of digoxin, a P-glycoprotein substrate. 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.

#### Colchicine

Colchicine intoxication, including fatal cases, has been reported in patients treated with colchicine and strong CYP3A4 inhibitors. Telithromycin is known to be a strong CYP3A4 inhibitor and is also a P-glycoprotein inhibitor. Exposure to colchicine, a CYP3A4 and P-glycoprotein substrate, may therefore be expected to increase if Ketek and colchicine are co-administered. Concomitant administration of Ketek and colchicine is contraindicated in patients with renal and/or hepatic impairment (see section 4.3).

#### Calcium channel blockers that are metabolized by CYP3A4

Concomitant administration of strong CYP3A4 inhibitors (such as telithromycin) and calcium channel blockers that are metabolized by CYP3A4 (e.g. verapamil, nifedipine, felodipine) may result in hypotension, bradycardia or loss of consciousness, and should therefore be avoided. In case the combination is considered necessary, the dose of the calcium channel blocker should be reduced and close clinical monitoring of efficacy and safety in the patient should be exercised.

#### Sotalol

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

- 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.

Strong CYP3A4 inhibitors must not be co-administered with Ketek in patients with severe renal/or hepatic dysfunction (see section 4.3).

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

#### 4.6 Fertility, pregnancy and lactation

##### Pregnancy

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.

##### Breastfeeding

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 breastfeeding women.

##### Fertility

In studies with rats a reduction in fertility indices was observed at parentally toxic doses (see section 5.3).

#### 4.7 Effects on ability to drive and use machines

Ketek may cause adverse reactions such as visual disturbances, confusion or hallucination 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, 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 (see sections 4.4 and 4.8).

Patients should be informed that these adverse reactions may occur as early as after the first dose of medicinal product. Patients should be cautioned about the potential effects of these events on the ability to drive or operate machinery.

#### 4.8 Undesirable effects

##### Tabulated list of adverse reaction

In 2,461 patients treated by Ketek in phase III clinical trials, and during post-marketing experience, the following undesirable effects possibly or probably related to telithromycin have been reported. This is shown in the table below. Diarrhoea, nausea and dizziness were the most commonly reported adverse reactions in phase III clinical trials.

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)	Not known (cannot be estimated from the available data)*
Blood and the lymphatic system disorders			Eosinophilia			



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)	Not known (cannot be estimated from the available data)*
Immune system disorders						Angio-neurotic oedema, anaphylactic reactions including anaphylactic shock, hypersensitivity
Psychiatric disorders						Confusion, hallucination
Nervous system disorders		Dizziness, headache, disturbance of taste	Vertigo, somnolence, nervousness, insomnia,	Transient loss of consciousness, paraesthesia	Parosmia	Cases of rapid onset of exacerbation of myasthenia gravis have been reported (see sections 4.3 and 4.4). Ageusia, anosmia, tremors, convulsions
Eye disorders			Blurred vision	Diplopia		
Cardiac disorders			Flush Palpitations	Atrial arrhythmia, hypotension, bradycardia		QT/QTc interval prolongation, ventricular arrhythmia (including ventricular tachycardia, torsade de pointes) with potential fatal outcome (see section 4.4)
Gastrointestinal disorders	Diarrhoea	Nausea, vomiting, gastro-intestinal pain, flatulence	Oral <i>Candida</i> infection, stomatitis, anorexia, constipation		Pseudo-membranous colitis (see section 4.4)	Pancreatitis

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)	Not known (cannot be estimated from the available data)*
Hepatobiliary disorders		Increase in liver enzymes (AST, ALT, alkaline phosphatase, gamma-glutamyl transferase)	Hepatitis	Cholestatic jaundice		Severe hepatitis and liver failure (see section 4.4)
Skin and subcutaneous tissue disorders			Rash, urticaria, pruritus	Eczema	Erythema multiforme	
Musculoskeletal and connective tissue disorders					Muscle cramps	Arthralgia, myalgia
Reproductive system and breast disorders		Vaginal <i>Candida</i> infection				

\*post-marketing experience

#### Description of selected adverse reactions

Visual disturbances (<1%) associated with the use of Ketek, including blurred vision, difficulty focusing and diplopia, were mostly mild to moderate, but severe reactions have also been reported. 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. The onset of the visual reaction may be sudden. 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  $\Delta$ QTc >30 msec in 7.6% and 7.0% of cases, respectively. No patient in either group developed a  $\Delta$ 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.

#### Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via **the national reporting system** listed in [Appendix V](#).

## 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: antibacterials for systemic use, 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 interacting with domains II and V of the 23S ribosomal RNA of the 50S ribosome subunit. Furthermore, telithromycin is able to block the formation of the 50S and 30S ribosomal subunits.

The affinity of telithromycin for the 50S ribosomal subunits of organisms susceptible to erythromycin A is 10-fold higher than that of erythromycin A.

Pharmacokinetic/Pharmacodynamic (PK/PD) relationship:

The AUC/MIC ratio has been shown to be the PK/PD parameter that correlates best with the efficacy of telithromycin.

#### Mechanisms of resistance

Telithromycin does not induce expression of macrolide-lincosamide-streptogramin B (MLS<sub>B</sub>)-mediated resistance *in vitro* in *Staphylococcus aureus*, *Streptococcus pneumoniae*, or *Streptococcus pyogenes*.

In some organisms that are resistant to erythromycin A due to inducible expression of the MLS<sub>B</sub> resistance determinant, the affinity of telithromycin for the 50S ribosomal subunit is more than 20-fold that of erythromycin A.

Telithromycin is not active against organisms that constitutively express the MLS<sub>B</sub> resistance determinant (cMLS<sub>B</sub>). The majority of methicillin-resistant *S. aureus* (MRSA) express cMLS<sub>B</sub>.

In *in vitro* studies the activity of telithromycin was reduced against organisms that express the erythromycin *erm*(R) or *mec*(A) related resistance mechanisms.

Exposure to telithromycin *in vitro* did select for pneumococcal mutants with increased MICs of telithromycin, generally resulting in MIC values of  $\leq 1$  mg/l.

*Streptococcus pneumoniae* does not demonstrate cross-resistance between erythromycin A and telithromycin.

*Streptococcus pyogenes* that show high-level resistance to erythromycin A are cross-resistant to telithromycin.

#### Breakpoints

The recommended European Committee for Antimicrobial Susceptibility Testing (EUCAST) MIC clinical breakpoints are presented below:

Pathogen	Susceptible	Resistant
<i>Streptococcus A, B, C, G</i>	$\leq 0.25$ mg/l	$>0.5$ mg/l
<i>Streptococcus pneumoniae</i>	$\leq 0.25$ mg/l	$>0.5$ mg/l

<i>Haemophilus influenzae</i> <sup>1</sup>	≤0.12 mg/l	>8 mg/l
<i>Moraxella catarrhalis</i>	≤0.25 mg/l	>0.5 mg/l

<sup>1</sup>The correlation between macrolide MICs and clinical outcome is weak for *H. influenzae*. Therefore the MIC breakpoint for telithromycin was set to categorise wild-type *H. influenzae* as having intermediate susceptibility.

### 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.

<p><b><u>Commonly susceptible species</u></b></p> <p><u>Aerobic Gram-positive bacteria</u>  <i>Staphylococcus aureus</i> methicillin susceptible (MSSA)*  <i>Streptococcus pneumoniae</i> *  <i>Streptococcus</i> species  Viridans group streptococci</p> <p><u>Aerobic Gram- negative bacteria</u>  <i>Haemophilus influenzae</i>\$*  <i>Haemophilus parainfluenzae</i>\$  <i>Legionella pneumophila</i>  <i>Moraxella catarrhalis</i>*</p> <p><u>Other</u>  <i>Chlamydophila pneumoniae</i>*  <i>Chlamydia psittaci</i>  <i>Mycoplasma pneumoniae</i>*</p>
<p><b><u>Species for which acquired resistance may be a problem</u></b></p> <p><u>Aerobic Gram-positive bacteria</u>  <i>Staphylococcus aureus</i> methicillin resistant (MRSA)+  <i>Streptococcus pyogenes</i>*</p>
<p><b><u>Inherently resistant organisms</u></b></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

+ Telithromycin is not active against organisms that constitutively express the MLS<sub>B</sub> resistance determinant (cMLS<sub>B</sub>). More than 80% of MRSA express cMLS<sub>B</sub>.

## 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  $2.9 \pm 1.6$  mg/l (range 0.02-7.6 mg/l) and  $0.2 \pm 0.2$  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  $2.9 \pm 1.0$  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  $14.9 \pm 11.4$  mg/l,  $318.1 \pm 231$  mg/l,  $3.83 \pm 1.87$  mg/kg,  $3.95 \pm 0.53$  mg/kg and  $6.96 \pm 1.58$  mg/kg, respectively. The total tissue concentration 24 h after dose in epithelial lining fluid, alveolar macrophages, bronchial mucosa, tonsils and sinus tissue were  $0.84 \pm 0.65$  mg/l,  $162 \pm 96$  mg/l,  $0.78 \pm 0.39$  mg/kg,  $0.72 \pm 0.29$  mg/kg and  $1.53 \pm 1.68$  mg/kg, respectively. The mean maximum white blood cell concentration of telithromycin was  $33 \pm 25$  mg/l.

### Biotransformation

Telithromycin is metabolised 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 metabolised 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 15% 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  $58 \pm 5$  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)<sub>ss</sub> 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 population

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 is similar between males and females.

### **5.3 Preclinical safety data**

Repeated dose toxicity studies of 1, 3 and 6 month 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. Slight reductions in fertility indices were seen in rats at parentally toxic doses higher than 150 mg/kg. 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**

This medicinal product does not require any special storage condition.

### **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.

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/1/01/191/001-004

**9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

Date of first authorisation: 9 July 2001

Date of latest renewal: 9 July 2011

**10. DATE OF REVISION OF THE TEXT**

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

Medicinal product no longer authorised



**ANNEX II**

- A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

**A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

Name and address of the manufacturer(s) responsible for batch release:

S.C. Zentiva S.A.  
B-dul Theodor Pallady nr. 50, sector 3, București, cod 032266, Romania

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

Medicinal product subject to medical prescription.

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

• **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

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

• **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Medicinal product no longer authorised

**ANNEX III**  
**LABELLING AND PACKAGE LEAFLET**

**A. LABELLING**

Medicinal product no longer authorised

**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. 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 SIGHT AND REACH OF CHILDREN**

Keep out of the sight and reach of children.

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

**8. EXPIRY DATE**

EXP

**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

**13. BATCH NUMBER**

Batch

**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

**4. BATCH NUMBER**

Batch

**5. OTHER**

Medicinal product no longer authorised

Medicinal product no longer authorised

**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 because it contains important information for you.**

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

#### **What is in this leaflet:**

1. What Ketek is and what it is used for
2. What you need to know before you take Ketek
3. How to take Ketek
4. Possible side effects
5. How to store Ketek
6. Contents of the pack and other information

#### **1. What Ketek is and what it is used for**

Ketek contains the active substance telithromycin.

Ketek is an antibiotic of the type macrolides. Antibiotics stop the growth of bacteria which cause infections.

Ketek is used to treat infections due to bacteria against which the medicine is active.

- In adults, Ketek is used to treat infections of the throat, infections of the sinuses (hollow cavities in the bones around the nose) and chest infections in patients with long standing breathing difficulties and lung infection (pneumonia).
- In adolescents of 12 years and older, Ketek is used to treat infections of the throat.

#### **2. What you need to know before you take Ketek**

##### **Do not take Ketek:**

- if you are **allergic** to telithromycin, to any of the macrolide antibiotics or to any of the other ingredients of this medicine (listed in section 6). If in doubt, talk to your doctor or pharmacist.
- if you suffer from **myasthenia gravis**, a rare disease which causes muscle weakness.
- if you have had a liver disease (**hepatitis** and/or **jaundice**) while taking Ketek in the past.
- if you are **taking other medicines** that can prolong the QT interval of the electrocardiogram (ECG), such as:
  - terfenadine or astemizole (allergic problems)
  - cisapride (digestive problems)
  - pimozone (psychiatric problems)
  - dronedarone (for atrial fibrillation)
  - saquinavir (anti-HIV treatment)
- if you are **taking other medicines** containing any of the following active substances:
  - ergotamine or dihydroergotamine (tablets or inhaler for migraine)

- if you are taking certain medicinal products to control the blood level of **cholesterol** or other lipids like simvastatin, lovastatin, or atorvastatin, as the side effects of these medicinal products could be increased.
- if you or someone in your family are known to have an **abnormality of electrocardiogram** (ECG) called “long QT syndrome”.
- if you have **kidney problems** (severely impaired renal function) and/or **liver problems** (severely impaired hepatic function), do not take Ketek while taking other medicines containing any of the following active substances:
  - ketoconazole or fluconazole (anti-fungal treatment)
  - a medicine called protease inhibitor (anti-HIV treatment)
  - colchicine (for gout)

### Warnings and precautions

Talk to your doctor, pharmacist or nurse before taking Ketek:

- if you have had certain **heart problems** such as coronary heart disease, ventricular arrhythmias, bradycardia (changes in heart rate or electrocardiogram) or if you have had certain abnormal blood tests due to medical conditions such as low levels of potassium (hypokalaemia), low levels of magnesium (hypomagnesaemia).
- if you have **liver disease**.
- if you experience **fainting** (transient loss of consciousness)

Talk to your doctor, pharmacist or nurse if you experience irregular heart beat.

Talk to your doctor, pharmacist or nurse if you experience visual disturbances (blurred vision, difficulty focusing, double vision). These visual disturbances may happen suddenly and last several hours. You may experience this within a few hours of taking your daily dose of Ketek the first or second time. It may happen again when you take the next dose of Ketek. These effects usually disappear during treatment or after completion of treatment with Ketek.

If any of these apply to you, or if you are not sure, tell your doctor before taking Ketek.

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 which can occur following treatment with antibiotics.

To reduce the potential impact of visual disturbances take the tablets before going to bed (see also section 3).

### Children and adolescents

Ketek is **not recommended** for use in children less than 12 years old.

Refer also to sections “Do not take Ketek”, “Other medicines and Ketek” and “Driving and using machines”.

### Other medicines and Ketek

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription, as some of them could affect or be affected by Ketek.

These **medicines must not be taken with Ketek**:

- medicinal products to control the blood level of **cholesterol** or other lipids like simvastatin, atorvastatin, or lovastatin, as the side effects of the medicinal products could be increased.
- other medicines that can **prolong the QT interval** of the electrocardiogram (ECG), such as:
  - terfenadine or astemizole (allergic problems)
  - cisapride (digestive problems)
  - pimozide (psychiatric problems)
  - dronedarone (for atrial fibrillation)
  - saquinavir (anti-HIV treatment)

- other medicines containing any of the **following active substances**:
  - ergotamine or dihydroergotamine (tablets or inhaler for migraine)
- if you have **kidney problems** (severely impaired renal function) and/or **liver problems** (severely impaired hepatic function), other medicines containing any of the **following active substances**:
  - ketoconazole or fluconazole (anti-fungal treatment)
  - a medicine called protease inhibitor (anti-HIV treatment)
  - colchicine (for gout).

It is important to **tell your doctor** if you are taking:

- medicines containing phenytoin, and carbamazepine (for epilepsy)
- rifampicin (antibiotic)
- phenobarbital or St John's wort (herbal medicine used to treat mild depression)
- medicines like tacrolimus, cyclosporin and sirolimus (for organ transplantation)
- metoprolol (for heart disorders)
- sotalol (for heart disorders)
- ritonavir (anti-HIV medicine).
- medicines known to affect the way your heart beats (drugs that prolong the QT interval). These include medicines used for abnormal heart rhythm (antiarrhythmics such as quinidine, amiodarone), for depression (citalopram, tricyclic antidepressants), methadone, some antipsychotics (phenothiazines), some antibiotics (fluoroquinolones such as moxifloxacin), some antifungals (fluconazole, pentamidine), and some antiviral drugs (telaprevir).
- medicines containing digoxin (for heart disorders) or dabigatran (for prevention of blood clots)
- colchicine (for gout)
- some calcium channel blockers (e.g. verapamil, nifedipine, felodipine) (for heart disorders).

#### **Ketek with food, drink and alcohol**

Ketek may be taken with or without food.

#### **Pregnancy, breast-feeding and fertility**

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

#### **Driving and using machines**

Limit driving or other hazardous activities while taking Ketek. If you have vision problems, faint or experience confusion or hallucination while taking Ketek, do not drive, operate heavy machinery or engage in dangerous activities.

Taking Ketek may cause side effects such as visual disturbances, confusion or hallucination which may reduce the capacity to carry out certain tasks. Rare cases of fainting (transient loss of consciousness), which may be preceded by a general feeling of being sick (e.g. nausea, stomach upsets) have been reported. These symptoms may appear as early as after the first dose of Ketek.

### **3. How to take Ketek**

Your doctor will tell you how many Ketek tablets to take, at what time and for how long. Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

The usual duration of treatment is 5 days for infections of the throat, infections of the sinuses, chest infections in patients with long standing breathing difficulties and 7 to 10 days for pneumonia.

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

If you have kidney problems (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. If possible take the tablets before going to bed, to reduce the potential impact of visual disturbances and loss of consciousness.

#### **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 forget 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. Do not take a double dose to make up for a forgotten dose.

#### **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 medicine, ask your doctor, pharmacist or nurse.

## **4. Possible side effects**

Like all medicines this medicine 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, including fatal cases, have been reported.

**If you notice** any of the following, 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 (frequency not known).
- Severe, persistent or bloody diarrhoea associated with abdominal pain or fever, which can be a sign of serious bowel inflammation which may occur following treatment with antibiotics (very rare).
- Signs and symptoms of liver disease (hepatitis) such as yellowing of skin and eyes, dark urine, itching, loss of appetite or abdominal pain (uncommon).
- Worsening of a condition called myasthenia gravis, a rare disease which causes muscle weakness (frequency unknown).
- Irregular heartbeat

The above serious side effects may require urgent medical attention.

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

**Very common** side effects (may affect more than 1 in 10 people)

- diarrhoea, usually mild and temporary.

**Common** side effects (may affect up to 1 in 10 people)

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

**Uncommon** (may affect up to 1 in 100 people) or **rare** side effects (may affect up to 1 in 1,000 people)

- constipation, loss of appetite (anorexia)
- inflammation in the mouth, fungal infection in the mouth (*Candida* infection)
- liver problem (hepatitis)
- rash, hives (urticaria), itching, eczema
- drowsiness, difficulties in falling asleep (insomnia), nervousness, vertigo
- tingling of the hands or feet (paraesthesia)
- visual disturbances (blurred vision, difficulty in focusing, double vision)(please read section 2)
- flushes, fainting (transient loss of consciousness)
- changes in heart rate (e.g. slow beating) or abnormality of electrocardiogram (ECG)
- low blood pressure (hypotension)
- increase of certain white blood cells, detected by blood test (eosinophilia).

**Very rare** side effects (may affect up to 1 in 10,000 people)

- disturbance of smell, muscle cramps.

Additional side effects (frequency not known – frequency cannot be estimated from available data) which may occur with Ketek are:

- tremors, convulsions
- abnormality of electrocardiogram (ECG), called prolongation of QT interval
- inflamed pancreas
- joint and muscle pain
- confusion
- hallucination (seeing or hearing things that are not there)
- loss of taste and smell
- liver failure.

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

### **Reporting of side effects**

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system listed in Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

### **3. How to store Ketek**

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the pack. The expiry date refers to the last day of that month.

This medicinal product does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Ketek contains

- The active substance is telithromycin. Each tablet contains 400 mg of 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 tablets 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, 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.  
20 Avenue Raymond Aron  
F-92160 ANTONY  
France

*The manufacturer of Ketek is:*

S.C. Zentiva S.A.  
B-dul Theodor Pallady nr. 50, sector 3, București, cod 032266, Romania

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder.

#### **België/Belgique/Belgien**

Sanofi Belgium  
Tél/Tel: +32 (0)2 710 54 00

#### **България**

sanofi-aventis Bulgaria EOOD  
Тел.: +359 (0)2 970 53 00

#### **Česká republika**

sanofi-aventis, s.r.o.  
Tel: +420 233 086 111

#### **Danmark**

sanofi-aventis Denmark A/S  
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#### **Lietuva**

UAB sanofi-aventis Lietuva  
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**France**

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Appel depuis l'étranger : +33 1 57 63 23 23

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**Ireland**

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**Ísland**

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**Nederland**

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**Portugal**

Sanofi - Produtos Farmacêuticos, Lda.  
Tel: +351 21 35 89 400

**România**

sanofi-aventis România S.R.L.  
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**Slovenija**

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**Slovenská republika**

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Tel: +421 2 33 100 100

**Suomi/Finland**

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Puh/Tel: +358 (0) 201 200 300

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This leaflet was last revised in <MM/YYYY> <month YYYY>.

Detailed information on this medicine is available on the European Medicines Agency web site:  
<http://www.ema.europa.eu>.