Ketek®

Télithromycine/Telithromycin

400mg

Aventis

This package insert is continually updated: please read carefully before using a new pack. In case of any question, please contact your physician or pharmacist.

KETEK® 400 mg, film-coated tablets

Composition

Active ingredient: telithromycin.

Each film-coated tablet contains 400 mg telithromycin.

Excipients: maize starch, lactose monohydrate, croscarmellose sodium, microcrystalline cellulose, magnesium stearate, talc, titanium dioxide E171, hypromellose 6 cp (hydroxypropyl methylcellulose), macrogol 8000 (polyethylene glycol), povidone K25 (polyvinylpyrrolidone), yellow iron oxide E172, red iron oxide E172.

Properties

Pharmaco-therapeutic class: antibacterial (J: antibacterials for sytemic use).

Telithromycin is an erythromycin A semi-synthetic derivative belonging to the ketolide family, a new class of antibacterial agents. Telithromycin inhibits protein synthesis by acting at the ribosome level. Telithromycin interacts with two sites (domains V and II) at the 23S ribosomal RNA level. Furthermore, telithromycin is able to block the formation of 50S and 30S ribosomal subunits. Telithromycin has potent activity against Gram-positive cocci such as *Streptococcus pneumoniae*, Streptococcus pyogenes* Strepcococcus agalactiae, Streptococci* of Viridans group, *Streptococci* of Lancefield group C, G* and *Staphylococcus aureus**, Gram-negative cocci such as *Moraxella catarrhalis** and some Gram-negative bacilli such as, *Haemophilus influenzae** and *Bordetella pertussis*. Telithromycin has good activity against atypical respiratory pathogens such as *Chlamydia pneumoniae**, *Chlamydia psittaci, Legionella pneumophila** and *Mycoplasma pneumoniae** (* Clinical efficacy has been demonstrated for susceptible isolates in the approved indications). Telithromycin' s activity against *S. pneumoniae* is irrespective of the susceptibility of the isolates to other antibacterial classes, eg penicillins, cephalosporins, macrolides and fluoroquinolones. Telithromycin shows a bactericidal activity against *S. pneumoniae*. Telithromycin does not induce Macrolide Lincosamide Streptogramin B resistance *in vitro* to *S. aureus, S. pneumoniae*, and *S. pyogenes*. It has been shown *in vitro* that resistance to telithromycin due to spontaneous mutation is a rare occurrence.

Following oral administration, telithromycin is rapidly absorbed. It has an absolute bioavailability of 57% in both young and elderly subjects after a single dose of 800mg. The rate and extent of absorption is unaffected by food intake, and thus KETEK tablets can be given without regard to food. In healthy subjects, peak plasma levels of telithromycin are rapidly attained within a median of 1 hour after an 800 mg oral dose. Steady state trough plasma concentrations are reached within 2 to 3 days with once daily dosing of telithromycin 800 mg. At steady state AUC is approximately 1.5 fold increased compared to the single dose. The mean terminal elimination half-life is 10 hours. Total in vitro protein binding is approximately 60% to 70% and is not modified in elderly subjects and in patients with hepatic impairment. *In vitro*, telithromycin is an inhibitor of CYP3A4 and CYP2D6. Concomitant administration of drugs mainly metabolised by these enzymes may lead to increased plasma concentrations, possibly resulting in increased adverse events. Caution should be exercised during concomitant administration of other drugs that are CYP3A4 substrates or CYP2D6 substrates. Telithromycin is primarily metabolized by cytochrome P450 3A4 (CYP3A4) and to a lesser extent by cytochrome P450 1A (CYP1A). Telithromycin is widely distributed throughout the body. Rapid distribution of telithromycin into tissues results in significantly higher telithromycin concentrations in most target tissues (such as respiratory tissues, white blood cells and alveolar macrophages) than in plasma. Telithromycin rapidly achieved high concentrations in white blood cells, from which is eliminated more slowly than from plasma. 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. After administration of radiolabeled telithromycin, 76% of the radioactivity was recovered from feces, with an additional 17% recovered from the urine. Approximately one-third of telithromycin was eliminated unchanged; 20% in feces and 12% in urine. The total clearance is approximately 70 L/h with renal clearance accounting for 17% of this.

When should this drug be used (Therapeutic indications)

Telithromycin is indicated for the treatment of the following infections:

In patients of 18 years and older:

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

In patients of 12 to 18 years old:

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

How should this drug be used

Strictly follow the recommended dosage unless directed otherwise by the physician.

Adults and adolescents of 12 years old and above

The recommended dose is 800 mg (i.e., two tablets of 400 mg) once daily.

Route of administration

Oral route with or without food.

Duration of treatment

- Community-acquired pneumonia: 7 to 10 days,
- Acute exacerbation of chronic bronchitis: 5 days,
- Acute sinusitis: 5 days,
- Tonsillitis/pharyngitis: 5 days.

Hepatic Impairment

No dosage adjustment is necessary in patients with mild, moderate, or severe hepatic impairment, unless renal function is severely impaired.

Renal Impairment

No dosage adjustment is necessary in patients with mild or moderate renal impairment. In the presence of severe renal impairment (creatinine clearance <30ml/min) with or without co-existing hepatic impairment, the dose should be halved.

Special Populations

No dosage adjustment is necessary in hemodialyzed patients. Tablets should be given after each dialysis session.

When should this drug not be used (Contraindications)

KETEK is contraindicated in patients with known hypersensitivity to telithromycin or to any of its excipients and/or to any of the macrolide antibacterial agents. Concomitant administration of telithromycin and any of the following drugs is contraindicated: cisapride, pimozide, astemizole and terfenadine.

Warnings and precautions

As with nearly all antibacterial agents, diarrhea, particularly if severe, persistent and/or bloody, during or after treatment with telithromycin may be symptomatic of pseudomembranous colitis. If pseudomembranous colitis is suspected, KETEK must be stopped immediately and patients should be treated with supportive measures and/or specific therapy. Telithromycin may have the potential to prolong the QTc interval of the electrocardiogram in some patients. QTc prolongation may lead to an increased risk for ventricular arrhythmias, including torsades de pointes. Thus, telithromycin should be avoided in patients with prolongation of the QTc interval, with uncorrected hypokalemia and in patients receiving Class IA (e.g. quinidine and procainamide) or Class III (e.g. dofetilide) antiarrhythmic agents. No cardiovascular morbidity or mortality attributable to the QTc prolongation occurred with telithromycin treatment in patients, including those having a prolonged QTc at baseline.

Pregnancy and lactation

The very limited clinical data available does not allow any conclusion to be reached. Therefore, telithromycin should not be used during pregnancy unless the expected benefit to the patient outweighs any possible risk to the foetus.

Telithromycin is excreted in animal milk. No data is available in humans. Therefore, telithromycin should not be used during lactation unless the expected benefit to the patient outweighs any possible risk to the baby.

Driving

Telithromycin may cause undesirable effects wich may reduce the capacity for the completion of certain tasks. Patients should be informed of the potential for these undesirable effects and should be aware of how they react to this medication before driving or operating machinery.

Overdose

In the event of acute oral overdosage, the stomach should be emptied by inducing vomiting and gastric lavage. Treatment of overdosage should be symptomatic and supportive. Adequate hydration should be maintained.

Interactions

In order to avoid possible interactions with other medicines, inform your physician or pharmacist about any other current treatment.

The following drug-drug interactions have been tested in clinical pharmacology studies:

- cisapride: peak plasma concentrations of cisapride at steady-state were increased when co-administered with repeated doses of telithromycin, resulting in significant increases in QTc. Therefore, the concomitant administration of telithromycin and cisapride is contraindicated (see Contraindications),
- digoxin: telithromycin has been shown to increase the plasma concentrations of digoxin. Nevertheless there were no significant changes in ECG parameters and no signs of digoxin toxicity were observed. Monitoring of serum digoxin level should be considered during concomitant administration of digoxin and telithromycin,
- statins: when simvastatin was coadministered with telithromycin, there was an increase in simvastatin Cmax and AUC. The interaction observed is on average of the same order of magnitude as that observed with erythromycin. In patients treated with simvastatin, precautions should be used when telithromycin is coadministered.
  In particular, the patients should be carefully monitored to detect any signs and symptoms of myopathy.
  Based on the results of this study, the pharmacokinetic properties of the other statins, and on the interactions reported for the other statins due to CYP3A4 inhibition, telithromycin may produce a similar interaction with lovastatin and a lesser interaction with atorvastatin and cerivastatin and little or no interaction with pravastatin and fluvastatin. Therefore, similar precautions should be used when telithromycin is coadministered with, lovastatin, atorvastatin and cerivastatin.
- theophylline: there is no relevant pharmacokinetic interaction of telithromycin and theophylline administered as an extended release formulation. However, the coadministration of both drugs should be separated by an hour in order to avoid possible digestive side effects such as nausea and vomiting,
- itraconazole, ketoconazole: maximum plasma concentrations of telithromycin were increased when coadministered with itraconazole and ketoconazole. These changes do not necessitate dosage adjustment,
- benzodiazepins: an increase of plasma level was observed when midazolam was coadministered with telithromycin. This could result in an increased pharmacological effect of midazolam; therefore, dosage of midazolam should be adjusted as necessary and monitoring of the patient be undertaken. The same precautions should also apply to triazolam which is highly metabolised by CYP3A4. For the other benzodiazepins, which have a good bioavailability and are metabolised mainly or partially by CYP3A4 (alprazolam, diazepam, zolpidem) the magnitude of the interaction after oral administration should be lower as compared to midazolam. Nevertheless precautions should be taken in case of coadministration with telithromycin.
- sotalol: there is no evidence to suggest a potential synergistic effect on QTc prolongation with concomitant administration of sotalol and telithromycin. Telithromycin has been shown to decrease the Cmax by 34% and AUC of sotalol by 20% due to decreased absorption.

The following drug-drug interactions have not been studied with telithromycin but have been reported with macrolides:

- ergot alkaloids derivatives: severe vasoconstriction has been reported with concomitant administration of ergot alkaloids derivatives and macrolides; therefore, telithromycin and ergot alkaloids derivatives should not be coadministered,
- pimozide, astemizole, terfenadine: macrolides have been reported to alter the metabolism of these drugs and to increase their serum levels. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointe. Therefore, the concomitant administration of telithromycin and any of these drugs is contraindicated (see Contraindications),

- the effect of ritonavir on telithromycin has not been studied and could lead to a larger increase in telithromycin exposure. The combination should be used with caution,
- for other drugs, which are metabolized by the cytochrome P450 system such as quinidine, carbamazepine, cyclosporine, hexobarbital, and phenitoin, elevation of serum levels may be observed when coadministered with telithromycin.

Undesirable effects

Please tell your physician or pharmacist, if you experience any adverse effect with the use of this product.

The following undesirable effects may occur with the use of KETEK:

- gastrointestinal: very common diarrhea; common nausea, vomiting, gastrointestinal pain and flatulence; uncommon constipation, anorexia (loss of appetite), oral moniliasis (infection caused by a fungus) and stomatitis (inflammation of the mouth mucous membranes),
- allergy: uncommon rash, urticaria and pruritus,
- liver and biliary system: common increase in liver enzymes (transaminases ALT and AST, alkaline phosphatase); rare cholestatic jaundice,
- nervous: common dizziness and headache; uncommon somnolence, insomnia and nervousness; rare paresthesia,
- hemic and lymphatic system: uncommon eosinophilia (increase in the number of certain white blood cells),
- special senses: common disturbance of taste; uncommon blurred vision,
- urogenital system: common vaginal moniliasis (infection caused by a fungus),
- skin: rare eczema,
- musculoskeletal: rare muscle cramps,
- cardiovascular: uncommon flush; rare atrial arrhythmia (irregularity of the heart beat), hypotension (reduced blood pressure) and bradycardia (slow heart rate).

In addition, the following undesirable effects have been reported in isolated cases: hepatitis, face edema, and erythema multiforme (red inflammatory rash with the formation of blisters).

Storage

Store at controlled room temperature (15°C to 30°C).

Expiry date

Do not use later than the date of expiry indicated on the outer packaging.

Keep out of the reach of children.

Presentation

Blister of 10 tablets.
Blister of 14 tablets.

Manufacturer

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Marketing Authorization Holder

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