Important information. Please read carefully.

Avexus Film-Coated Tablet

COMPOSITION

Avexus Film-Coated Tablet 250mg: Each tablet contains Clarithromycin 250mg
Avexus Film-Coated Tablet 500mg: Each tablet contains Clarithromycin 500mg

ACTIONS AND MECHANISMS OF ACTION

Clarithromycin is a semi-synthetic macrolide derived from erythromycin. It exhibits similar but has slightly greater activity than the parent compound. Clarithromycin exerts its antibacterial activity by inhibiting the synthesis of proteins via binding to the 50S ribosomal subunit of susceptible microorganisms. Highly potent against a wide variety of aerobic and anaerobic Gram-positive and Gram-negative organisms, the *in vitro* antibacterial spectrum of clarithromycin generally includes: *Staphylococci* spp.; *Streptococci* spp.; *Haemophilus influenzae* and *Haemophilus parainfluenzae; Mycobacterium* spp.; *Neisseria gonorrhoeae; Listeria monocytogenes; Legionela pneumophila; Pasteurella multocida; Mycoplasma pneumoniae; Helicobacter pylori* and *Campylobacter jejuni; Chlamydia trachomatis* and *Chlamydia pneumoniae* (TWAR); *Moraxella catarrhalis; Bordetella pertussis; Borrelia burgdorferi; Clostridium perfringens; Peptococcus niger; Propionibacterium acnes; Bacteroides melaninogenicus.*

PHARMACOKINETICS

Clarithromycin is rapidly absorbed from the gastrointestinal tract following oral administration. Clarithromycin undergoes first-pass metabolism; the bioavailability of the parent drug is about 50%. Food slightly delays the onset of absorption of clarithromycin but the extent of its bioavailability is unaffected. In addition, food does not affect the onset of formation nor peak plasma concentration of its principal (antimicrobially) active metabolite, 14-hydroxyclarithromycin. Therefore, clarithromycin may be given without regard to meals. Peak plasma concentrations of clarithromycin and its principal metabolite are reported to be about 0.6 and 0.7 µg per mL respectively (following a single 250 mg dose by mouth). These are attained within 2 to 3 hours after oral dosing in nonfasting, healthy subjects. Steady-state peak plasma concentrations (of the same dose administered every 12 hours), C_{max} attained within 3 days, were about 1 to 2 µg per mL; C_{max} values of 3 to 4 µg per mL were obtained with a 500 mg dose administered every 8 to 12 hours and 5 to 10 µg per mL with 1000 mg doses every 12 hours. The pharmacokinetics of clarithromycin are non-linear and dose dependent; high doses may produce disproportionate increases in peak concentration and prolongs elimination half-lives of the parent drug and its principal metabolite, due to saturation of the metabolic pathways. For example, the elimination half-lives, $T_{½}$ of clarithromycin and 14-hydroxyclarithromycin were about 3 to 4 hours and 5 to 6 hours, respectively with a 250 mg dose administered every 12 hours; the half-lives increased to 5 to 7 hours and 7 to 9 hours, respectively with a 500 mg dose administered every 8 to 12 hours. Half-lives are prolonged in renal failure. The drug and its principal metabolite are widely distributed, and tissue concentrations exceed those in serum, in part because of intracellular uptake. It is extensively metabolised in the liver, and excreted in faeces via the bile. Renal clearance of clarithromycin is relatively independent of the dose size and approximates the normal glomerular filtration rate. Substantial amounts of the unchanged drug are excreted in urine; about 20% and 30% respectively of a 250 mg or 500 mg dose (both given every 12 hours). 14-Hydroxyclarithromycin as well as other metabolites are also excreted in the urine; the former accounts for an additional 10% to 15% of the dose with either a 250 mg or 500 mg dose administered every 12 hours.

INDICATIONS

Avexus is indicated for treatment of infections due to susceptible organisms in respiratory-tract infections; mild to moderate skin and soft tissue infections; acute otitis media and (in triple-therapy regimens for) *Helicobacter pylori* eradication.

DOSAGE AND ADMINISTRATION

For oral administration only.

Adults:
250 mg every 12 hours for 7 days, increased in severe infections to 500 mg every 12 hours for up to 14 days.
500 mg every 12 hours for 7 to 14 days in triple-therapy regimen for *Helicobacter pylori* eradication.

Children:
Body-weight under 8 kg: 7.5 mg per kg twice daily
(7 - 9 years) 20 - 29 kg: 187.5 mg twice daily
(10 - 12 years) 30 - 40 kg: 250 mg twice daily
A course is usually for 1 0 days.

Triple Therapy:
Clarithromycin 500 mg twice daily should be given with amoxycillin 1000 mg twice daily and omeprazole 20 mg daily for 1 0 days.

Dosage adjustment in renal impairment:
Half the normal dose if creatinine clearance is less than 30 mL per minute.

Dosage adjustment in liver impairment:
May not be necessary if there is normal renal function.

CONTRAINDICATIONS

Clarithromycin is contraindicated in patients with a known hypersensitivity to any of the macrolide antibiotics and ergot derivatives. Concomitant administration of clarithromycin with cisapride, pimozide, astemizole or terfenadine is contraindicated. Cardiac arrhythmias and fatalities have been reported when clarithromycin is co-administered with these drugs.

Concomitant administration of Clarithromycin and the following drugs is contraindicated: Domperidone as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see section Interactions).

PRECAUTIONS/ WARNINGS

Pregnancy: Animal studies have shown that high doses of clarithromycin have been associated with embryotoxicity.
Breast-feeding: Clarithromycin passes into breast milk. ***Avoid use during pregnancy and in nursing mothers unless potential benefit outweighs potential risk to the fetus. In such circumstances, use of the drug must be under close medical supervision.*** **Children and Adolescents:** Safety and effectiveness of clarithromycin have not been established in children under 6 months of age. **Geriatrics:** Clarithromycin has been tested in a limited number of elderly patients and has not been shown to cause different side effects in the elderly than it does in younger adults. However, changes in pharmacokinetic parameters parallel to known age-related decreases in renal function have been noted. Hence, dosage adjustment should be considered in elderly patients with severe renal impairment. **Liver impairment:** Hepatic dysfunction including jaundice reported. Use with caution in liver disease. **Renal impairment:** Patients with severe kidney disease may have an increased chance of side effects. Use half the normal dose if creatinine clearance is less than 30 mL per minute.
In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCARs) [e.g. Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalized exanthematous pustulosis (AGEP)], Avexus should be discontinued immediately and appropriate treatment should be urgently initiated. There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

ADVERSE REACTIONS

Gastrointestinal disturbances are the most frequently reported adverse effect i.e. diarrhoea, nausea, dyspepsia, abdominal pain/ discomfort and heartburn. Sense of taste and smell disturbances, stomatitis, glossitis, oral moniliasis, tongue discolouration, tooth, anorexia, pancreatitis, thrombocytopenia, leukopenia and neutropenia and have been spontaneously reported. Isolated reports of hearing loss in elderly women and hypoglycemia have also been reported. Headache and allergic reactions ranging from urticaria and mild skin eruptions to rare cases of anaphylaxis, severe cutaneous adverse reactions (SCARs) including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), drug reaction with eosinophilia and systemic symptoms (DRESS) & acute generalized exanthematous pustulosis (AGEP) have occurred. Transient elevations of liver, cholestatic jaundice and hepatitis have been infrequently reported. Hepatic dysfunction may be severe but is usually reversible; fatal outcomes occur very rarely and (generally) only in instances where serious underlying diseases and/or concomitant medications are present. There have also been reports of transient central nervous system effects i.e. anxiety, behavioural changes, dizziness, vertigo, tinnitus, insomnia, disorientation, hallucinations, psychosis, nightmares and confusion. These usually resolve with discontinuation of the drug. Similar to other antibiotics, superinfections by resistant bacteria or fungi may rarely arise during therapy with clarithromycin. In such instances, clarithromycin should be withdrawn and other suitable therapy adopted. And like other macrolides, clarithromycin has been associated with QT prolongation and ventricular arrhythmias.

DRUG INTERACTIONS

Atorvastatin and **simvastatin**: Increased plasma concentrations of atorvastatin and simvastatin. Rhabdomyolysis reported. Concomitant use should be avoided; **Carbamazepine**, **phenytoin** and **theophylline**: Increased plasma concentrations of carbamazepine, phenytoin and theophylline. Blood level monitoring of the anticonvulsants should be considered; **Ciclosporin**: Increased plasma concentration of ciclosporin; **Coumarins**: Enhanced oral anticoagulant effects. Prothrombin times should be carefully monitored; **Digoxin**: Increased plasma concentration of digoxin. Serum digoxin concentration should be carefully monitored; **Disopyramide** and **quinidine**: Increased plasma concentrations of disopyramide and quinidine. Electrocardiograms and serum disopyramide and quinidine concentrations should be carefully monitored; **Ergotamine** and **dihydroergotamine**: Acute ergot toxicity in some patients. Concomitant use should be avoided; **Itraconazole**: Increased plasma concentration of itraconazole. **Midazolam** and **triazolam**: Increased plasma concentrations of midazolam and triazolam; profound sedation, somnolence and confusion reported; **Repaglinide**: Enhanced repaglinide effect; **Rifabutin**: Increased plasma concentration of rifabutin. Reduce rifabutin dose to reduce risk of uveitis; **Ritonavir**: Increased plasma concentration of clarithromycin. Reduce clarithromycin dose in patients with renal impairment; **Tacrolimus**: Increased plasma concentration of tacrolimus; **Zidovudine**: Reduced absorption of zidovudine. Take clarithromycin at least 2 hours prior to oral zidovudine.

Co-administration of Clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug. The following drugs or drug classes are known or suspected to be metabolized by CYP3A isoenzyme: Domperidone.

SYMPTOMS AND TREATMENT FOR OVERDOSAGE

Overdosage of clarithromycin can cause gastrointestinal symptoms i.e. abdominal pain, vomiting, nausea and diarrhoea. In case of overdosage, clarithromycin should be discontinued immediately. Accompanying adverse reactions should be treated by the prompt elimination of unabsorbed drug and supportive measures (eg.gastric lavage). Clarithromycin is not removed by hemodialysis or peritoneal dialysis.

SHELF-LIFE

The expiry date is indicated on the packaging.

DESCRIPTION

Avexus Film-Coated Tablet 250 mg: Yellow, oval-shaped, film-coated tablet engraved with XS on one side and plain on the other side. In packs of 60's, 10's per blister.
Avexus Film-Coated Tablet 500 mg: Light yellow, oval-shaped, film-coated tablet engraved with logo on one side and plain on the other side. In packs of 60's, 10's per blister.

STORAGE

Store below 30°C.
KEEP ALL MEDICINES OUT OF REACH OF CHILDREN
JAUHI DARI KANAK-KANAK

For further information, please consult your pharmacist or physician.

Revision Date : 27-Aug-2019

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08.19
AV0400/AV0500-003