PACKAGE INSERT TEMPLATE FOR CLARITHROMYCIN TABLET

Brand or Product Name

[Product name] Tablet 500mg

Name and Strength of Active Substance(s)

Clarithromycin 500mg

Product Description

[Visual description of the appearance of the product (eg colour, markings etc) eg :
Tablet - White, circular flat beveled edge film-coated tablets marked '100' on one side]

Pharmacodynamics

Clarithromycin is a semi-synthetic macrolide antibiotic obtained and exerts its antibacterial action by binding to the 5OS ribosomal subunits of susceptible bacteria and suppressing protein synthesis.

Clarithromycin has demonstrated excellent in vitro activity against both standard strains of bacteria and clinical isolates. It is highly potent against a wide variety of aerobic and anaerobic Gram-positive and Gram-negative organisms. The minimum inhibitory concentrations (MIC's) of clarithromycin are generally one $\log_2$ dilution more potent than the MIC's of erythromycin.

In vitro data also indicate clarithromycin has excellent activity against *Legionella pneumophila*, and *Mycoplasma pneumoniae*. It is bactericidal to *Helicobacter pylori*; this activity of clarithromycin is greater at neutral pH than at acid pH. *In vitro* and *in vivo* data show this antibiotic has activity against clinically significant mycobacterial species. The *in vitro* data indicate *Enterobacteriaceae*, pseudomonas species and other non-lactose fermenting gram negative bacilli are not sensitive to clarithromycin.

Clarithromycin has been shown to be active against most strains of the following microorganisms

Aerobic Gram-Positive microorganisms
Staphylococcus aureus
Streptococcus pneumoniae
Streptococcus pyogenes
Listeria monocytogenes

Aerobic Gram-negative microorganisms
Haemophilus influenzae

Haemophilus parainfluenzae
Moraxella catarrhalis
Neisseria gonorrhoeae
Legionella pneumophila

Other microorganisms
Mycoplasma pneumoniae
Chlamydia pneumoniae (TWAR)

Mycobacteria
Mycobacterium leprae
Mycobacterium kansasii
Mycobacterium chelonae
Mycobacterium fortuitum
Mycobacterium avium complex (MAC) consisting of:
- *Mycobacterium avium*
- *Mycobacterium Intracellulare*

Beta-lactamase production should have no effect on clarithromycin activity.

Most strains of methicillin-resistant and oxacillin-resistant staphylococci are resistant to clarithromycin.

Helicobacter
Helicobacter pylori

Clarithromycin exhibits *in vitro* activity against most strains of the following microorganisms; however, the safety and effectiveness of clarithromycin in treating clinical infections due to these microorganisms have not been established.

Aerobic Gram-positive microorganisms
Streptococcus agalactiae
Streptococci (Group C,F,G)
Viridans group streptococci

Aerobic Gram-negative microorganisms
Bordetella pertussis
Pasteurella multocida

Anaerobic Gram-positive microorganisms
Clostridium perfringens
Peptococcus niger

Propionibacterium acnes

Anaerobic Gram-negative microorganisms
Bacteroides melaninogenicus

Spirochetes
Borrelia burgdorferi
Treponema pallidum

Campylobacter
Campylobacter jejuni

The principal metabolite of clarithromycin in man and other primates is a microbiologically active metabolite, 14-OH-clarithromycin. This metabolite is as active or 1- to 2-fold less active than the parent compound for most organisms, except for *H. influenzae* against which it is twice as active. The parent compound and the 14-OH-metabolite exert either an additive or synergistic effect on *H. influenzae in vitro* and *in vivo*, depending on bacterial strains.

Pharmacokinetics

The kinetics of orally administered clarithromycin has been studied extensively in a number of animal species and adult humans. These studies have shown clarithromycin is readily and rapidly absorbed with an absolute bioavailability of approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in any species following multiple dosing. Food intake immediately before dosing increases clarithromycin bioavailability by a mean of 25%. Overall, this increase is minor and should be of little clinical significance with the recommended dosing regimens. Clarithromycin may thus be administered in either the presence or absence of food.

In vitro

In vitro studies showed the protein binding of clarithromycin in human plasma averaged about 70% at concentrations of 0.45 to 4.5 mcg/mL. A decrease in binding to 41% at 45.0 mcg/mL suggested the binding sites might become saturated, but this only occurred at concentrations far in excess of the therapeutic drug levels.

In vivo

Results of animal studies showed clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were usually found in the liver and lung where the tissue to plasma (T/P) ratios reached 10 to 20.

Normal Subjects

With b.i.d. dosing at 250 mg, the peak steady state plasma concentration was attained in two to three days and averaged about 1 mcg/mL for clarithromycin and 0.6 mcg/mL for 14-hydroxyclarithromycin, while the elimination half-lives of the parent drug and metabolite were three to four hours and five to six hours, respectively. With b.i.d. dosing at 500 mg, the steady state C_{max} for clarithromycin and its hydroxylated metabolite was achieved by the fifth dose. After the fifth and seventh doses, the steady state C_{max} for clarithromycin averaged 2.7 and 2.9 mcg/mL; its hydroxylated metabolite averaged 0.88 and 0.83 mcg/mL, respectively. The half-life of the parent drug at the 500 mg dose level was 4.5 to 4.8 hours, while that of the 14-hydroxyclarithromycin was 6.9 to 8.7 hours. At steady state the 14-hydroxyclarithromycin levels did not increase proportionately with the clarithromycin dose, and the apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at the higher doses. This non-linear pharmacokinetic behavior of clarithromycin, coupled with the overall decrease in the formation of 14-hydroxylation and N-demethylation products at the higher doses, indicates the non-linear metabolism of clarithromycin becomes more pronounced at high doses.

Patients

Clarithromycin and its 14-OH metabolite distribute readily into body tissues and fluids. Limited data patients suggests clarithromycin does not achieve significant levels in cerebrospinal fluid after oral doses (i.e., only 1 to 2% of serum levels in CSF in patients with normal blood-CSF barriers). Concentrations in tissues are usually several fold higher than serum concentrations.

Indication

Treatment of infections caused by pathogens sensitive to clarithromycin.
Infections of nose-pharynx tract (tonsillitis, pharyngitis) and of paranasal sinuses.
Infections of lower respiratory tract : bronchitis, bacterial pneumonia and atypical pneumonia.
Skin infections : impetigo, erysipelas, folliculitis, furunculosis and septic wounds.

Recommended Dosage

Patients with respiratory tract/skin and soft tissue infections
Adults : The usual dose is 250 mg twice daily for 7 days although this may be increased to 500 mg twice daily for up to 14 days in severe infections.
Children older than 12 years: As for adults
Children younger than 12 years: Use Clarithromycin Paediatric Suspension.

Eradication of H.pylori in patients with duodenal ulcers
Adults: The usual dose of clarithromycin is 500 mg three times daily for 14 days.
Dual therapy: Clarithromycin should be administered with oral omeprazole 40 mg once daily.

Triple therapy: Clarithromycin Tablet 500 mg twice daily should be given with amoxycillin 1000mg twice daily and omeprazole 20 mg daily for 10 days.

Elderly
As for adults.

Renal impairment
In patients with renal impairment with creatinine clearance less than 30 mL/min, the dosage of clarithromycin should be reduced by one-half, i.e., 250 mg once daily, or 250 mg twice daily in more severe infections.

No adjustment of dosage is necessary for subjects with moderate or severe hepatic impairment but with normal renal function.

Clarithromycin Tablet may be given without regards to meals as food does not affect the extent of bioavailability.

Mode of Administration
Oral

Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to macrolide antibiotic drugs.

Concomitant administration of clarithromycin and any of the following drugs is contraindicated : astemizole, cisapride, pimozide, terfenadine and ergotamine or dihydroergotamine.

Warnings and Precautions

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening.

Clarithromycin is principally excreted by the liver. Therefore, caution should be exercised in administering the antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromycin to patients with moderate to severe renal impairment.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients.

Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin

Interactions with Other Medicaments

Cytochrome P450 interactions
Clarithromycin is metabolized primarily by the hepatic cytochrome P450 3A (CYP3A) isozyme. This is an important mechanism determining many drug interactions. The metabolism of other drugs by this system may be inhibited by concomitant administration with clarithromycin and may be associoated with elevations in serum levels of these other drugs.

The following drugs or drug classes are known or suspected to be metabolized by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, cyclosporine, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Theophylline, carbamazepine
There was a modest increase of circulating theophylline or carbamazepine levels when either of these drugs were administered concomitantly with clarithromycin.

HMG-CoA reductase inhibitors
Rhabdomyolysis, co-incident with the co- administration of clarithromycin, and HMG-CoA reductase inhibitors, such as lovastatin and simvastatin has been reported.

Cisapride
Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly.

Terfenadine
Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes. The

concomitant administration of clarithromycin and terfenadine resulted in a two to three fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Quinidine & disopyramide
There have been postmarketed reports of Torsade de Pointes occurring with the concurrent use of clarithromycin and quinidine or disopyramide. Levels of these medications should be monitored during clarithromycin therapy.

Ergotamine/dihydroergotamine
Co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated.

Digoxin
Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Colchicine
Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine. Patients should be monitored for clinical symptoms of colchicine toxicity.

Antiretroviral
Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine. This interaction does not appear to occur in pediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine.

Statement on Usage During Pregnancy and Lactation

The safety of clarithromycin during pregnancy and breast feeding of infants has not been established. Clarithromycin should thus not be used during pregnancy or lactation unless the benefit is considered to outweigh the risk. Some animal studies have suggested an embryotoxic

effect, but only at dose levels which are clearly toxic to mothers. Clarithromycin has been found in the milk of lactating animals and in human breast milk.

Adverse Effects / Undesirable Effects

Clarithromycin is generally well tolerated. Side effects include nausea, dyspepsia, diarrhoea, vomiting, abdominal pain and paraesthesia. Stomatitis, glossitis, oral monilia and tongue discolouration have been reported.

As with other macrolides, hepatic dysfunction (which is usually reversible) including altered liver function tests, hepatitis and cholestasis with or without jaundice, has been reported. Dysfunction may be severe and very rarely fatal hepatic failure has been reported.

Cases of increased serum creatinine, interstitial nephritis, renal failure, pancreatitis and convulsions have been reported rarely.

Other side-effects include headache, arthralgia, myalgia and allergic reactions ranging from urticaria, mild skin eruptions and angioedema to anaphylaxis have been reported. There have been reports of Stevens-Johnson syndrome / toxic epidermal necrolysis with orally administered clarithromycin.

There have been reports of hearing loss with clarithromycin which is usually reversible on withdrawal of therapy. Reports of alteration of the sense of smell, usually in conjunction with taste perversion have also been received.

There have been reports of tooth discolouration in patients treated with clarithromycin. Tooth discolouration is usually reversible with professional dental cleaning.

There have been rare reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic agents or insulin.

Isolated cases of leukopenia and thrombocytopenia have been reported.

As with other macrolides, QT prolongation, ventricular tachycardia and Torsade de Pointes have been rarely reported with clarithromycin.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients.

Overdose and Treatment

Reports indicate the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. One patient who had a history of bipolar disorder ingested eight grams of clarithromycin and showed altered mental status, paranoid behavior, hypokalemia, and hypoxemia.

Adverse reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by hemodialysis or peritoneal dialysis.

Storage Conditions
Store below ….°C

Dosage Forms and Packaging Available
[Packaging type & pack size eg
Tablet - Alu-alu blister of 10s X 10/box, HDPE bottle of 30s/box]

Name and Address of Manufacturer
[Name & full address of manufacturer]

Name and Address of Marketing Authorization Holder
[Name & full address of marketing authorization holder]

Date of Revision of Package Insert
[day/month/year]