PACKAGE INSERT TEMPLATE FOR CLARITHROMYCIN MODIFIED RELEASE TABLET

Brand or Product Name

[Product name] MR 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 modified release 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 MR has been studied in adult humans and compared with clarithromycin 250 mg and 500 mg immediate release tablets. The extent of absorption was found to be equivalent when equal daily doses were administered. The absolute bioavailability is approximately 50%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in humans following multiple dosing. Based upon the finding of equivalent extent of absorption, the following in vitro and in vivo data is applicable to the modified release formulation.

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

In fed patients given 500 mg clarithromycin MR once-daily, the peak steady state plasma concentration of clarithromycin and 14-OH-clarithromycin were 1.3 and 0.48 mcg/mL, respectively. Elimination half-lives of the parent drug and metabolite were approximately 5.3 hours and 7.7 hours, respectively. When clarithromycin MR 1000 mg once-daily (2 x 500 mg) was administered, the steady state C_{max} for clarithromycin and its hydroxylated metabolite averaged 2.4 mcg/mL and 0.67 mcg/mL, respectively. The half-life of the parent drug at the 1000 mg dose level was approximately 5.8 hours, while that of the 14-OH-clarithromycin was approximately 8.9 hours. The T_{max} for both the 500 mg and 1000 mg doses was approximately six hours. At steady state the 14-OH-clarithromycin 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. Urinary excretion accounts for approximately 40% of the clarithromycin dose. Fecal elimination accounts for approximately 30%.

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

Clarithromycin MR is indicated for treatment of:
1. Lower respiratory tract infections (e.g., bronchitis, pneumonia),
2. Upper respiratory tract infections (e.g., pharyngitis, sinusitis), and
3. Skin and soft tissue infections (e.g., folliculitis, cellulitis, erysipelas).

Recommended Dosage

The usual recommended dosage of clarithromycin MR tablets in adults is 500 mg once daily with food. In more severe infections, the dosage may be increased to 1000 mg once daily (2 x 500 mg). The usual duration of therapy is 5 – 14 days for all indications except for sinusitis and community-acquired pneumonia which need 6 to 14 days of treatment.

Clarithromycin MR tablets should not be used in patients with significant renal impairment (creatinine clearance less than 30 mL/mini). Clarithromycin 250 mg and 500 mg immediate release tablets may be utilized in this patient population.
No adjustment of dosage is necessary for subjects with moderate or severe hepatic impairment but with normal renal function.

Do not crush or chew clarithromycin modified release tablets.

Mode of Administration
Oral

Contraindications

Clarithromycin is contraindicated in patients with known hypersensitivity to macrolide antibiotic drugs.
As the dose cannot be reduced from 500 mg once-daily, clarithromycin modified release is contraindicated in patients with creatinine clearance less than 30 mL/min. Clarithromycin immediate release tablets may be utilized in this patient population.
Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, pimozide, terfenadine, ergotamine, dihydroergotamine, lovastatin or simvastatin

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.

Long-term use may, as with other antibiotics, result in colonization with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. Clostridium difficileassociated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, which may lead to overgrowth of C.difficile. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Exacerbation of symptoms of myasthenia gravis has been reported in patients receiving clarithromycin therapy.

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 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.

Oral Hypoglycemic Agents/Insulin
The concomitant use of clarithromycin and oral hypoglycemic agents and/or insulin can result in significant hypoglycemia. With certain hypoglycemic drugs such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypolgycemia when used concomitantly. Careful monitoring of glucose is recommended.

Oral Anticoagulants
There is a risk of serious hemorrhage and significant elevations in INR and prothrombin time when clarithromycin is co-administered with warfarin. INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

HMG-CoA Reductase Inhibitors
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated. As with other macrolides, clarithromycin has been reported to increase concentrations of HMG-CoA reductase inhibitors. Rare reports of rhabdomyolysis have been reported in patients taking these drugs concomitantly. Patients should be monitored for signs and symptoms of myopathy.

Rare reports of rhabdomyolysis have also been reported in patients taking atorvastatin or rosuvastatin concomitantly with clarithromycin. When used with clarithromycin, atorvastatin or rosuvastatin should be administered in the lowest possible doses. Adjustment of the statin dose or use of a statin that is not dependent on CYP3A metabolism (e.g.fluvastatin or pravastatin) should be considered.

Interactions with Other Medicaments

The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

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.

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.

Effects of Other Medicinal Products on clarithromycin

The following drugs are known or suspected to affect circulating concentrations of clarithromycin; clarithromycin dosage adjustment or consideration of alternative treatments may be required.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine
Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14(R)-hydroxyclarithromycin (14-OH-clarithromycin), a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Fluconazole
Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily led to increases in the mean steady-state minimum clarithromycin concentration (C_{min}) and area under the curve (AUC). Steady state concentrations of the active metabolite 14-OH-

clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir
Concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with creatinine clearance 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%, resulting in a maximum dose of one clarithromycin modified release tablet per day. For patients with severe renal impairment (creatinine clearance <30 mL/min), clarithromycin MR should not be used as appropriate clarithromycin dosage reduction is not possible when administering this product. Clarithromycin immediate release tablets may be used in these patient populations. Doses of clarithromycin greater than 1 gm/day should not be co-administered with ritonavir.

Effect of Clarithromycin on Other Medicinal Products

Antiarrhythmics
There have been postmarketed reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during coadministration of clarithromycin with these drugs. Serum levels of these medications should be monitored during clarithromycin therapy.

CYP3A-based Interactions
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. Clarithromycin should be used with caution in patients receiving treatment with other drugs known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g., carbamazepine) and/or the substrate is extensively metabolized by this enzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolized by CYP3A should be monitored closely in patients concurrently receiving clarithromycin.

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.

Omeprazole
The steady-state plasma concentrations of omeprazole were increased, by the concomitant administration of clarithromycin.

Sildenafil, tadalafil, and vardenafil
Each of these phosphodiesterase inhibitors is metabolized, at least in part, by CYP3A, and CYP3A may be inhibited by concomitantly administered clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil would likely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosages should be considered when these drugs are co-administered with clarithromycin.

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

Tolterodine
The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metabolizer population.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)
Concomitant administration of oral midazolam and clarithromycin should be avoided. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. The same precautions should also apply to other benzodiazepines that are metabolized by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been reports of drug interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

<u>Other Drug Interactions</u>

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.

Digoxin
Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine
Simultaneous oral administration of clarithromycin immediate release 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. Similar interaction studies with clarithromycin modified release and zidovudine have not been conducted.

Bi-directional Drug Interactions

Atazanavir
Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Co-administration of clarithromycin with atazanavir resulted in a 2-fold increase in exposure to clarithromycin and a 70% decrease in exposure to 14-OH-clarithromycin, with a 28% increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of clarithromycin should be decreased by 50%. For patients with creatinine clearance <30 mL/min, the dose of clarithromycin should be decreased by 75% using an appropriate clarithromycin formulation. Doses of clarithromycin greater than 1000 mg per day should not be co-administered with protease inhibitors.

Itraconazole
Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. Clarithromycin may increase the plasma levels of itraconazole,

while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin and saquinavir resulted in steady-state AUC and C_{max} values of saquinavir which were higher than those seen with saquinavir alone. No dose adjustment is required when the two drugs are co-administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is coadministered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin.

Verapamil

Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

Statement on Usage During Pregnancy and Lactation

The safety of clarithromycin for use during pregnancy and breast-feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

Adverse Effects / Undesirable Effects

Adverse events reported in patients taking clarithromycin are as follow :

Nervous system disorders

Common : Headache, taste perversion

Gastrointestinal disorders

Common : Diarrhea, nausea, abdominal pain, dyspepsia, vomiting

Investigations

Common : Hepatic enzyme increased

Adverse reactions for all formulations including clarithromycin MR are as follow :

Infections and infestations

Oral candidiasis

Blood and lymphatic system disorders
Leucopenia, thrombocytopenia

Immune system disorders
Anaphylactic reaction, hypersensitivity

Metabolism and nutrition disorders
Hypoglycemia

Psychiatric disorders
Psychotic disorder, hallucination, disorientation, confusional state, depersonalization, depression, anxiety, insomnia, abnormal dreams

Nervous system disorders
Convulsion, dizziness, ageusia, anosmia, dysgeusia, parosmia

Ear and labyrinth disorders
Deafness, vertigo, tinnitus

Cardiac disorders
Torsade de pointes, electrocardiogram QT prolonged, ventricular tachycardia

Gastrointestinal disorders
Pancreatitis acute, glossitis, stomatitis, tongue discoloration, tooth discoloration

Hepatobiliary disorders
Hepatic failure, hepatitis, hepatitis cholestatic, jaundice cholestatic, jaundice hepatocellular, hepatic function abnormal

Skin and subcutaneous tissue disorders
Stevens-Johnson syndrome, toxic epidermal necrolysis, urticaria, rash, drug rash with eosinophilia and systemic symptoms (DRESS)

Musculoskeletal and connective tissue disorders
Myalgia, rhabdomyolysis

Renal and urinary disorders
Nephritis interstitial

Investigations
Blood creatinine increase, hepatic enzyme increased

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]