PACKAGE INSERT TEMPLATE FOR CLARITHROMYCIN POWDER FOR INTRAVENOUS INFUSION

Brand or Product Name

[Product name] Powder for IV Infusion 500mg

Name and Strength of Active Substance(s)

Clarithromycin 500mg

Product Description

[Visual description of the appearance of the product (eg colour, odour etc)
White lyophilized powder. On reconstitution with water yields a white to off-white suspension]

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

Normal Subjects
In a single-dose study of clarithromycin I.V., the mean peak concentration (C_{max}) of parent drug ranged from 5.16 mcg/mL after the 500 mg dose to 9.40 mcg/mL after the 1000 mg dose (60 minute infusion). The mean peak concentration (C_{max}) of the 14-hydroxy metabolite ranged from 0.66 mcg/mL after the 500 mg dose to 1.06 mcg/mL after the 1000 mg dose (60 minute infusion).
The mean terminal phase plasma half-life of parent drug was dose-dependent and ranged from 3.8 hours after the 500 mg dose to 4.5 hours after the 1000 mg dose (60 minute infusion). The mean estimated plasma half-life for the 14-hydroxy metabolite showed some dose-dependent increases at higher doses and ranged from 7.3 hours after the 500 mg dose to 9.3 hours after the 1000 mg dose (60 minute infusion). The mean area under the concentration vs. time curve (AUC) showed a nonlinear dose-dependent increase for parent drug of 22.29 h•mcg/mL after the 500 mg dose to 53.26 h•mcg /mL after the 1000 mg dose. The mean area under the concentration vs. time curve (AUC) for the 14-hydroxy metabolite ranged from 8.16 h•mcg /mL after the 500 mg dose to 14.76 h•mcg /mL after the 1000 mg dose (60 minute infusion).

In a multiple dose study, the observed mean steady-state peak clarithromycin (C_{max}) concentration increased from 5.5 with the 500 mg dose to 8.6 mcg/mL with the 750 mg dose. The mean apparent terminal half-life was 5.3 hours after infusion of the 500 mg dose over a 60-minute period and 4.8 hours after a 60 minute infusion of 750 mg.

The observed mean steady-state C_{max} for the 14-hydroxy metabolite increased from 1.02 mcg/mL with the 500 mg dose to 1.37 mcg/mL with the 750 mg dose. The mean terminal phase half-lives for this metabolite were 7.9 and 5.4 hours for the 500 and 750 mg dose groups, respectively. No dose-related trend was evident.

With b.i.d. oral dosing at 250 mg, the peak steady state plasma concentrations were attained in two to three days and averaged about 1 mcg/mL for clarithromycin and 0.6 mcg/mL for 14- hydroxy-clarithromycin, 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. oral 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- hydroxy-clarithromycin was 6.9 to 8.7 hours. At steady state the 14-hydroxy-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 that metabolism of clarithromycin approaches saturation at high doses.

The major metabolite in human plasma was 14-OH-clarithromycin, with peak levels of 0.5 mcg/mL and 1.2 mcg/mL after oral doses of 250 mg and 1200 mg, respectively. In humans given single oral doses of 250 mg or 1200 mg clarithromycin, urinary excretion accounted for 37.9% of the lower dose and 46.0% of the higher dose. Fecal elimination accounted for 40.2% and 29.1% (this included a subject with only one stool sample containing 14.1%) of these respective doses.

Patients
Clarithromycin and its 14-OH metabolite distribute readily into body tissues and fluids.

Patients with Mycobacterial Infections
Although summarized data are not currently available for the use of clarithromycin I.V. in mycobacterial infections, there are pharmacokinetic data from the use of clarithromycin tablets in these infections. Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of usual clarithromycin doses to adult patients with HIV infection were similar to those observed in normal subjects. However, at the higher doses which may be required to treat mycobacterial infections, clarithromycin concentrations were much higher than those observed at usual doses. Elimination half-lives appeared to be lengthened at these higher doses, as compared to that seen with usual doses in normal subjects. The higher clarithromycin concentrations and longer elimination half-lives observed at these doses are consistent with the known nonlinearity in clarithromycin pharmacokinetics.

Indication

Clarithromycin I.V. is indicated whenever parenteral therapy is required for treatment of sensitive microorganisms in the following conditions:

1. Upper respiratory tract infections
2. Lower respiratory tract infections
3. Skin and soft tissue infections
4. Disseminated or localized mycobacterial infections due to *Mycobacterium avium* or *Mycobacterium intracellulare*. Localized infections due to *Mycobacterium chelonae*, *Mycobacterium fortuitum* or *Mycobacterium kansasii*.

Recommended Dosage

The recommended dosage of clarithromycin I.V. is 1.0 g daily, divided into two equal doses, each infused after further dilution with an appropriate I.V. diluent, over a 60-minute time period. At the present time, there are no data supporting intravenous use of clarithromycin in children. Clarithromycin should not be given as a bolus or an intramuscular injection.

Dosage in Patients With Mycobacterial Infections
Although there currently is no data regarding use of clarithromycin I.V. in immunocompromised patients, data are available regarding the use of oral clarithromycin in HIV-infected patients. In disseminated or localized infections (*M. avium, M. intracellulare, M. chelonae, M. fortuitum, M. kansasii*), the recommended treatment, in adults, is 1000 mg/day in two divided doses. Intravenous therapy may be limited for up to two to five days in the very ill patient and should be changed to oral therapy whenever possible as determined by the physician.

In patients with renal impairment who have creatinine clearance less than 30 mL/min, the dosage of clarithromycin should be reduced to one half of the normal recommended dose.

Mode of Administration
Intravenous infusion

Contraindications

Clarithromycin IV is contraindicated in patients with known hypersensitivity to macrolide antibiotic drugs. Allergic or hypersensitive reactions should be managed by prompt supportive measures.
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 I.V. 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 from mild to life-threatening. Clostridium difficile-associated 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 failure.

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.

<u>Effects of Other Medicinal Products on clarithromycin</u>

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.

<u>Effect of Clarithromycin on Other Medicinal Products</u>

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 was 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.

Other Drug Interactions

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 tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. This interaction does not appear to occur in pediatric HIV-infected patients taking a clarithromycin suspension formulation concurrently with zidovudine or dideoxyinosine. Because clarithromycin appears to interfere with the absorption in adults of simultaneously administered oral zidovudine, this interaction would most likely not be a problem when clarithromycin is administered intravenously.

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 I.V. use during pregnancy has not been established. The safety of clarithromycin I.V. use during 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 IV 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

Immunocompromised Pediatric Patients
Although there currently is no data regarding use of clarithromycin I.V. in this patient population, data is available regarding the use of oral clarithromycin in HIV-infected patients.

In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it is often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of HIV disease or intercurrent illness.

In adult patients, the most frequently reported adverse events by patients treated with total daily oral doses of 1000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhea, rash, flatulence, headache, constipation, hearing disturbance, SGOT and SGPT elevations. Additional low-frequency events included dyspnea, insomnia and dry mouth.

Overdose and Treatment

In the case of overdosage, clarithromycin I.V. should be discontinued and all other appropriate supportive measures should be instituted.

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.

Incompatibilities

None known. However, Clarithromycin IV should only be diluted with the diluents recommended.

Instruction for Use

The final solution for infusion is prepared as follows:
1. Prepare the initial solution of clarithromycin I.V. by adding 10 mL of Sterile Water for Injection to the 500 mg vial. Use only Sterile Water for Injection, as other diluents may cause precipitation during reconstitution. Do not use diluents containing preservatives or inorganic salts. When the product is reconstituted as directed above, the resulting solution contains an effective antimicrobial preservative; each mL contains 50 mg of clarithromycin I.V.

2. The reconstituted product (500 mg in 10 mL Water for Injection) should be added to a minimum of 250 mL of one of the following diluents before administration: 5% dextrose in Lactated Ringer's Solution, 5% dextrose, Lactated Ringer's, 5% dextrose in 0.3% sodium chloride, Normosol-M in 5% dextrose, Normosol-R in 5% dextrose, 5% dextrose in 0.45% sodium chloride, and 0.9% sodium chloride.

No drug or chemical agent should be added to a clarithromycin I.V. fluid admixture unless its effect on the chemical and physical stability of the solution has first been determined.

Storage Conditions

Finished product - Store below ….°C
Reconstituted solution - Store below ….°C for ….days.
Final diluted solution - Store below ….°C for ….days.
* If not, please include this statement - For single use only. Discard any unused portion after reconstitution/dilution

Dosage Forms and Packaging Available
[Packaging type & pack size eg 10 ml type I clear glass vial, capped with a butyl rubber stopper/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]