PACKAGE INSERT TEMPLATE FOR CLARITHROMYCIN GRANULES FOR ORAL SUSPENSION

Brand or Product Name

[Product name] Granules for Oral Suspension 125mg/5ml
[Product name] Granules for Oral Suspension 250mg/5ml

Name and Strength of Active Substance(s)

Clarithromycin 125mg/5ml
Clarithromycin 250mg/5ml

Product Description

[Visual description of the appearance of the product (eg colour, odour, flavour etc)
eg White, dry granules. 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

Initail pharmacokinetic data indicated the drug is rapidly absorbed from the gastrointestinal tract and the absolute bioavailability of a clarithromycin 50 mg tablet was approximately 50%. Both the onset of absorption and the formation of the antimicrobially-active metabolite, 14-OH-clarithromycin, were slightly delayed by food, but the extent of bioavailability was not affected by administration of drug in the nonfasting state.

In vitro
In vitro studies showed that protein binding of clarithromycin in human plasma averaged about 70% at clinically-relevant concentrations of 0.45 to 4.5 mcg/mL.

Normal Subjects
The bioavailability and pharmacokinetics of Clarithromycin Granules for Oral Suspension were investigated in adult subjects and in pediatric patients. The overall bioavailability of the pediatric formulation to be equivalent to or slightly greater than that of the tablet (dosage with each was 250 mg). As with the tablet, administration of the pediatric formulation with food leads to a slight delay in the onset of absorption, but does not affect the overall bioavailability of clarithromycin.

The elimination half-life of clarithromycin was about three to four hours with a 250 mg tablet administered every 12 hours but increased to five to seven hours with 500 mg administered every

12 hours. The principal metabolite, 14-OH-clarithromycin, attains a peak steady state concentration of about 0.6 mcg/mL and has an elimination half-life of five to six hours after a dose of 250 mg every 12 hours. With a dose of 500 mg every 12 hours, the peak steady-state concentrations of 14-OH-clarithromycin are slightly higher (up to 1 mcg/mL), and its elimination half-life is about seven hours. With either dose, the steady-state concentration of this metabolite is generally attained within two to three days.

Approximately 20% of a 250 mg oral dose given every 12 hours is excreted in the urine as unchanged clarithromycin. After a dose of 500 mg every 12 hours, urinary excretion of unchanged parent drug is approximately 30%. The renal clearance of clarithromycin is, however, relatively independent of the dose size and approximates the normal glomerular filtration rate. The major metabolite found in urine is 14-OH-clarithromycin which accounts for an additional 10% to 15% of either a 250 mg or 500 mg dose administered every 12 hours.

Patients
Clarithromycin and its 14-OH metabolite distribute readily into body tissues and fluids. Concentrations in tissues are usually several fold higher than serum concentrations.

In pediatric patients requiring oral antibiotic treatment, clarithromycin demonstrated good bioavailability with a pharmacokinetic profile consistent with previous results from adult subjects using the same suspension formulation. The results indicated rapid and extensive drug absorption in children and, except for a slight delay in onset of absorption, food seemed to have no significant affect on drug bioavailability or pharmacokinetic profiles. Elimination half-life was estimated to be approximately 2.2 hr and 4.3 hr for the parent compound and metabolite, respectively.

Hepatic Impairment
The steady-state concentrations of clarithromycin in subjects with impaired hepatic function did not differ from those of normal subjects; however, the 14-OH-clarithromycin concentrations were lower in the hepatically-impaired subjects. The decreased formation of 14-OH- Clarithromycin was at least partially offset by an increase in renal clearance of clarithromycin in the subjects with impaired hepatic function when compared to healthy subjects.

Renal Impairment
The pharmacokinetics of clarithromycin were also altered in subjects with impaired renal function who received multiple 500 mg oral doses. The plasma levels, half-life, C_{max} and C_{min} for both clarithromycin and its 14- H metabolite were higher and the AUC was larger in subjects with renal impairment than in normal subjects. The extent to which these parameters differed was correlated with the degree of renal impairment; the more severe the renal impairment, the more significant the difference.

Elderly Subjects

There was no difference between the two groups when renal clearance of clarithromycin was correlated with creatinine clearance. It was concluded from these results that any effect on the handling of clarithromycin is related to renal function and not to subject age.

Patients with Mycobacterial Infections
Steady-state concentrations of clarithromycin and 14-OH clarithromycin observed following administration of usual doses to patients with HIV infections (tablets for adults; granular suspension for children) were similar to those observed in normal subjects. However, at the higher doses which may be required to treat mycobacterial infections, Clarithromycin concentrations can be much higher than those observed at usual doses.

Elimination half-lives appeared to be lengthened at these higher doses as compared to that observed with usual doses in normal subjects. The higher plasma concentrations and longer elimination half-lives observed at these doses are consistent with the known nonlinearity in clarithromycin pharmacokinetics.

Indication

Clarithromycin Granules for Oral Suspension is indicated for treatment of infections in children due to susceptible organisms, in the following conditions:

1. Upper respiratory infections (e.g., streptococcal pharyngitis).
2. Lower respiratory infections (e.g., bronchitis, pneumonia).
3. Acute otitis media.
4. Skin and skin structure infections (e.g., impetigo, folliculitis, cellulitis, abscesses).
5. 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 daily dosage of Clarithromycin Granules for Oral Suspension in children is 7.5 mg/kg b.i.d. up to a maximum dose of 500 mg b.i.d. for non-mycobacterial infections. The usual duration of treatment is for five to ten days depending on the pathogen involved and the severity of the condition. The prepared suspension can be taken with or without meals, and can be taken with milk.

The following table is a suggested guide for determining dosage:

Dosage guidelines for pediatric patients (based on body weight)	
Weight *	Dosage in standard 5 mL teaspoonful given twice daily

Kg	Lbs.	125 mg/5 mL	250 mg/5 mL
8-11	18-25	0.5	--
12-19	26-43	1	0.5
20-29	44-64	1.5	0.75
30-40	65-88	2	1
* Children < 8 kg or < 18 lbs. should be dosed on a per kg or per lb. basis (approx. 7.5 mg/kg b.i.d. or 3.4 mg/lb b.i.d.)			

Dosage in Patients with Renal Impairment
In children with creatinine clearance less than 30 mL/min, the dosage of clarithromycin should be reduced by one-half, i.e., up to 250 mg once daily, or 250 mg twice daily in more severe infections. Dosage should not be continued beyond 14 days in these patients.

Dosage in Patients with Mycobacterial Infections
In children with disseminated or localized mycobacterial infections (*M. avium, M. intracellulare, M. chelonae, M. fortuitum, M. kansasii*), the recommended dose is 15 to 30 mg/kg clarithromycin per day in two divided doses. \
Treatment with clarithromycin should continue as long as clinical benefit is demonstrated. The addition of other antimycobacterial agents may be of benefit.

Dosage guidelines for pediatric AIDS patients (based on body weight)			
Weight *		Dosage in standard 5 mL teaspoonful given twice daily (Clarithromycin Granules for Oral Suspension 250mg/5ml)	
Kg	Lbs.	15 mg/kg	30 mg/kg
8-11	18-25	0.5	1
12-19	26-43	1	2
20-29	44-64	1.5	3
30-40	65-88	2	4
* Children < 8 kg (18 lbs.) should be dosed on a per kg basis (15 to 30 mg/kg/day)			

Mode of Administration
Oral

Contraindications

Clarithromycin Granules for Oral Suspension 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, ergotamine, dihydroergotamine, lovastatin or simvastatin

Warnings and Precautions

If Clarithromycin Granules for Oral Suspension is considered for patients of post-pubertal age, the physician should carefully weigh the benefits against the risk when pregnancy is either suspected or confirmed.

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.

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 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.

<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

The safety profile of the pediatric formulation is similar to that of the clarithromycin tablet in adult patients. 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 granules for oral suspension 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
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.

A limited number of pediatric AIDS patients have been treated with Clarithromycin Granules for Oral Suspension for mycobacterial infections. The most frequently reported adverse events, excluding those due to the patient's concurrent condition, were tinnitus, deafness, vomiting, nausea, abdominal pain, purpuric rash, pancreatitis, and increased amylase.

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.

Instruction for Use

An appropriate amount of water should be added to the granules in the bottle and shaken to yield a reconstituted suspension. The concentration of clarithromycin in the reconstituted suspension is either 125 mg per 5 mL or 250 mg per 5 mL.

Shake well before each use.

Storage Conditions
Finished product - Store below ….°C
Reconstituted suspension - Store below ….°C for ….days.
* If not, please include this statement - For single use only. Discard any unused portion after reconstitution.
Do not refrigerate the reconstituted suspension

Dosage Forms and Packaging Available
[Packaging type & pack size eg HDPE bottle of 50ml/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]