ABBOTIC
Clarithromycin

1. NAME OF THE MEDICINAL PRODUCT
Abbotic 125 mg/5 ml, Granules for Oral Suspension (Pediatric Suspension)
Abbotic 250 mg/5 ml, Granules for Oral Suspension (Pediatric Suspension)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
Clarithromycin 125 mg/5 ml, Granules for Oral Suspension (Pediatric Suspension):
Each 5 ml of the granules for suspension contains 125 mg of clarithromycin.
Excipient: Sucrose 2,6793 mg/ 5 ml

Clarithromycin 250 mg/5 ml, Granules for Oral Suspension (Pediatric Suspension):
Each 5 ml of the granules for suspension contains 250 mg of clarithromycin.
Excipient: Sucrose 2276,2 mg/ 5 ml

For the full list of excipients, see section List of Excipients.

3. PHARMACEUTICAL FORM
White to off-white granules for suspension

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Abbotic® Granules 125 mg or 250 mg/5 ml is indicated for treatment of infections 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)

4.2 Posology and method of administration
The recommended daily dosage of ABBOTIC® GRANULES (125 mg/5 ml or 250 mg/5 ml) in children is 7.5 mg/kg b.i.d. up to a maximum dose of 500 mg b.i.d. for severe infections. The usual duration of treatment is for 5 to 10 days depending on the pathogen involved and the severity of the condition.
Treatment for Streptococcal pharyngitis should be at least 10 days. 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	**125 mg/5 mL**	**250 mg/5 mL**
8 - 11	0.5	--

12 - 19	1	0.5
20 - 29	1.5	0.75
30 - 40	2	1
* Children < 8 kg should be dosed on a per kg basis (approx. 7.5 mg/kg b.i.d.)		

4.3 Contraindications

Hypersensitivity to macrolide antibiotic drugs or any of the excipients (see section 6.1).

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, pimozide, terfenadine as this may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation, and *torsades de pointes* (see section 4.5).

Concomitant administration of clarithromycin and ergot alkaloids (e.g., ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity (see section 4.5).

Concomitant administration of clarithromycin and oral midazolam is contraindicated (see section 4.5).

Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including *torsades de pointes* (see sections 4.4 and 4.5).

Clarithromycin should not be given to patients with electrolyte disturbances (hypokalemia or hypomagnesaemia, due to risk of prolongation of QT interval).

Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis (see section 4.4).

Clarithromycin (and other strong CYP3A4 inhibitors) should not be used concomitantly with colchicine (see sections 4.4 and 4.5).

Concomitant administration with ticagrelor or ranolazine is contraindicated.

Concomitant administration of clarithromycin and lomitapide is contraindicated (see section 4.5).

4.4 Special warnings and precautions for use

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.

Clarithromycin is principally metabolized 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 (see section 4.3).

Caution is advised in patients with severe renal insufficiency.
Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. This hepatic dysfunction may be severe and is usually reversible. In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications. Discontinue clarithromycin immediately if signs and symptoms of hepatitis occur, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

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

Colchicine
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 (see section 4.5). Concomitant administration of clarithromycin and colchicine is contraindicated (see section 4.3).

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam (see section 4.5).

Cardiovascular Events
Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and *torsades de pointes*, have been seen in treatment with macrolides including clarithromycin (see section 4.8). Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including *torsades de pointes*), clarithromycin should be used with caution in the following patients;

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia

- Clarithromycin must not be given to patients with hypokalaemia or hypomagnesaemia (see section 4.3).
- Patients concomitantly taking other medicinal products associated with QT prolongation (see section 4.5).
- Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfenadine is contraindicated (see section 4.3).
- Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

Carefully consider the balance of benefits and risks before prescribing clarithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

Epidemiological studies investigating the risk of adverse cardiovascular outcomes with macrolides have shown variable results. Some observational studies have identified a rare short-term risk of arrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin. Consideration of these findings should be balanced with treatment benefits when prescribing clarithromycin.

Pneumonia
In view of the emerging resistance of Streptococcus pneumoniae to macrolides, it is important that sensitivity testing be performed when prescribing clarithromycin for community-acquired pneumonia.
In hospital-acquired pneumonia, clarithromycin should be used in combination with additional appropriate antibiotics.

Skin and soft tissue infections of mild to moderate severity
These infections are most often caused by Staphylococcus aureus and Streptococcus pyogenes, both of which may be resistant to macrolides. Therefore, it is important that sensitivity testing be performed.
In cases where beta–lactam antibiotics cannot be used (e.g. allergy), other antibiotics, such as clindamycin, may be the drug of first choice. Currently, macrolides are only considered to play a role in some skin and soft tissue infections, such as those caused by *Corynebacterium minutissimum*, acne vulgaris, and erysipelas and in situations where penicillin treatment cannot be used.

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g. Acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson Syndrome, toxic epidermal necrolysis and DRESS); clarithromycin therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Clarithromycin should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see section 4.5).

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

HMG-CoA Reductase Inhibitors (statins):
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathyIn situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered (see 4.5).

Oral Hypoglycemic Agents/Insulin
The concomitant use of clarithromycin and oral hypoglycemic agents (such as sulphonylurias) and/or insulin can result in significant hypoglycemia. 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.

Caution should be exercised when clarithromycin is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk of bleeding (see section 4.5).

Excipients
Clarithromycin Modified Release tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take these medicines.
When prescribing to diabetic patients, the sucrose content should be taken into account.

4.5 Interaction with other medicinal products and other forms of interaction
The use of the following drugs is strictly contraindicated due to the potential for severe drug interaction effects:

Cisapride, pimozide, astemizole and terfenadine
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 (see section 4.3).

Macrolides have been reported to alter the metabolism of terfenadine resulting in increasing levels of terfenadine which has occasionally been associated with cardiac arrhytmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and *torsades de pointes* (see section 4.3). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a 2 to 3 fold increase in the serum level of the acid metabolites of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect.

Ergot alkaloids
Postmarketing reports indicate that 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 ergot alkaloids is contraindicated (see section 4.3).

Oral Midazolam
When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 7-fold after oral administration of midazolam. Concomitant administration of oral midazolam and clarithromycin is contraindicated (see section 4.3)

HMG-CoA Reductase Inhibitors (statins)
Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see 4.3) as these statins are extensively metabolized by CYP3A4 and concomitant treatment with clarithromycin increases their plasma concentration, which increases the risk of myopathy, including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking clarithromycin concomitantly with these statins. If treatment with clarithromycin cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing clarithromycin with statins. In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g.fluvastatin) can be considered. Patients should be monitored for signs and symptoms of myopathy.

Lomitapide
Concomitant administration of clarithromycin with lomitapide is contraindicated due the potential for markedly increased transaminases (see section 4.3).

Effects of Other Medicinal Products on Clarithromycin
Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Because of the potential for a similar risk with other macrolides when used in combination with hydroxychloroquine or chloroquine, careful consideration should be given to the balance of benefits and risks before prescribing <clarithromycin/erythromycin> for any patients taking hydroxychloroquine or chloroquine.

Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's Wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inducer administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

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)-hydroxy-clarithromycin (14-OHclarithromycin), 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.

Etravirine

Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.

Fluconazole

Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18% respectively. 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

A pharmacokinetic study demonstrated that the 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. The clarithromycin Cmax increased by 31%, Cmin increased 182% and AUC increased by 77% with concomitant administration of ritonavir. 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 CLCR 30 to 60 ml/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 ml/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 gm/day should not be coadministered with ritonavir.

Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see Bi-directional Drug Interactions).

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 co administration of clarithromycin with these drugs. Serum levels of these medications should be monitored during clarithromycin therapy.
There have been post marketing reports of hypoglycemia with the concomitant administration of clarithromycin and disopyramide. Therefore blood glucose levels should be monitored during concomitant administration of clarithromycin and disopyramide.

Oral hypoglycemic agents/Insulin
With certain hypoglycemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypolgycemia when used concomitantly. Careful monitoring of glucose is recommended.

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, rivaroxaban, apixaban), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, tacrolimus, terfenadine, triazolam and vinblastine, but this list is not comprehensive. Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

Direct acting oral anticoagulants (DOACs)
The DOAC dabigatran is a substrate for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co-administered with these agents particularly to patients at high risk of bleeding (see section 4.4).

Omeprazole
Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max}, AUC_{0-24}, and $t_{1/2}$ increased by 30%, 89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with 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

Results of clinical studies indicate there was a modest but statistically significant ($p \leq 0.05$) 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)

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. 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 post-marketing 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. Concomitant use of clarithromycin and colchicine is contraindicated (see sections 4.3 and 4.4).

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. 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 to allow for a 4-hour interval between each medication. This interaction does not appear to occur in pediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be metabolized by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have been reported.

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 (500 mg twice daily) with atazanavir (400 mg once daily) 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 coadministered with protease inhibitors.

Calcium Channel Blockers

Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers metabolized by CYP3A4 (e.g., verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of clarithromycin as well as calcium channel blockers may increase due to the interaction. Hypotension, bradyarrhythmias and lactic acidosis have been observed in patients taking clarithromycin and verapamil concomitantly.

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 (500 mg bid) and saquinavir (soft gelatin capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state AUC and Cmax values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax values were approximately 40% higher than those seen with clarithromycin 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 co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see section 4.5).

4.6 Fertility, Pregnancy, and lactation

Pregnancy

The safety of clarithromycin for use in pregnancy has not been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofetal development cannot be excluded. Some observational studies evaluating exposure to clarithromycin during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including clarithromycin during pregnancy provide conflicting results. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

Breastfeeding

Clarithromycin is excreted into human breast milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin. The safety of clarithromycin use during breast-feeding of infants has not been established.

Fertility

In the rat, fertility studies have not shown any evidence of harmful effects.

4.7 Effects on ability to drive and use machines

There are no data on the effect of clarithromycin on the ability to drive or use machines. The potential for dizziness, vertigo, confusion and disorientation, which may occur with the medication, should be taken into account before patients drive or use machines.

4.8 Undesirable effects

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and pediatric populations are abdominal pain, diarrhea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics.

There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without preexisting mycobacterial infections.

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin granules for oral suspension.
The reactions considered at least possibly related to clarithromycin are displayed by system organ class and frequency using the following convention: very common (≥1/10), common (≥ 1/100 to < 1/10), uncommon (≥1/1,000 to < 1/100) and not known (adverse reactions from post-marketing experience; cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness when the seriousness could be assessed.

Adverse Reactions Reported with Clarithromycin				
MedDRA System Organ Class	**Very common ≥ 1/10**	**Common ≥ 1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Not Known* (cannot be estimated from the available data)**
Infections and infestations			Candidiasis, vaginal infection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system			Leukopenia, thrombocythemia	Agranulocytosis, thrombocytopenia
Immune system disorders			Hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety, nervousness	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia headache	Dizziness, somnolence, tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Electrocardiogram QT prolonged, palpitations	Torsade de pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders				Hemorrhage

Respiratory, thoracic and mediastinal disorder				
Gastrointestinal disorders		Diarrhea, vomiting, dyspepsia, nausea, abdominal pain	Gastritis, stomatitis, glossitis, constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discolouration, tooth discoloration
Hepatobiliary disorders		Liver function test abnormal	Alanine aminotransferase increased, aspartate aminotransferase increased	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Pruritus, urticaria, rash	Severe cutaneous adverse reactions (SCAR) (e.g. Acute generalized exanthematous pustulosis (AGEP), Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne
Musculoskeletal and connective tissue disorders			Muscle spasms, Musculoskeletal	Myopathy
Renal and urinary disorders				Renal failure, nephritis interstitial
General disorders and administration site conditions			Pyrexia, asthenia	
Investigations				International normalised ratio increased, prothrombin time prolonged, urine color abnormal

* Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.
**In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with other drugs known to be associated with rhabdomyolysis (such as statins, fibrates, colchicine or allopurinol).

Immunocompromised Patients
In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was 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 events treated with total doses of 1,000 mg and 2,000 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 dyspepsia, insomnia, and dry mouth.

In these immunocompromised patients evaluations of laboratory values were made by analyzing those values outside the seriously abnormal level (i.e., the extreme high or low limit) for the specified test. On the basis of this criteria, about 2 to 3% of these patients who received 1000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients also had elevated BUN levels.

4.9 Overdose
Symptoms
Reports indicate that 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.

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

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antibacterial for systemic use, macrolide
ATC-Code: J01FA09

Clarithromycin is a semi-synthetic macrolide antibiotic obtained by substitution of a CH_3O group for the hydroxyl (OH) group at position 6 of the erythromycin lactonic ring. Specifically

clarithromycin is 6-O-methyl erythromycin A. The white to off white antibiotic powder is bitter, practically odorless, essentially insoluble in water, and slightly soluble in ethanol, methanol, and acetonitrile. Its molecular weight is 747.96.

Microbiology

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunits of susceptible bacteria and suppresses 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 susceptible to clarithromycin.

Clarithromycin has been shown to be active against most strains of the following micro- organisms both in vitro and in clinical infections as described in section 4.1:

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 avium complex (MAC) consisting of: Mycobacterium avium
Mycobacterium Intracellulare

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

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

Helicobacter
Helicobacter pylori
In cultures performed prior to therapy, *H. pylori* was isolated and clarithromycin MIC's were determined pre-treatment in 104 patients. Of these, four patients had resistant strains, two patients had strains with intermediate susceptibility, and 98 patients had susceptible strains. The following *in vitro* data are available, **but their clinical significance is unknown.** 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 in adequate and well-controlled clinical trials.

Aerobic Gram-positive microorganisms
Streptococcus agalactiae

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.

Clarithromycin was found to be two to ten times more active than erythromycin in several experimental animal infection models. It was shown, for example, to be more effective than erythromycin in mouse systemic infection, mouse subcutaneous abscess, and mouse respiratory tract infections caused by *S. pneumoniae*, *S. aureus*, *S. pyogenes*, and *H. influenzae*. In guinea pigs with Legionella infection this effect was more pronounced; an intraperitoneal dose of 1.6 mg/kg/day of clarithromycin was more effective than 50 mg/kg/day of erythromycin.

Susceptibility Tests
Quantitative methods that require measurement of zone diameters give the most precise estimates of susceptibility of bacteria to antimicrobial agents. One recommended procedure uses discs impregnated with 15 µg of clarithromycin for testing susceptibility (Kirby-Bauer diffusion test); interpretations correlate inhibition zone diameters of this disc test with MIC values for clarithromycin. The MICs are determined by the broth or agar dilution method.

With these procedures, a report from the laboratory of "susceptible" indicates the infecting organism is likely to respond to therapy. A report of "resistant" indicates the infective organism is not likely to respond to therapy. A report of "Intermediate Susceptibility" suggests the therapeutic effect of the drug may be equivocal or the organism would be susceptible if higher doses were used. (Intermediate susceptibility is also referred to as moderately susceptible.)

Clinical Studies

Clinical Experience in Patients with Non-Mycobacterial Infections
In clinical studies, clarithromycin at a dose of 7.5 mg/kg b.i.d. was demonstrated to be safe and effective in the treatment of pediatric patients with infections requiring oral antibiotic treatment. It has been evaluated in over 1200 children, ages six months to 12 years, with otitis media, pharyngitis, skin infections and lower respiratory tract infections.

In these studies, clarithromycin at a dose of 7.5 mg/kg b.i.d. showed comparable clinical and bacteriological efficacy to the reference agents which included penicillin V, amoxicillin, amoxicillin/clavulanate, erythromycin ethylsuccinate, cefaclor and cefadroxil.

Clinical Experience in Patients with Mycobacterial Infections
A preliminary study in pediatric patients (some were HIV positive) with mycobacterial infections demonstrated that clarithromycin was a safe and effective treatment when given alone and in combination with zidovudine or dideoxyinosine. Clarithromycin Pediatric Suspension was administered as 7.5, 15 or 30 mg/kg/day in two divided doses.

Some statistically significant effects on pharmacokinetic parameters were observed when clarithromycin was administered with antiretroviral compounds; however, these changes were minor and not likely to be of clinical significance. Clarithromycin at doses of up to 30 mg/kg/day was well-tolerated.

Clarithromycin was effective in the treatment of disseminated *M. avium* complex infections in pediatric patients with AIDS, with some patients demonstrating continued efficacy after more than one year of therapy.

5.2 Pharmacokinetic properties

Absorption
Initial pharmacokinetic data were obtained with clarithromycin tablet formulations. These data indicated the drug is rapidly absorbed from the gastrointestinal tract and the absolute

bioavailability of a clarithromycin 250 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.

Distribution, Biotransformation and Elimination

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 µg/ml. A decrease in binding to 41 % at 45.0 µg/ml suggested that the binding sites might become saturated, but this only occurred at concentrations far in excess of the therapeutic drug level.

Normal Subjects

The bioavailability and pharmacokinetics of Clarithromycin Pediatric Suspension were investigated in adult subjects and in pediatric patients. A single-dose study in adult subjects found 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 comparative clarithromycin Cmax, AUC, and T ½ for the pediatric formulation (nonfasted state) were 0.95 µg/ml, 6.5 µg hr/ml, and 3.7 hours, respectively, and for the 250 mg tablet (fasted state) were 1.10 µg/ml, 6.3 µg hr/ml, and 3.3 hours, respectively.

In a multiple dose study in which adult subjects were administered 250 mg of the Clarithromycin Pediatric Suspension every 12 hours, steady state blood levels were nearly reached by time of the fifth dose. Pharmacokinetic parameters after the fifth dose for Clarithromycin Pediatric Suspension were: Cmax 1.98 µg/ml, AUC 11.5 µg hr/ml, Tmax 2.8 hours and T ½ 3.2 hours for clarithromycin, and 0.67, 5.33, 2.9 and 4.9, respectively, for 14-OH-clarithromycin.

In fasting healthy human subjects, peak serum concentrations were attained within two hours after oral dosing. With b.i.d. dosing using a 250 mg tablet every 12 hours, steady-state peak serum concentrations of clarithromycin were attained in two to three days and were approximately 1 µg/ml. Corresponding peak serum concentrations were 2 to 3 µg/ml with a 500 mg dose administered every 12 hours.

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 µg/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 µg/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. Examples from tissue and serum concentrations are presented below:

CONCENTRATION (after 250 mg q12 h)		
Tissue Type	Tissue (mcg/g)	Serum (mcg/mL)
Tonsil	1.6	0.8
Lung	8.8	1.7

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 effect on drug bioavailability or pharmacokinetic profiles. Steady-state pharmacokinetic parameters obtained after the ninth dose on treatment day five were as follows for the parent drug: Cmax 4.60 µg/ml, AUC 15.7 µg/hr/ml and Tmax 2.8 hr; the corresponding values for the 14-OH metabolite were: 1.64 µg/ml, 6.69 µg/hr/ml, and 2.7 hr, respectively. Elimination half-life was estimated to be approximately 2.2 hr and 4.3 hr for the parent compound and metabolite, respectively.

In another study, information was obtained regarding the penetration of clarithromycin in middle ear fluid in patients with otitis media. Approximately 2.5 hours after receiving the fifth dose (dosage was 7.5 mg/kg b.i.d.), the mean concentration of clarithromycin was 2.53 µg/g fluid in the middle ear and for the 14-OH metabolite was 1.27 µg/g. The concentrations of parent drug and 14-OH metabolite were generally twice as high as the corresponding concentrations in serum.

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, Cmax and Cmin for both

clarithromycin and its 14 OH 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 (see section 4.2).

Elderly Subjects
In a comparative study of healthy, young adults and healthy, elderly subjects given multiple 500 mg oral doses of clarithromycin, the circulating plasma levels were higher and elimination was slower in the elderly group compared to the younger group. However, 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.

In children with HIV infection taking 15 to 30 mg/kg/day of clarithromycin in two divided doses, steady-state Cmax values generally ranged from 8 to 20 μg/ml. However, Cmax values as high as 23 μg/ml have been observed in HIV-infected pediatric patients taking 30 mg/kg/day in two divided doses as Clarithromycin Pediatric Suspension. 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.

5.3 Preclinical safety data

Acute and Subchronic Oral Toxicity Studies
The acute oral LD50 values for a clarithromycin suspension administered to three-day old mice were 1290 mg/kg for males and 1230 mg/kg for females. The LD50 values in three-day old rats were 1330 mg/kg for males and 1270 mg/kg for females. For comparison, the LD50 for orally-administered clarithromycin is about 2700 mg/kg for adult mice and about 3000 mg/kg for adult rats. These results are consistent with other antibiotics of the penicillin group, cephalosporin group and macrolide group in that the LD50 is generally lower in juvenile animals than in adults.

In both mice and rats, body weight was reduced or its increase suppressed and suckling behavior and spontaneous movements were depressed for the first few days following drug administration. Necropsy of animals that died disclosed dark-reddish lungs in mice and about 25% of the rats; rats treated with 2197 mg/kg or more of a clarithromycin suspension were also noted to have a reddish-black substance in the intestines, probably because of bleeding. Deaths of these animals were considered due to debilitation resulting from the depressed suckling behavior or bleeding from the intestines.

Pre-weaning rats (five days old) were administered a clarithromycin suspension formulation for two weeks at doses of 0, 15, 55, and 200 mg/kg/day. Animals from the 200 mg/kg/day group had decreased body weight gains, decreased mean hemoglobin and hematocrit values, and increased mean relative kidney weights compared to animals from the control group. Treatment-related minimal to mild multifocal vacuolar degeneration of the intrahepatic bile duct epithelium and an increased incidence of nephritic lesions were also observed in animals from this treatment group. The "no-toxic effect" dosage for this study was 55 mg/kg/day.

An oral toxicity study was conducted in which immature rats were administered a clarithromycin suspension for six weeks at daily dosages of 0, 15, 50, and 150 mg base/kg/day. No deaths occurred and the only clinical sign observed was excessive salivation for some of the animals at the highest dosage from one to two hours after administration during the last three weeks of treatment. Rats from the 150 mg/kg dose group had lower mean body weights during the first three weeks, and were observed to have decreased mean serum albumin values and increased mean relative liver weight compared to the controls.

No treatment-related gross or microscopic histopathological changes were found. A dosage of 150 mg/kg/day produced slight toxicity in the treated rats and the "no effect dosage" was considered to be 50 mg/kg/day.

Juvenile beagle dogs, three weeks of age, were treated orally daily for four weeks with 0, 30, 100, or 300 mg/kg of clarithromycin, followed by a four week recovery period. No deaths occurred and no changes in the general condition of the animals were observed. Necropsy revealed no abnormalities. Upon histological examination, fatty deposition of centrilobular hepatocytes and cell infiltration of portal areas were observed by light microscopy, and an increase in hepatocellular fat droplets was noted by electron microscopy in the 300 mg/kg dose group. The toxic dose in juvenile beagle dogs was considered to be greater than 300 mg/kg and the "no effect dose" 100 mg/kg.

Fertility, Reproduction, and Teratogenicity

Fertility and reproduction studies in female rats have shown that daily dosages of 150 mg/kg/day (highest dose tested) caused no adverse effects on the estrous cycle, fertility, parturition, and number and viability of offspring. In male rats there was no evidence of adverse toxicity on fertility upto 250mg/kg. Two teratogenicity studies in both Wistar (p.o.) and Sprague Dawley (p.o. and i.v.) rats, one study in New Zealand white rabbits and one study in cynomolgus monkeys failed to demonstrate any teratogenicity from clarithromycin. Only in one additional study in Sprague-Dawley rats at similar doses and essentially similar conditions did a very low, statistically insignificant incidence (approximately 6%) of cardiovascular anomalies occur. These anomalies appeared to be due to spontaneous expression of genetic changes within the colony. Two studies in mice also revealed a variable incidence of cleft palate (3 to 30%) following doses of 70 times the upper range of the usual daily human clinical dose (500 mg, b.i.d.), but not at 35 times the maximal daily human clinical dose, suggesting maternal and fetal toxicity but not teratogenicity.

Clarithromycin has been shown to produce embryonic loss in monkeys when administered at approximately ten times the upper range of the usual daily human dose (500 mg b.i.d.), starting at gestation day 20. This effect has been attributed to maternal toxicity of the drug at very high doses.

An additional study in pregnant monkeys at dosages of approximately 2.5 to 5 times the maximal intended daily dosage of 500 mg b.i.d. produced no unique hazard to the conceptus.

A dominant lethal test in mice given 1000 mg/kg/day (approximately 70 times the maximal human daily clinical dose of 500 mg b.i.d.) was clearly negative for any mutagenic activity, and, in a Segment I study of rats treated with up to 500 mg/kg/day (approximately 35 times the maximal daily human
clinical dose of 500 mg b.i.d.) for 80 days, no evidence of functional impairment of male fertility due to this long-term exposure to these very high doses of clarithromycin was exhibited.

Mutagenicity
Studies to evaluate the mutagenic potential of clarithromycin were performed using both nonactivated and rat-liver-microsome-activated test systems (Ames Test). Results of these studies provided no evidence of mutagenic potential at drug concentrations of 25 µg/Petri plate or less. At a concentration of 50 µg the drug was toxic for all strains tested.

5 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Clarithromycin 125 mg/5 ml Granules for Oral Suspension (Pediatric Suspension)
Clarithromycin 250 mg/5 ml Granules for Oral Suspension (Pediatric Suspension)

Sucrose
Xanthan gum
Silicon dioxide
Potassium sorbate
Citric acid
Maltodextrin
Titanium dioxide
Fruit punch flavor

6.2 Special precautions for disposal and other handling

Preparation for Use
An appropriate amount of water should be added to the granules in the bottle and shaken until all of the particles are suspended. Avoid vigorous and/or lengthy shaking. Shake prior to each subsequent use to ensure resuspension. The concentration of clarithromycin in the reconstituted suspension is either 125 mg/5 ml or 250 mg/5 ml.
Administration
Several devices can be used to dose and administer Clarithromycin Pediatric Suspension.
Conservation
Abbotic granules 125 mg/ 5 ml or 250 mg/ 5 ml:
After reconstitution, store at temperature not exceed 30°C and use within 14 days.

HOW SUPPLIED

Abbotic granules 250 mg/ 5 ml: bottle of 50 ml and 70 ml
Reg. No.: DKL0800202238B1
Abbotic granules 125 mg/ 5 ml: bottle of 30 ml and 60 ml

Reg. No.: DKL9400202238A1

Store at temperature not exceed 30°C

ON MEDICAL PRESCRIPTION ONLY
HARUS DENGAN RESEP DOKTER

Manufactured by:
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Depok 16415, Indonesia

Under license:
Abbott Laboratories, ILL, USA

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