Summary of Product Characteristics for Pharmaceutical Products

1. Name of the medicinal product:
Claritek (Clarithromycin) Granules 250mg/5mL

2. Qualitative and quantitative composition
Each reconstituted 5mL contains: Clarithromycin USP...250mg

Excipients with known effects:
Each 5 ml reconstituted suspension contains 3194 mg of sucrose
For a full list of excipients, see section 6.1.

3. Pharmaceutical form
Granules for oral suspension
White to off-white granular powder

4. Clinical particulars

4.1 Therapeutic indications
CLARITEK (Clarithromycin) is indicated for treatment of infections due to susceptible organisms. Such infections include:
- Lower respiratory tract infections (e.g., bronchitis, pneumonia).
- Upper respiratory tract infections (e.g., pharyngitis, sinusitis, tonsillitis).
- Acute otitis media in children.
- Skin and soft tissue infections (e.g., folliculitis, cellulitis, erysipelas, impetigo, abscesses).
- Disseminated or localized mycobacterial infections due to MAC.
- To eradicate Helicobacter pylori in treatment regimens for peptic ulcer disease.
- To prevent disseminated Mycobacterium avium complex (MAC) disease in patients with advanced HIV infection.
- As an alternative treatment to penicillins for prophylaxis of endocarditis.
Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration
Posology

Paediatric patients under 12 years of age:
Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin pediatric suspension
The dosage of clarithromycin depends on the clinical condition of the patient and has to be defined in any case by the physician.
The usual recommended daily dosage of CLARITEK (Clarithromycin) suspension is 7.5mg/kg B.I.D up to a maximum of 500mg twice daily. The usual duration of treatment is 5 to 10 days depending on the pathogen involved and the severity of the condition.
For some children, depending on body weight, it may be more appropriate to administer the 125mg/ 5ml oral suspension.

The following table is a suggested guide for determining dosage

Table 1: Dose recommendation

PEDIATRIC DOSAGE GUIDELINES (Based on Body Wt.)			
Weight*	**Dosage in mg**	**Dosage in mL 125mg/5mL**	**Dosage in mL 250mg/5mL**
8-11 kg	62.5mg b.i.d	2.5mL b.i.d	1.25 mL b.i.d
12-19 kg	125mg b.i.d	5mL b.i.d	2.5mL b.i.d
20-29 kg	187.5mg b.i.d	7.5mL b.i.d	3.75mL b.i.d
30-40 kg	250mg b.i.d	10mL b.i.d	5mL b.i.d
*Children <8kg should be dosed on a per kg basis (approx 7.5mg/kg B.I.D)			

In order to avoid the need to estimate quarter teaspoonfuls, it is recommended that the 125mg/ 5ml oral suspension is used for children in these weight bands (please consult the prescribing information for the 125mg/ 5ml oral suspension for details).

A graduated syringe is provided with the bottle for use as a pipette. This enables more accurate dosing than the 5 ml spoon (also provided with the bottle) when fractions of a spoonful are needed to achieve the right dose.

Patients with renal and hepatic insufficiency:

Clarithromycin should not be administered to paediatric patients with severe hepatic or renal insufficiency. Caution is required when administering clarithromycin to children with lesser degrees of renal or hepatic insufficiency.

In children with creatinine clearance less than 30 ml/min/1.73 m^2, the dosage of clarithromycin should be reduced by half to 7.5 mg/kg per day. Dosage should not be continued beyond 14 days in these patients.

Method of Administration:

Clarithromycin 250 mg/5 ml Oral Suspension may be given without regard to meals, as food does not affect the extent of bioavailability.

Clarithromycin 250 mg/5 ml Oral Suspension should be administered twice daily as recommended in the table above. The doses should be given at 12-hour intervals.

Clarithromycin oral suspension can cause a bitter after-taste. This can be avoided by drinking juice or water soon after intake of the suspension.

4.3 Contraindications

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

Concomitant administration of Clarithromycin and ergot alkaloids (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).

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 pointe* (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 pointe* (see sections 4.4 and 4.5).

Concomitant administration with ticagrelor or ranolazine is contraindicated

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

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4 (lovastatin or simvastatin) or atorvastatin, due to the increased risk of myopathy, including rhabdomyolysis (see section 4.5).

As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine (see sections 4.4 and 4.5).

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

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 (see section 4.6).

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

Cases of fatal hepatic failure (see section 4.8) have been reported. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products. Patients should be advised to stop treatment and contact their doctor if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Caution is advised in patients with severe renal insufficiency (see section 4.2).

Use of antimicrobial therapy, such as Clarithromycin to treat *H. pylori infection* may select for drug-resistant organisms.

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.

Attention should also be paid to the possibility of cross resistance between clarithromycin and other macrolide drugs, as well as lincomycin and clindamycin. Therefore caution is required when prescribing clarithromycin for such patients.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. *Clostridium difficile*-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including clarithromycin, and may range in severity from mild diarrhoea 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 diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents. Therefore, discontinuation of clarithromycin therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic drugs, especially with aminoglycosides. Monitoring of vestibular and auditory function should be carried out during and after treatment.

<u>Cardiovascular Events</u>

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 (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 cardiac arrhythmia (see section 4.3).

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.

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 patient taking Clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy.

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 (see 4.5).

Oral hypoglycaemic agents/Insulin: The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulphonylurias) and/or insulin can result in significant hypoglycaemia. Careful monitoring of glucose is recommended (see section 4.5).

Oral anticoagulants: There is a risk of serious hemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin (see section 4.5). 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).

In areas with a high incidence of erythromycin A resistance, it is especially important to take into consideration the evolution of the pattern of susceptibility to clarithromycin. Clarithromycin is a semi-synthetic derivative of erythromycin A.

Pneumonia: Due to 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.

Clarithromycin is not the first choice for the therapy of pharyngitis. It is only required, especially in streptococcus-infection, if hypersensitivity to penicillin is present or if penicillin is contraindicated for other reasons.

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 generalised 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 CYP3A4 enzyme due to the possibility of subtherapeutic levels of clarithromycin (see section 4.5).

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.

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

Clarithromycin 250mg/5ml Oral Suspension contains 20 mg of aspartame (E951) per 5 ml, a source of phenylalanine. This medicine should be used with caution in patients with phenylketonuria.

Excipients:

Patients with rare hereditary problems of fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take

this medicine. 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 increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias 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 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.

Ergot alkaloids

Post-marketing reports indicate that co-administration of clarithromycin with ergotamine or dihydroergotamine associated with acute ergot toxicity characterized by vasospasm, and ischaemia 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.

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.

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

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 inhibitor 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-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.

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 (C_{min}) 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 C_{max} increased by 31%, C_{min} 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 CL_{CR} 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CL_{CR} <30mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1g/day should not be co-administered 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 section below, Bi-directional drug interactions)

Effect of clarithromycin on other medicinal products

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 see section 4.4), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, 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.

Antiarrhythmics

There have been postmarketing reports of torsades de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QT prolongation during co-administration of clarithromycin with these drugs. Serum levels of quinidine and disopyramide should be monitored during clarithromycin therapy.

There have been post marketing reports of hypoglycaemia 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 hypoglycaemia when used concomitantly. Careful monitoring of glucose is recommended.

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 that 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. Dose reduction may need to be considered.

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.

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).

Other drug interactions

Hydroxychloroquine and chloroquine

Clarithromycin should be used with caution in patients receiving medicines known to prolong the QT interval with potential to induce cardiac arrhythmia, e.g. hydroxychloroquine and chloroquine.

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 (see section 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 paediatric 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 co-administered 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 twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in steady-state AUC and C_{max} values of saquinavir which were

177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} 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 Ritonavir).

Patients taking oral contraceptives should be warned that if diarrhoea, vomiting or breakthrough bleeding occur there is a possibility of contraceptive failure.

4.6 Pregnancy and Lactation

Pregnancy

The safety of clarithromycin for use during 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

The safety of clarithromycin for use during breast feeding of infants has not been established. Clarithromycin and its active metabolite are excreted in breast milk in small amounts. Therefore, diarrhea and fungus infection of the mucous membranes could occur in the breast-fed infant, so that nursing might have to be discontinued. The possibility of sensitisation should be born in mind. It has been estimated that an exclusively breastfed infant would receive about 1.7% of the maternal weight-adjusted dose of clarithromycin. The benefit of treatment of the mother should be weighed against the potential risk for the infant.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and paediatric populations are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics (see section b of section 4.8).

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.

Tabulated summary of adverse reactions

The following table displays adverse reactions reported in clinical trials and from post-marketing experience with clarithromycin immediate-release tablets, granules for oral suspension, powder for solution for injection, extended-release tablets and modified-release tablets.

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.

Table 2: Summary of Adverse reactions

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			Cellulitis[1], candidiasis, gastroenteritis[2],infection[3], vaginal infection	Pseudomembranous colitis, erysipelas,
Blood and lymphatic system			Leukopenia, neutropenia[4], thrombocythemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders			Anaphylactoid reaction[1], hypersensitivity	Anaphylactic reaction,

				angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety, nervousness[3]	Psychotic disorder, confusional state[5], depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache, taste perversion	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[5], tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged, extrasystoles[1], palpitations	*Torsade de pointes,* ventricular tachycardia ventricular fibrillation
Vascular disorders		Vasodilation[1]		Haemorrhage
Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	
Gastrointestinal disorders		Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Oesophagitis[1], gastrooesophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence,	Pancreatitis acute, tongue discolouration, tooth discolouration
Hepatobiliary disorders		Liver function test abnormal	Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased[4]	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Dermatitis bullous[1], pruritus, urticaria, rash maculo-papular[3]	Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders			Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis[2,6], myopathy

Renal and urinary disorders			Blood creatinine increased[1], blood urea increased[1]	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis[1]	Injection site pain[1], injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue[4]	
Investigations			Albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]	International normalised ratio increased, prothrombin time prolonged, urine colour abnormal

[1] ADRs reported only for the Powder for Solution for Injection formulation

[2]ADRs reported only for the Extended-Release Tablets formulation

[3] ADRs reported only for the Granules for Oral Suspension formulation

[4] ADRs reported only for the Immediate-Release Tablets formulation

[5,6] See section c)

** 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 1billion patient treatment days for clarithromycin.*

Description of selected adverse reactions

Injection site phlebitis, injection site pain, and injection site inflammation are specific to the clarithromycin intravenous formulation.

In some of the reports of rhabdomyolysis, clarithromycin was administered concomitantly with statins, fibrates, colchicine or allopurinol (see section 4.3 and 4.4).

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 (see section 4.5).

Special population: Adverse Reactions in Immunocompromised Patients (see section e)

Paediatric populations

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. There are insufficient data to recommend a dosage regimen for use of the clarithromycin IV formulation in patients less than 18 years of age.

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Other special populations

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 Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1000 mg and 2000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhea, rash, flatulence, headache, constipation, hearing disturbance, **Serum Glutamic Oxaloacetic Transaminase** (SGOT) and **Serum Glutamic Pyruvate Transaminase** (SGPT) elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1000 mg and 2000 mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000 mg of clarithromycin.

In these immunocompromised patients, evaluations of laboratory values were made by analysing those values outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2% to 3% of those patients who received 1000 mg or 2000 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 in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidences of abnormal values were noted for patients who received 4000 mg daily for all parameters except White Blood Cell.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms of intoxication:

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastrointestinal symptoms. Symptoms of overdose may largely correspond to the profile of adverse reactions. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia.

Therapy of intoxication:

There is no specific antidote on overdose. Serum levels of clarithromycin cannot be reduced by haemodialysis or peritoneal dialysis.

Adverse reactions accompanying overdosage should be the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis. Severe acute allergic reactions may be seen very rarely, e.g. anaphylactic shock. At first signs of hypersensitivity reactions therapy with clarithromycin must be discontinued and the required measures should be initiated immediately.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use, macrolides
ATC code: J01FA09

Mechanism of action

Clarithromycin is an antibiotic belonging to the macrolide antibiotic group. It exerts its antibacterial action by selectively binding to the 50s ribosomal sub-unit of susceptible bacteria preventing translocation of activated amino acids. It inhibits the intracellular protein synthesis of susceptible bacteria. Clarithromycin demonstrates excellent in-vitro activity against standard strains of clinical isolates. It is highly potent against a wide variety of aerobic and anaerobic gram-positive and gram-negative organisms. The minimum inhibitory concentrations (MICs) of clarithromycin, are generally two-fold lower than the MICs of erythromycin.

The 14-hydroxy metabolite of clarithromycin, a product of parent drug metabolism also has antimicrobial activity. The metabolite is less active than the parent compound for most organisms, including mycobacterium spp. An exception is Haemophilus influenza where the 14-hydroxy metabolite is twofold more active than the parent compound. Clarithromycin is also bactericidal against several bacterial strains.

Breakpoints

According to the EUCAST (European Committee on Antimicrobial Susceptibility Testing) the following breakpoints have been defined for clarithromycin:

Table 3: Breakpoints

Breakpoints (MIC, mg/L)		
Microorganism	Susceptible (≤)	Resistant (>)
Staphylococcus spp.	1 mg/L	2 mg/L
Streptococcus spp. (A, B, C, G)	0.25 mg/L	0.5 mg/L
Streptococcus pneumonia	0.25 mg/L	0.5 mg/L
Viridans group streptococcus	IE	IE

Haemophilus spp.	1 mg/L	32 mg/L
Moraxella catarrhalis	0.25 mg/L	0.5 mg/L[1]
Helicobacter pylori	0.25 mg/L[1]	0.5 mg/L

[1] The breakpoints are based on epidemiological cut-off values (ECOFFs), which distinguish wild-type isolates from those with reduces susceptibility.

" IE" indicates that there is insufficient evidence that the species in question is a good target for therapy with the drug.

Susceptibility

The prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections This information gives only an appropriate guidance on the probabilities whether micro-organisms will be susceptible to clarithromycin or not. As far as applicable the information on the European range of acquired resistance for the individual micro-organism is indicated in brackets.

Clarithromycin is usually active against the following organisms in vitro:

Gram-positive Bacteria: Staphylococcus aureus (methicillin susceptible); Streptococcus pyogenes [1] (Group A beta-hemolytic streptococci); alpha-hemolytic streptococci (viridans group); Streptococcus (Diplococcus) pneumoniae; Streptococcus agalactiae; Listeria monocytogenes.

Gram-negative Bacteria: Haemophilus influenza [$]; Haemophilus parainfluenza; Moraxella (Branhamella) catarrhalis ° ; Neisseria gonorrhoeae; Legionella pneumophila° ; Bordetella pertussis; Campylobacter jejuni, Helicobacter pylori[2].

Mycoplasma: Mycoplasma pneumoniae° ; Ureaplasma urealyticum.

Other Organisms: Chlamydia trachomatis; Mycobacterium avium° ; Mycobacterium leprae; Mycobacterium kansasii° ; Mycobacterium chelonae° ; Mycobacterium fortuitum; Mycobacterium intrazellulare ° ; Chlamydia pneumonia° ,

Anaerobes: Macrolide-susceptible Bacteroides fragilis; Clostridium perfringens; Peptococcus species; Peptostreptococcus species; Propionibacterium acnes.

Clarithromycin also has bactericidal activity against several bacterial strains. The organisms include Haemophilus influenza [$]; Streptococcus pneumoniae; Streptococcus pyogenes; Streptococcus agalactiae; Moraxella (Branhamella) catarrhalis; Neisseria gonorrhoeae and Campylobacter spp.

Species for which acquired resistance may be a problem

Aerobic Gram-positive micro-organisms: Staphylococcus aureus (Methicillin-resistant) [+]

Inherently resistant organisms

Aerobic Gram-negative micro-organisms Escherichia coli; Klebsiella spp. And Pseudomonas aeruginosa

° No updated data were available at release of tables. Primary literature, scientific standard literature and therapeutic recommendations assume susceptibility.

[$] Inherent susceptibility of most of the isolates shows intermediate resistance.
[+] At least one region shows resistance rates higher than 50%.
[1] The resistance rates are in some studies ≥ 10%.
[2] The resistance rate is ≥ 10% by pre-treated patients.
Other information
Susceptibility and resistance of Streptococcus pneumoniae and Streptococcus spp. to clarithromycin can be predicted by testing erythromycin.
The mechanisms of acquired resistance in macrolides are: efflux of active substance by an active pump mechanism, inducible or constitutive production of a methylase enzyme that modifies the ribosomal target, hydrolysis of macrolides by esterases, chromosomal mutations that alter a 50s ribosomal protein. Cross-resistance between clarithromycin and other macrolides and clindamycin and lincomycin may therefore occur. Methicillin-resistant and oxacillin-resistant staphylococci (MRSA) and penicillin-resistant Streptococcus pneumoniae are resistant to all currently available Beta-lactam antibiotics and macrolides such as clarithromycin. Most available clinical experience from controlled randomised clinical trials indicate that Clarithromycin Ranbaxy 500 mg twice daily in combination with another antibiotic e.g. amoxicillin or metronidazole and e.g. omeprazole (given at approved levels) for 7 days achieve > 80% H. pylori eradication rate in patients with gastro-duodenal ulcers. As expected, significantly lower eradication rates were observed in patients with baseline metronidazole-resistant H. pylori isolates. Hence, local information on the prevalence of resistance and local therapeutic guidelines should be taken into account in the choice of an appropriate combination regimen for H. pylori eradication therapy. Furthermore, in patients with persistent infection, potential development of secondary resistance (in patients with primary susceptible strains) to an antimicrobial agent should be taken into the considerations for a new retreatment regimen.

5.2 Pharmacokinetic properties

Absorption:

Clarithromycin is rapidly and well absorbed from the gastrointestinal tract but undergoes extensive firstpass metabolism after oral administration. The absolute bioavailability of a 250mg clarithromycin tablet is approximately 50%. The bioavailability of the suspension is identical to or slightly higher than the bioavailability of the tablets. The pharmacokinetic profile of the suspension in children corresponds to the pharmacokinetic profile of the suspension in adults. Due to its chemical structure (6-OMethylerythromycin) clarithromycin is quite resistant to degradation by stomach acid. After oral administration of 250mg & 500mg clarithromycin twice daily, peak plasma levels of 1-2 µg/mL & 2.8µg/mL were observed respectively in adults. The peak plasma concentration of pharmacological active 14-hydroxy metabolite

was 0.6µg/mL after the administration of 250mg clarithromycin twice daily. Steady state is attained within 2 days of dosing.

Effect of Food
Food slightly delays the absorption of clarithromycin but does not affect the extent of bioavailability, therefore it may be given without regard to food.

Distribution:
Clarithromycin penetrates well into different compartments, with an estimated volume of distribution of 200-400L. Clarithromycin provides concentrations in some tissues that are several times higher than the circulating level of the active substance. Increased levels have been found in both tonsils and lung tissue. Clarithromycin also penetrates the gastric mucus. Clarithromycin is approximately 80% bound to plasma proteins at therapeutic levels.

Metabolism:
Clarithromycin is rapidly and extensively metabolised in the liver. Metabolism involves mainly Ndealkylation, oxidation and stereospecific hydroxylation at position C14.

Excretion:
Clarithromycin is excreted in the feces (5-10%) via the bile. At steady state approximately 20% and 30% of clarithromycin is excreted as unchanged drug in urine. 14-hydroxy clarithromycin as well as other metabolites are also excreted in the urine accounting for 10% to 15% of the dose. The elimination half-life of clarithromycin is reportedly about 3 to 4 hours in patients receiving 250mg doses twice daily, and about 5 to 7 hours in those receiving 500mg twice daily. The principal metabolite, 14-OH-clarithromycin has an elimination half-life of 5 to 6 hours after a dose of 250mg twice daily and about 7 to 9 hours in those receiving 500mg twice daily.

Special Populations Renal impairment:
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.

Geriatric: Elderly patients with severe renal impairment may require dose adjustment.

5.3 Preclinical safety data

The acute oral LD_{50} values for a clarithromycin suspension administered to 3-day old mice were 1290 mg/kg for males and 1230 mg/kg for females. The LD_{50} values in 3-day old rats were 1330 mg/kg for males and 1270 mg/kg

for females. For comparison, the LD_{50} of 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 LD_{50} is generally lower in juvenile animals than in adults.

In both mice and rats, body weight was reduced or its increase suppressed and suckling behaviour 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 depressed suckling behaviour or bleeding from the intestines.

Pre-weaning rats (5 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 haemoglobin and haematocrit 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 (granules for suspension) for 6 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 1 to 2 hours after administration during the last 3 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, 3 weeks of age, were treated orally daily for four weeks with 0, 30, 100, or 300 mg/kg of clarithromycin, followed by a 4-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 have shown daily dosages of 150-160 mg/kg/day to male and female rats caused no adverse effects on the oestrus cycle, fertility, parturition and number and viability of offspring. 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.

6. Pharmaceutical Particulars

6.1 List of Excipients

- Sucrose (Extra Fine)
- Titanium Dioxide
- Colliodal Anhydrous Silica (Aerosil 200)
- Xanthan Gum
- Methyl Paraben
- Trusil Powder Orange Flavour (B/B)
- Sodium Saccharine

6.2 Incompatibilities

Not Applicable

6.3 Shelf-Life

Granules: Two years.
Reconstituted suspension: 14 days

6.4 Special Precautions for storage

- Do not store above 30°C.
- Protect from sunlight and moisture.
- The reconstituted suspension can be used for up to 14 days, when stored at room temperature.
- The expiration date refers to the product correctly stored at the required conditions. - Keep all the medicines out of reach of children.

6.5 Nature and Content of container

Claritek (Clarithromycin) granules 250mg/5mL are available in HDPE Plastic bottle (1x70 ml) in a printed unit carton, along with package insert.

6.6 Special precautions for disposal and other handling

Preparation for use:

Required quantity of water should be added to the granules in the bottle and shaken well. The concentration of clarithromycin in the reconstituted suspension is 250 mg per 5 ml.

The quantity of water required for each pack is tabulated below:

Table 4: Volume of water required for each pack

Pack	**Volume of water to be added**
50 ml Bottle	28 ml
60 ml Bottle	34 ml
70 ml Bottle	40 ml
100 ml Bottle	55 ml
140 ml Bottle	80 ml

7. Marketing Authorization Holder

Getz Pharma (Private) Limited
29-30/27, Korangi Industrial Area
Karachi 74900, Pakistan Tel: (92-21) 5063100-03
Fax: (92-21) 5060141

8. Marketing Authorization Number

CTD9417

9. Date of first authorization/renewal of the authorization

23/04/2024

10. Date of revision of the text

9/5/2025