1.3.1 Summary of Product Characteristics.

1. Name of the medicinal product
CLARITHROMYCIN TABLETS USP 500 MG (CLARIDEX-500)

2. Qualitative and quantitative composition

Each film coated tablet contains:
Clarithromycin USP……..500 mg
Excipients…….QS
Colour: Quinoline Yellow, Titanium Dioxide

3. Pharmaceutical form
Film-coated tablet.

4. Clinical particulars
4.1 Therapeutic indications
Clarithromycin is indicated in adults and children 12 years and older. (Adult only formulations, e.g. tablets, IV)
Clarithromycin Tablets are indicated for treatment of the following infections caused by susceptible organisms Indication include:
Lower respiratory tract infections for example: acute and chronic bronchitis, and pneumonia
Upper respiratory tract infections for example: sinusitis and pharyngitis.
Clarithromycin is appropriate for initial therapy in community acquired respiratory infections and has been shown to beactive in vitro against common and atypical respiratory pathogens as listed in the microbiology section.
Clarithromycin is also indicated in skin and soft tissue infections of mild to moderate severity e.g. folliculitis, cellulitis,erysipelas. Clarithromycin in the presence of acid suppression effected by omeprazole or lansoprazole is also indicated for the eradication of *H. pylori* in patients with duodenal ulcers. See Dosage and Administration section.
Clarithromycin is usually active against the following organisms in vitro:
Gram-positive Bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A beta-hemolytic streptococci); alpha-hemolytic streptococci (viridans group); *Streptococcus (Diplococcus) pneumoniae;Streptococcus agalactiae; Listeria monocytogenes*.
Gram-negative Bacteria: *Haemophilus influenzae; Haemophilus parainfluenzae; Moraxella (Branhamella) catarrhalis;Neisseria gonorrhoeae; Legionella pneumophila; Bordetella pertussis; Helicobacter pylori; Campylobacter jejuni.*

4.2 Posology and method of administration
Patients with respiratory tract/skin and soft tissue infections

Adults: The usual dose is 250 mg twice daily although this may be increased to 500mg twice daily in severe infections. The usual duration of treatment is 6 to 14 days. (Adult only formulation)
Children older than 12 years: As for adults.
Children younger than 12 years: Use of clarithromycin tablets are not recommended for children younger than 12 years. 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 (granules for oral suspension). Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability.

Eradication of H. pylori in patients with duodenal ulcers (Adults)
The usual duration of treatment is 6 to 14 days.
Triple Therapy:
Clarithromycin 500mg twice daily and lansoprazole 30mg twice daily should be given with amoxicillin 1000mg twice daily.
Triple Therapy:
Clarithromycin 500mg twice daily and lansoprazole 30mg twice daily should be given with metronidazole 400mg twice daily.
Triple Therapy:
Clarithromycin 500mg twice daily and omeprazole 40mg daily should be given with amoxicillin 1000mg twice daily or metronidazole 400mg twice daily.
Triple Therapy:
Clarithromycin 500mg twice daily and omeprazole 20mg daily should be given with amoxicillin 1000mg twice daily..
Elderly
As for adults.
Renal impairment
In pateints with renal impairment with creatinine clearance less than 30 Ml/min, the dosage of clarithromycin should bereduced by one- half, i.e. 250 mg once daily or 250 mg twice daily in more severe infections. Treatment should not becontinued beyond 14 days in these patients.
Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability.

4.3 Contraindications
Hypersensitivity to macrolide antibiotic drugs or to any of its excipients.
Concomitant administration of clarithromycin and ergot alkaloids (e.g. ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity.
Concomitant administration of clarithromycin and oral midazolam is contraindicated.
Concomitant administration of clarithromycin and any of the following drugs is contraindicated: astemizole, cisapride, pimozide and terfenadine as this may result in QT

prolongation and cardiac arrhythmias, including ventriculartachycardia, ventricular fibrillation, and torsades de pointes.
Concomitant administration of clarithromycin and lomitapide is contraindicated.
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.
Concomitant administration with ticagrelor or ranolazine is contraindicated.
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.
As with other strong CYP3A4 inhibitors, Clarithromycin should not be used in patients taking colchicine.
Clarithromycin should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due tothe risk of prolongation of the QT interval).
Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

4.4 Special warnings and precautions for use
Use of any antimicrobial therapy, such as clarithromycin, to treat *H. pylori* infection may select for drug-resistant organisms.
The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy.
Caution is advised in patients with severe renal insufficiency.
Clarithromycin is principally metabolised by the liver. Therefore, caution should be exercised in administering this antibiotic to patients with impaired hepatic function. Caution should also be exercised when administering clarithromyc into patients with moderate to severe renal impairment.

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. Cases of fatal hepatic failure 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.
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.

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. Concomitant administration of clarithromycin and colchicine is contraindicated.

Caution is advised regarding concomitant administration of clarithromycin and triazolobenzodiazepines, such astriazolam, and intravenous or oromucosal midazolam.

Cardiovascular Events:

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac arrhythmia and torsades depointes, have been seen in treatment with macrolides including clarithromycin. 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

• Patients concomitantly taking other medicinal products associated with QT prolongation.

• Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfendine is contraindicated.

• Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia.

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 infraction 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* (erythrasma), 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 drug rash with eosinophilia and systemic symptoms (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 cytochromeCYP3A4 enzyme.
HMG-CoA reductase inhibitors (statins): Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated. 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 myopathy.
In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribethe lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered.
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.
Oral anticoagulants: There is a risk of serious haemorrhage and significant elevations in International Normalized Ratio (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.
Long-term use may, as with other antibiotics, result in colonisation with increased numbers of non-susceptible bacteria and fungi. If super infections 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.

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 mayresult in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsadesde pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly.
Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine whichhas occasionally been associated with cardiac arrhythmias, such

as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes. In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in 2- to 3-fold increase in the serum level of the acid metaboliteof 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 has been associated with acute ergot toxicity characterized by vasospasm, and ischaemia of the extremities and other tissuesincluding the central nervous system. Concomitant administration of clarithromycin and ergot alkaloids is contraindicated.

Oral Midazolam

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased7fold 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 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 to the potential for markedly increased transaminases.

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 owingto 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 (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 1gm/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.

Effect of Clarithromycin on Other Medicinal Products

CYP3A-based interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolised by CYP3A may beassociated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects ofthe concomitant drug. Clarithromycin should be used with caution in patients receiving treatment with other drugs knownto be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolised by this enzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolised byCYP3A should be monitored closely in patients concurrently receiving clarithromycin.

The following drugs or drug classes are known or suspected to be metabolised by the same CYP3A isozyme:alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin, 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 exhaustive. Drugs interacting by similar mechanisms throughother 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 viaCYP3A4 and are also substrates for P-gp. Caution should be exercised when clarithromycin is co-administered withthese agents particularly to patients at high risk of bleeding.

Antiarrhythmics

There have been post-marketed reports of torsade de points occurring with the concurrent use of clarithromycin andquinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during co-administration ofclarithromycin with these drugs. Serum levels of quinidine and disopyramide should be monitored during clarithromycintherapy.

There have been post marketing reports of hypoglycemia with the concomitant administration of clarithromycin anddisopyramide. Therefore blood glucose levels should be monitored during concomitant administration of clarithromycinand disopyramide.

Oral hypoglycemic agents/Insulin

With certain hypoglycemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycinmay be involved and could cause hypolgycemia when used concomitantly. Careful monitoring of glucose isrecommended.

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 (Cmax, AUC0-24, and t1/2 increased by 30%,89%, and 34%, respectively), by the concomitant administration of clarithromycin. The mean 24-hour gastric pH valuewas 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 metabolised, at least in part, by CYP3A, and CYP3A may be inhibited byconcomitantly administered clarithromycin. Co-administration of clarithromycin with sildenafil, tadalafil or vardenafil wouldlikely result in increased phosphodiesterase inhibitor exposure. Reduction of sildenafil, tadalafil and vardenafil dosagesshould 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 circulatingtheophylline 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 asubset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this populationsubset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodinedosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metaboliserpopulation.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased2.7-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, whichcould bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed afterintravenous midazolam rather than oral administration. The same precautions should also apply to otherbenzodiazepines that are metabolised by CYP3A, including triazolam and alprazolam. For benzodiazepines which arenot dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction withclarithromycin 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 forincreased 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 othermacrolides 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 inhibitPgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead toincreased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxinconcomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signsconsistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefullymonitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result indecreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption ofsimultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses ofclarithromycin and zidovudineto allow for a 4-hour interval between each medication. This interaction does not appear tooccur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. Thisinteraction 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 withdrugs not thought to be metabolised by CYP3A (e.g. phenytoin and valproate). Serum level determinations arerecommended for these drugs when administered concomitantly with clarithromycin. Increased serum levels have beenreported.

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 reductionshould 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, brady arrhythmias 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 ofclarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs orsymptoms 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 druginteraction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200mg three times daily) to 12 healthy volunteers resulted in steady-state AUC and Cmax values of saquinavir which were177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax values were approximately40% 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 thesoft 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 effectsseen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be givento 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 apossibility of contraceptive failure.

4.6 Fertility, 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 embryo foetal 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 risks.

Breast-feeding

The safety of clarithromycin for using during breast-feeding of infants has not been established. 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.

Fertility

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

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and peadiatricpopulations are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These adverse reactions are usuallymild 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 trialsbetween the patient population with or without pre-existing mycobacterial infections.

b. 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.

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], thrombocythaemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders[5]			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[9]
Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	
Gastrointestinal disorders		Diarrhoea, vomiting,	Oesphagitis[1], gastrooesophageal	Pancreatitis acute, tongue

		dyspepsia, nausea, abdominal pain	reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence,	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]	Severe cutaneous adverse reactions (SCAR) (e.g. Acute generalised 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[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	Injection site	Injection site pain[1],	Malaise[4], pyrexia[3], asthenia, chest	

administration site conditions	phlebitis[1]	injection site inflammation[1]	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[9], prothrombin time prolonged[9], urine color 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
* 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.
c. Description of selected adverse reactions
Injection site phlebitis, injection site pain, vessel puncture 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.
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.

4.8 UNDESIRABLE EFFECTS:
a. Summary of the safety profile
The most frequent and common adverse reactions related to clarithromycin therapy for both adult and peadiatric 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.
There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without pre-existing mycobacterial infections.
b. 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.

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], thrombocythaemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders[5]			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			Vertigo, hearing	Deafness

labyrinth disorders			impaired, tinnitus	
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[9]
Respiratory, thoracic and mediastinal disorder			Asthma[1], epistaxis[2], pulmonary embolism[1]	
Gastrointestinal disorders		Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Oesphagitis[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]	Severe cutaneous adverse reactions (SCAR) (e.g. Acute generalised 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[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[9], prothrombin time prolonged[9], urine color abnormal

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

c. Description of selected adverse reactions

Injection site phlebitis, injection site pain, vessel puncture 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.

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.

There have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhoea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g. suspension) or another antibiotic.

Special population: Adverse Reactions in Immunocompromised Patients

d. 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.

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

e. 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 2000mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, 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 1000mg and 2000mg, but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000mg 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 1000mg or 2000mg 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 4000mg 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.

4.9 OVERDOSE:

Reports indicate that the ingestion of large amounts of clarithromycin can be expected to produce gastro-intestinal symptoms. One patient who had a history of bipolar disorder ingested 8 grams of clarithromycin and showed altered mental status, paranoid behaviour, hypokalemia and hypoxemia. Adverse reactions accompanying overdose should be treated by the prompt elimination of unabsorbed drug and supportive measures. As with other macrolides, Clarithromycin serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PARTICULARS:

5.1 Pharmacodynamic properties

Pharmacotherapeutic Group: Antibacterial for systemic use, macrolide

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 subunit of susceptible bacteria preventing translocation of activated amino acids. It inhibits the intracellular protein synthesis of susceptible bacteria.

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 two-fold more active than the parent compound.

Clarithromycin is usually active against the following organisms in vitro:-

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

Gram-negative Bacteria: Haemophilus influenzae; Haemophilus parainfluenzae; Moraxella (Branhamella) catarrhalis; Neisseria gonorrhoeae; Legionella pneumophila; Bordetella pertussis; Helicobacter pylori; Campylobacter jejuni.

Mycoplasma: Mycoplasma pneumoniae; Ureaplasma urealyticum.

Other Organisms: Chlamydia trachomatis; Mycobacterium avium; Mycobacterium leprae;

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

Clarithromycin has bactericidal activity against several bacterial strains. The organisms include Haemophilus influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Moraxella (Branhamella) catarrhalis, Neisseria gonorrhoeae, H. pylori and Campylobacter spp.

Breakpoints

The following breakpoints have been established by the European Committee for Antimicrobial Susceptibility Testing (EUCAST).

Breakpoints (MIC, mg/L)

Microorganism	Susceptible (≤)	Resistant (>)
Staphylococcus spp.	1 mg/L	2 mg/L
Streptococcus A, B, C and 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[1]	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.

Pharmacokinetic properties

H. pylori is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95% and 80% of patients respectively are infected with the agent. H. pylori is also implicated as a major contribution factor in the development of gastric and ulcer recurrence in such patients.

Clarithromycin has been used in small numbers of patients in other treatment regimens. Possible kinetic interactions have not been fully investigated. These regimens include:

Clarithromycin plus tinidazole and omeprazole; clarithromycin plus tetracycline, bismuth subsalicylate and ranitidine; clarithromycin plus ranitidine alone.

Clinical studies using various different H. pylori eradication regimens have shown that eradication of H. pylori prevents ulcer recurrence.

Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of Clarithromycin tablets. The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism. Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability of Clarithromycin tablets. Food does slightly delay the onset of absorption of Clarithromycin and formation of the 14-hydroxymetabolite.

The pharmacokinetics of Clarithromycin are non linear; however, steady-state is attained within 2 days of dosing. At 250 mg b.i.d. 15-20% of unchanged drug is excreted in the urine. With 500 mg b.i.d. daily dosing urinary excretion is greater (approximately 36%). The 14-hydroxyclarithromycin is the major urinary metabolite and accounts for 10-15% of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10% of the parent drug is recovered from the faeces.

When Clarithromycin 500 mg is given three times daily, the Clarithromycin plasma concentrations are increased with respect to the 500 mg twice daily dosage.

Clarithromycin provides tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue. Clarithromycin is 80% bound to plasma proteins at therapeutic levels.
Clarithromycin also penetrates the gastric mucus. Levels of Clarithromycin in gastric mucus and gastric tissue are higher when Clarithromycin is co-administered with omeprazole than when Clarithromycin is administered alone.

5.3 PRE-CLINICAL SAFETY:
In acute mouse and rat studies, the median lethal dose was greater than the highest feasible dose for administration (5g/kg).
In repeated dose studies, toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. In all species the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included the stomach, thymus and other lymphoid tissues and the kidneys. At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.
Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Spraque-Dawley (p.o. and i.v.), New Zealand White rabbits and cynomolgous monkeys failed to demonstrate any teratogenicity from Clarithromycin. However, a further similar study in Sprague-Dawley rats indicated a low (6%) incidence of cardiovascular abnormalities, which appeared to be due to spontaneous expression of genetic changes. Two mouse studies revealed a variable incidence (3-30%) of cleft palate and embryonic loss was seen in monkeys but only at dose levels, which were clearly toxic to the mothers.

6 PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients
Lactose Monohydrate, Microcrystalline Cellulose, Croscarmellose Sodium, Povidone K – 30, Purified Water, Purified Talc, Magnesium Stearate**,** Spraycel Sc-2199 Quinoline yellow Isopropyl Alcohol, Dichloromethane

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
3 Years

6.4 Special precautions for storage
Store below 30°C. Protect from Light. Keep out of reach of children

6.5 Nature and contents of container

2x7 Tablets in Alu/PVDC Blister pack

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL AND OTHER HANDLING:

No special requirements.

7.0 Manufactured By

Novagen Healthcare Pvt. Ltd.
Plot No. 102-111, Horizon Industrial park,
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