SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE DRUG PRODUCT:

Clarithromycin Tablets 250 mg
Clarithromycin Tablets 500 mg

(TRADE) NAME OF THE PRODUCT:
KLAR 250
KLAR 500

STRENGTH: 250 mg & 500 mg.

PHARMACEUTICAL DOSAGE FORM

Film-Coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSTIONS

Clarithromycin Tablets 250 mg
Each Film-coated Tablet contains Clarithromycin Ph.Eur. 250 mg.
Clarithromycin Tablets 500 mg
Each Film-coated Tablet contains Clarithromycin Ph.Eur. 500 mg.

3. PHARMACEUTICAL FORM

Clarithromycin Tablets 250 mg: Light yellow coloured, oval shaped, biconvex film – coated tablets,with 'D' debossed on one side and '62' on the other side.

Clarithromycin Tablets 500 mg: Light yellow coloured, oval shaped, biconvex film – coated tablets,with 'D' debossed on one side and '63' on the other side.

4. CLINICAL PARTICULARS

Therapeutic Indications

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

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 susceptibleorganisms 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 andhas been shown to be active in vitro against common and atypical respiratory pathogens.

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 alsoindicated for the eradication of *H. pylori* in patients with duodenal ulcers.

Clarithromycin is usually active against the following organisms in vitro:

Gram-positive Bacteria: *Staphylococcus aureus* (methicillin susceptible); *Streptococcus pyogenes* (Group A betahemolytic 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.*

The activity of clarithromycin against *H. pylori* is greater at neutral pH than at acid pH.

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 500 mg 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. Use clarithromycin paediatric suspension (granules for oral Suspension) in children 6 months to 12 years of age. 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 500 mg twice daily and lansoprazole 30mg twice daily should be given with amoxycillin1000 mg twice daily.

Triple Therapy:

Clarithromycin 500 mg twice daily and lansoprazole 30 mg twice daily should be given withmetronidazole 400 mg twice daily.

Triple Therapy:

Clarithromycin 500 mg twice daily and omeprazole 40 mg daily should be given with amoxycillin 1000mg twice daily or metronidazole 400mg twice daily.

Triple Therapy:

Clarithromycin (500 mg) twice daily and omeprazole 20 mg daily should be given with amoxycillin 1000 mg twice daily.

Elderly As for adults.

Renal impairment

In patients with renal impairment with creatine clearance less than 30Ml/min, the dosage should be reduced by one- half, i.e., 250 mg once daily or 250 mg twice daily in more severe infections. Treatment should not be continued beyond 14 days in these patients. Clarithromycin may be given without regard to meals as food does not affect the extent of bioavailability.

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 ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

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 HMGCoA 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 hypokalaemia (risk of prolongation of QT-time).

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

Special warnings and precautions for use

Use of any antimicrobial therapy, such as clarithromycin, to treat *H. pylori* infection may select fordrug-resistant organisms.

The physician should not prescribe clarithromycin to pregnant women without carefully weighing thebenefits 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 clarithromycin to 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. Carefulmedical 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 andcolchicine is contraindicated.

Caution is advised regarding concomitant administration of clarithromycin and Triazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam.

Cardiovascular Events:

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, 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 with electrolyte disturbances such as hypomagnesaemia. Clarithromycin must not be given to patients with hypokalaemia.
- Patients concomitantly taking other medicinal products associated with QT prolongation.

- Concomitant administration of clarithromycin with astemizole, cisapride, pimozide and terfenadine 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 combinationwith 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 adversereactions (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 cytochrome CYP3A4 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 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.

Oral hypoglycaemic agents/Insulin: The concomitant use of clarithromycin and oral hypoglycaemic agents (such as sulphonylureas) 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.

Long-term use may, as with other antibiotics, result in colonization 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.

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:

<u>Cisapride, pimozide, astemizole and terfenadine</u>

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.

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. 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 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 has been 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.

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 oralmidazolam 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 thelowest 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.

Effects of Other Medicinal Products on Clarithromycin

Drugs that are inducers of CYP3A (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St John'swort) 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} <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 gm/day should not be co-administered with ritonavir.

Similar dose adjustments should be considered in patients with reduced renal function when ritonaviris used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir (see section below, Bidirectional drug interactions).

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 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 cautionin 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 metabolised by this enzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of drugs primarily metabolised by CYP3A 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, 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 through other isozymes within them cytochrome P450 system include phenytoin,theophylline and valproate.

Antiarrhythmics

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

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

Oral hypoglycemic agents/Insulin

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

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 metabolised, 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 metaboliser 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 metabolised by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely.

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other drug interactions

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). Clarithromycin and other macrolides are known to inhibit CYP3A and Pgp. When clarithromycin and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine.

Digoxin

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin isknown 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 metabolised 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 takingclarithromycin and verapamil concomitantly.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectionaldrug 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 thoseseen 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 interactionstudies 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.

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

FERTILITY, PREGNANCY AND LACTATION:

Pregnancy

The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from studies in mice, rats, rabbits and monkeys, the possibility of adverse effects on embryo foetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk.

Breast-feeding
The safety of clarithromycin for using during breast-feeding of infants has not been established. Clarithromycin is excreted into human breast milk.

Effects on ability to drive and use machines

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

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 profileof macrolide antibiotics.

Tabulated summary of adverse reactions

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, adversereactions are presented in order of decreasing seriousness when the seriousness could be assessed.

Very common	Common	Uncommon	Not known
Infections and infestations			
		Cellulitis, candidiasis, gastroenteritis, infection, vaginal infection	Pseudomembranouscolitis, erysipelas,
Blood and lymphatic system			
		Leukopenia, neutropenia, thrombocythemia, eosinophilia	Agranulocytosis, thrombocytopenia
Immune system disorders			
		Anaphylactoidreaction, hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and Nutrition disorders			
		Anorexia, decreased appetite	
Psychiatric disorders			

	Insomnia	Anxiety, nervousness	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders			
	Dysgeusia, headache, taste perversion	Loss of consciousness, dyskinesia, dizziness, tremor somnolence,	Convulsion, ageusia ,parosmia, anosmia paraesthesia
Ear and labyrinth disorders			
		Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			
		Cardiac arrest, atrial fibrillation, electrocardiogram QT prolonged, extrasystoles, palpitations	Torsade de pointes, ventricular tachycardia,ventricular fibrillation
Vascular disorders			
	Vasodilation		Haemorrhage
Respiratory, thoracic and mediastinal disorder			
		Asthma, epistaxis,pulmonary embolism	
Gastrointestinal disorders			
	Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Oesphagitis, gastrooesophageal reflux disease, gastritis, proctalgia, stomatitis, glossitis,abdominal distension, constipation, dry mouth, eructation ,flatulence,	Pancreatitis acute ,tongue discolouration, tooth discolouration
Hepatobiliary disorders			

	Liver function test abnormal	Cholestasis, hepatitis,alanine aminotransferase increased, aspartat eaminotransferase increased, gammaglutamyl transferase increased	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders			
	Rash, hyperhidros is	Dermatitis bullous, pruritus, urticaria, rashmaculo-papular	Severe cutaneou sadverse 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, musculoskelet al stiffness, myalgia	Rhabdomyolys is,myopathy
Renal and urinary disorders			
		Blood creatinin eincreased, blood urea increased	Blood creatinine increased, blood urea increased
General disorders and administration site conditions			
Injection site phlebitis	Injection site pain, injection site inflammation	Injection site pain, injection site inflammation	

Investigations			
		Albumin globulin ratio abnormal, blood	International normalized ratio increased,
		alkaline phosphatas eincreased, blood lactate dehydrogenase increased	prothrombin time prolonged, urine color abnormal

Overdosage

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 PROPERTIES

Pharmacodynamic properties

ATC Classification:

Pharmacotherapeutic Group: Antibacterial for systemic use, macrolideATC 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 betahemolytic 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.*

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 asa 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. Possiblekinetic 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 formedby 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 nonlinear; 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 areincreased 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% boundto 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 Clarithromycinis administered alone.

6. PHARMACEUTICAL PARTICULARS

List of excipients

Core Tablet:

Cellulose Microcrystalline, Croscarmellose sodium, Povidone, Silica colloidal anhydrous, Magnesiumstearate.

Coating Material composition for Opadry yellow 20H82975:

HPMC2910 / Hypromellose 15cP, Propylene Glycol, Titanium Dioxide, Hydroxypropyl Cellulose 500 cP, Vanillin, Sorbic acid, Iron oxide yellow.

Incompatibilities

None known.

Shelf life
Please refer outer package for expiry date.

Special precautions for storage Store in a dry place below 30°C. **Nature and contents of container**
PVC/PVdC –Aluminium foil blister pack: It comprises of 250µ clear PVC coated with 60 gsm PVdC asforming material and 25 µ Aluminium foil with 7gsm heat seal lacquer coating as the lidding material.

Blister of 10 tablets.

7. MARKETING AUTHORISATION HOLDER

Aurobindo Pharma Ltd.,
Plot No.: 2, Maitrivihar,
Ameerpet, Hyderabad-500
038,Telangana State,
India.

8. MARKETING AUTHORIZATION NUMBER

Clarithromycin Tablets 250 mg - TAN 21 HM 0012
Clarithromycin Tablets 500 mg - TAN 21 HM 0013

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

December 24, 2020

10. DATE OF REVISION OF THE TEXT

March, 2021