SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CLARIE OD (Clarithromycin Extended-Release Tablet USP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film coated extended-release tablet contains
Clarithromycin USP 500 mg
Colors: Quinoline Yellow & Titanium Dioxide

For a full list of Excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film Coated Extended-Release Tablet

Yellow colored, film coated, oblong shaped, biconvex tablet, with both sides plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

Consideration should be given to official guidance on the appropriate use of antibacterial agents.
Clarithromycin film-coated tablets are indicated in adults and children 12 years and older.
Clarithromycin is indicated for treatment of infections caused by susceptible organisms.

Indications include:
Lower respiratory tract infections for example, acute and chronic bronchitis, and pneumonia (see sections 4.4 and 5.1regarding Sensitivity Testing).

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) (see sections 4.4 and 5.1 regarding Sensitivity Testing).

Clarithromycin in the presence of acid suppression effected by omeprazole or lansoprazole is also indicated for theeradication 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-haemolytic streptococci); alpha-haemolytic 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.

4.2 Posology and Method of Administration

Posology:

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

Children older than 12 years: As for adults.

Children younger than 12 years:
Use of Clarithromycin film-coated tablets is 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, child renunder 12 years of age should use clarithromycin paediatric 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 amoxycillin 1000mg twice daily ormetronidazole 400mg twice daily.

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

Elderly: As for adults.

Renal impairment:
In patients with renal impairment with creatinine clearance less than 30 mL/min, the dosage of clarithromycin 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.

Method of administration:
Dose to be taken with food and tablets should be swallowed whole and not chewed, broken or crushed.

4.3 Contra-indications

Clarithromycin is contraindicated in patients with a known hypersensitivity to macrolide antibiotic drugs or to any of the excipients listed in section 6.1.

As the dose cannot be reduced from 500mg daily, Clarithromycin Extended-Release Tablets USP are contraindicated in patients with creatinine clearance less than 30 mL/min.

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, domperidone, pimozide and terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointe

Clarithromycin should not be given to patients with history of QT prolongation or ventricular cardiac arrhythmia, including torsades de pointe.

Concomitant administration with ticagrelor or ranolazine is contraindicated.

Clarithromycin should not be used concomitantly with HMG-CoA reductase inhibitors (statins), lovastatin or simvastatin, due to the risk of rhabdomyolysis. Treatment with these agents should be discontinued during clarithromycin treatment.

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.

Concomitant administration of clarithromycin and colchicine is contraindicated in patients with renal or hepatic impairment.

4.4 Special Warnings and Special Precautions for Use

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk; particularly during the first three months of pregnancy.

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. 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 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 as triazolam, and intravenous or oromucosal midazolam.

Cardiovascular Events:

Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac arrhythmia and *torsades de pointes,* have been seen in patients treated with macrolides including clarithromycin. Due to increased risk of QT prolongation and ventricular arrhythmias (including *torsades de pointes*), the use of clarithromycin is contraindicated: in patients taking any of astemizole, cisapride, domperidone, pimozide and terfenadine; in patients who have hypokalaemia; and in patients with a history of QT prolongation or ventricular cardiac arrhythmia.

Furthermore, clarithromycin should be used with caution in the following:
• Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia;
• Patients with hypomagnesaemia;
• Patients concomitantly taking other medicinal products associated with QT prolongation other than those which are contraindicated

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

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

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

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, severe cutaneous adverse reactions (SCAR) (e.g. Acute 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 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. Long-term use may, as with other antibiotics, result in colonisation with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

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

Excipients:
Clarithromycin Extended-Release Tablet USP contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take these medicines

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:

Astemizole, cisapride, domperidone, pimozide, and terfenadine:
Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly.

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:
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 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.

Effects of Other Medicinal Products on Clarithromycin

Drugs that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin. 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-OHclarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered; therefore alternatives to clarithromycin should be considered for the treatment of MAC.

Fluconazole

Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily to 21 healthy volunteers led to increases in the mean steady-state minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33% and 18% respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin were not significantly affected by concomitant administration of fluconazole. No clarithromycin dose adjustment is necessary.

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31%, Cmin increased 182% and AUC increased by 77% with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50%. For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75%. Doses of clarithromycin greater than 1 g/day should not be co-administered with ritonavir.

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

Effect of Clarithromycin on Other Medicinal Products

CYP3A-based interactions

Co-administration of clarithromycin, which is 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.
The use of clarithromycin is contraindicated in patients receiving the CYP3A substrates astemizole, cisapride, domperidone, pimozide and terfenadine due to the risk of QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes.

The use of clarithromycin is also contraindicated with ergot alkaloids, oral midazolam, HMG CoA reductase inhibitors metabolised mainly by CYP3A4 (e.g. lovastatin and simvastatin), colchicine, ticagrelor and ranolazine.

Caution is required if clarithromycin is co-administered 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. Drugs or drug classes that are known or suspected to be metabolised by the same CYP3A isozyme include (but this list is not comprehensive) alprazolam, carbamazepine, cilostazole, ciclosporin, disopyramide, ibrutinib, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g. warfarin), atypical antipsychotics (e.g. quetiapine), quinidine, rifabutin, sildenafil, sirolimus, tacrolimus, triazolam and vinblastine.

Drugs interacting by similar mechanisms through other isozymes within the cytochrome P450 system include phenytoin, theophylline and valproate.

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

There have been 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 (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 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 metabolizer population.

Triazolobenzodiazepines (e.g., alprazolam, midazolam, triazolam)
When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also apply to other benzodiazepines that are 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 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 is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported. 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 taking clarithromycin and verapamil concomitantly.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and clarithromycin concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir

Both clarithromycin and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional drug interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 mg three times daily) to 12 healthy volunteers resulted in steady-state AUC and Cmax values of saquinavir which were 177% and 187% higher than those seen with saquinavir alone. Clarithromycin AUC and Cmax values were approximately 40% higher than those seen with clarithromycin alone. No dose adjustment is required when the two drugs are coadministered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin.

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

4.6 Pregnancy and Lactation

Pregnancy

The safety of clarithromycin for use during pregnancy has not been established. Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on 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 withoutcarefully weighing the benefits against risks (see section 5.3).

Breast Feeding

The safety of clarithromycin for use during breast feeding of infants has not been established. Clarithromycin is excretedinto human breast milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about1.7% of the maternal weight-adjusted dose of clarithromycin.

Fertility

In the rat, fertility studies have not shown any evidence of harmful effects (see section 5.3).

4.7 Effects on Ability to Drive and Use Machines

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

4.8 Undesirable Effects

The majority of side effects observed in clinical trials were of a mild and transient nature. Fewer than 3% of adult patients without mycobacterial infections and fewer than 2% of pediatric patients without mycobacterial infections discontinued therapy because of drug-related side effects. Fewer than 2% of adult patients taking Clarithromycin Extended-Release Tablets USP discontinued therapy because of drug - related side effects.

The most frequently reported events in adults taking Clarithromycin Extended-Release Tablets USP were diarrhea (3%), nausea (3%), abnormal taste (3%), dyspepsia (2%), abdominal pain/discomfort (2%), and headache (2%). Most of these events were described as mild or moderate in severity. Of the reported adverse events, only 1% was described as severe.

Adverse Reactions Observed During Clinical Trials of Clarithromycin

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.

Blood and lymphatic system
Uncommon: Leukopenia, neutropenia, thrombocythemia, eosinophilia.
Not Known: Agranulocytosis, thrombocytopenia.

Gastrointestinal Disorders
Common: Diarrhea, vomiting, dyspepsia, nausea, abdominal pain.
Uncommon: Oesophagitis, gastrooesophageal reflux disease, gastritis, proctalgia, stomatitis, glossitis, abdominal distension , constipation, dry mouth, eructation, flatulence.
Not Known: Pancreatitis acute, tongue discolouration, tooth discolouration.

Hepatobiliary Disorders
Common: Liver function test abnormal.
Uncommon: Cholestasis, hepatitis, alanine aminotransferase increased, aspartateamino transferase increased, gamma-glutamyltransferase increased.
Not Known: Hepatic failure, jaundice hepatocellular.

Immune System Disorders
Uncommon: Anaphylactoid reaction, Hypersensitivity.
Not Known: Anaphylactic reaction, angioedema.

Infection and Infestations

Uncommon: Cellulitis, Candidiasis, gastroenteritis, vaginal infection.
Not Known: Pseudomembranous colitis, erysipelas.

Nervous System Disorders
Common: Dysgeusia, headache, taste perversion.
Uncommon: Loss of consciousness, dyskinesia, dizziness, somnolence, tremor.
Not Known: Convulsion, ageusia, parosmia, anosmia, paraesthesia

Psychiatric Disorders
Common: Insomnia
Uncommon: Anxiety, nervousness
Not Known: Psychotic disorder, depersonalization, depression, disorientation, hallucination, abnormal dreams, mania

Skin and Subcutaneous Tissue Disorders
Common: Rash, hyperhidrosis
Uncommon: Dermatitis bullous, pruritus, urticaria, rashmaculo-papular
Unknown: Severe cutaneous adverse reactions (SCAR) (e.g. Acute generalized exanthematous pustulosis (AGEP),Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS)), acne

Investigations
Uncommon: Albumin globulin ratio abnormal, blood alkaline phosphatase increased, blood lactated hydrogenase increased
Not Known: International normalised ratio increased, prothrombin time prolonged, urine colour abnormal

Metabolism and Nutrition Disorders
Uncommon: Anorexia, decreased appetite

Musculoskeletal and Connective Tissue Disorders
Uncommon: Muscle spasms, musculoskeletal stiffness, myalgia
Not Known: Rhabdomyolysis, myopathy

Renal and Urinary Disorders

Uncommon: Blood creatinine increased, blood urea increased
Not Known: Renal failure, nephritis interstitial

Respiratory, Thoracic and Mediastinal Disorders
Uncommon: Asthma, epistaxis, pulmonary embolism.

Ear and labyrinth disorders:
Uncommon: Vertigo, hearing, impaired, tinnitus.
Not Known: Deafness.

Cardiac disorders
Uncommon: Cardiac arrest, atrial fibrillation, electrocardiogram QTprolonged, extrasystoles palpitations
Not Known: Torsades de pointes, ventricular tachycardia and ventricular fibrillation.

Vascular disorders:
Common: Vasodilation.
Not Known: Haemorrhage.

General disorders and administration site conditions
Very Common: Injection site phlebitis
Common: Injection site pain, injection site inflammation.
Not Known: Malaise, pyrexia, asthenia, chest pain, chills, fatigue.

Description of selected adverse reactions
Injection site phlebitis, injection site pain, and injection site inflammation are specific to the clarithromycin intravenous formulation.

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

There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g. somnolenceand confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested (see section 4.5).

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.

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.

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 1,000 mg and 2,000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, Serum Glutamic Oxaloacetic Transaminase (SGOT) and Serum GlutamicPyruvate Transaminase (SGPT) elevations. Additional low-frequency events included dyspnoea, insomnia and dry mouth. The incidences were comparable for patients treated with 1,000 mg and 2,000 mg, but were generally about 3 to4 times as frequent for those patients who received total daily doses of 4,000 mg of clarithromycin.

In these immunocompromised patients, evaluations of laboratory values were made by analysing those values out side the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about2% to 3% of those patients who received 1,000 mg or 2,000 mg of clarithromycin daily had seriously abnormal elevated levels of SGOT and SGPT, and abnormally low white blood cell and platelet counts. A lower percentage of patients in these two dosage groups also had elevated Blood Urea Nitrogen levels. Slightly higher incidence of abnormal values were noted for patients who received 4,000 mg daily for all parameters except White Blood Cell.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the marketing authorization holder.

4.9 Overdose

Over dosage of Clarithromycin can cause gastrointestinal symptoms such as abdominal pain, vomiting, nausea, and diarrhea.

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, hypokalaemia and hypoxaemia.

Adverse reactions accompanying over dosage 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

5.1. Pharmacodynamic Properties

ATC Classification: Pharmacotherapeutic group: Antibacterial for systemic use, macrolide
ATC-Code: J01FA09

Clarithromycin exerts its antibacterial action by binding to the 50S ribosomal subunit of susceptible microorganisms resulting in inhibition of protein synthesis. Clarithromycin is active in vitro against a variety of aerobic and anaerobic gram positive and gram - negative microorganisms as well as most *Mycobacterium avium* complex (MAC) microorganisms.

Additionally, the 14-OH Clarithromycin metabolite also has clinically significant antimicrobial activity. The 14-OH Clarithromycin is twice as active against Haemophilus influenzae microorganisms as the parent compound. However, for *Mycobacterium avium* complex (MAC) isolates the 14-OH metabolite is 4 to 7 times less active than Clarithromycin. The clinical significance of this activity against *Mycobacterium avium* complex is unknown. Clarithromycin has been shown to be active against most strains like *Staphylococcus aureus, Staphylococcus pneumoniae, Haemophilus parainfluenzae, Streptococcus pyogenes, Haemophilus influenzae, Mycoplasma pneumoniae, Mycobacterium avium* complex (MAC) both in vitro and in clinical infections. Beta - lactamase production should have no effect on Clarithromycin activity.

Note: Most strains of methicillin-resistant and oxacillin resistant staphylococci are resistant to Clarithromycin.

5.2 Pharmacokinetic Properties

Clarithromycin is rapidly absorbed from the gastrointestinal tract after oral administration. The kinetics of orally administered extended-release clarithromycin have been studied in adult humans and compared with clarithromycin 250mg and 500mg immediate release tablets. The extent of absorption was found to be equivalent when equal total daily doses were administered. The absolute bioavailability is approximately 50%. Food also increases the Clarithromycin peak plasma concentration by about 24%, but does not affect the extent of Clarithromycin bioavailability.

Food does not affect the onset of formation of the antimicrobially active metabolite, 14-OH Clarithromycin or its peak plasma concentration but does slightly decrease the extent of metabolite formation, indicated by an 11% decrease in area under the plasma concentration-time curve (AUC).

Therefore, Clarithromycin Extended-Release Tablets USP may be given without regard to food. While the extent of formation of 14-OH Clarithromycin following administration of Clarithromycin Extended-Release Tablets USP (2 x 500 mg once daily) is not affected by food.

Administration under fasting conditions is associated with approximately 30% lower Clarithromycin AUC relative to administration with food. Therefore, Clarithromycin Extended-Release Tablets USP should be taken with food. The pharmacokinetics of Clarithromycin was also altered in subjects with impaired renal function.

The pharmacokinetic behaviour of clarithromycin is non-linear. In fed patients given 500mg clarithromycin extended-release daily, the peak steady state plasma concentration of clarithromycin and 14 hydroxy clarithromycin were 1.3 and 0.48μg/mL, respectively.

When the dosage was increased to 1000mg daily, these steady-state values were 2.4μg/mL and 0.67μg/mL respectively. Elimination half-lives of the parent drug and metabolite were approximately 5.3 and 7.7 hours respectively. The apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at higher doses.

Urinary excretion accounted for approximately 40% of the clarithromycin dose. Faecal elimination accounts for approximately 30%.

5.3 Preclinical Safety Data

In repeated dose studies, clarithromycin toxicity was related to dose and duration of treatment. The primary target organ was the liver in all species, with hepatic lesions seen after 14 days in dogs and monkeys. Systemic exposure levels associated with this toxicity are not known but toxic mg/kg doses were higher than the dose recommended for patient treatment.

No evidence of mutagenic potential of clarithromycin was seen during a range of in vitro and in vivo tests.

Fertility and reproduction studies in rats have shown no adverse effects. Teratogenicity studies in rats (Wistar (p.o.) and Sprague-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 in monkeys embryonic loss was seen but only at dose levels which were clearly toxic to the mothers.

No other toxicological findings considered to be of relevance to the dose level recommended for patient treatment have been reported.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Tablet core

Lactose Monohydrate
Hydroxypropyl methylcellulose
Purified Water
Hydroxypropyl methyl cellulose phthalate

Purified Talc
Magnesium Stearate

Film Coat

Opadry II Yellow 31G52300 (consist of Hypromellose, Lactose Monohydrate, Titanium Dioxide, Polyethylene Glycol, Talc and Quinoline Yellow Aluminium Lake)
Purified Water

6.2 Incompatibilities
Not applicable.

6.3 Shelf Life
48 months

6.4 Special Precautions for Storage
Store below 30°C. Protect from light and moisture.

6.5 Nature and Contents of Container
Available in Blister pack.

Blister pack of 7 tablets using Rigid PVC film coated with PVdC Pharma Grade (Clear, 90gsm coated) and Printed Aluminium Foil. One blister pack of 7 tablets is packed in mono carton along with insert. Such 10 inner cartons are packed in an outer carton.

6.6 Special precautions for disposal
No special requirements

7. MARKETING AUTHORISATION HOLDER
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