1.4.1 PRESCRIBING INFORMATION (SUMMARY OF PRODUCT CHARATERISTICS)

1. NAME OF THE MEDICINAL PRODUCT

CLARIE OD (Clarithromycin Extended-Release Tablets USP)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated extended-release tablet contains;

Clarithromycin USP 500mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Extended-Release Tablet.

Yellow coloured, 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 Extended-Release Tablets USP 500mg are indicated in adults and children 12 years and older.

Clarithromycin Extended-Release Tablets USP 500mg are indicated for treatment of infections caused by susceptible organisms. Indications include:

Lower respiratory tract infections for example, acute and chronic bronchitis, and pneumonia.
Upper respiratory tract infections for example, sinusitis and pharyngitis.

Clarithromycin Extended-Release Tablets USP 500mg are also indicated in skin and soft tissue infections of mild to moderate severity, for example folliculitis, cellulitis and erysipelas.

4.2 Posology and method of administration

Clarithromycin Extended-Release Tablets USP 500mg should be taken with food and must be swallowed whole and not chewed.

Adults and Children over 12 years:

The usual dosage is one 500 mg extended-release tablet daily for seven to fourteen days. In more severe infections, the dosage can be increased to two 500 mg extended release tablets taken as one dose daily. Dose must be taken at the same time every day.

Children younger than 12 years:

These tablets are not recommended for children under 12 years as liquid medicines are generally preferable. An alternative formulation of Clarithromycin suitable for children should be used in this patient population.

Patients with renal impairment:

Clarithromycin Extended-Release Tablets USP 500mg should not be used in patients with renal impairment (creatinine clearance less than 30 mL/min). Clarithromycin immediate release tablets may be used in this patient population. (See 4.3 Contraindications). 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. For patients with moderate renal function (creatinine clearance 30 to 60 ml/min), a 50% dosage reduction should be implemented resulting in a maximum dose of one Clarie OD 500 mg Tablet per day.

Patients with hepatic impairment:

The use of Clarithromycin Extended-Release Tablets USP 500mg is not recommended in patients with severe liver impairment.

4.3 Contraindications

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

Clarithromycin should not be used in patients who suffer from severe hepatic failure in combination with renal impairment. As the dose cannot be reduced from 500 mg daily, Clarie ODtablets are contra-indicated in patients with creatinine clearance less than 30 ml/min. All other formulations may be used in this patient population.

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

Concomitant administration of clarithromycin and any of the following drugs is contraindicated: ergot derivatives, cisapride, domperidone, pimozide, astemizole and terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see section 4.4 and 4.5).

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

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

Concomitant administration 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. (see section 4.5).

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

Patients with congenital or acquired hypokalaemia (risk of prolongation of QT-time).

4.4 Special warnings and precautions for use

The physician should not prescribe clarithromycin to pregnant women without carefully weighing the benefits against risk; particularly during the first three months of pregnancy (see section 4.6).

Clarithromycin is principally excreted by the liver and kidney. Caution should be exercised in administering this antibiotic to patients with impaired hepatic and renal function.

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

Prolonged or repeated used of clarithromycin may result in an overgrowth of non-susceptible bacteria or fungi. If super-infection occurs, clarithromycin should be discontinued and appropriate therapy instituted.

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in the elderly, some of which occurred in patients with renal insufficiency. Deaths have been reported in some such patients (see section 4.5). Concomitant administration of clarithromycin and colchicine is contraindicated (see section 4.3).

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

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including clarithromycin, 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.

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.

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

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 (see section 4.8). 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 (see section 4.3). The use of clarithromycin is contraindicated in patients with congenital or acquired QT prolongation (see sections 4.3 and 4.5).

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.

Caution should be exercised, if clarithromycin is indicated for patients receiving concomitant treatment with a CYP3A4 inducer, because it is possible that clarithromycin concentrations may not reach therapeutic levels (see section 4.5). Clarithromycin is a CYP3A4 inhibitor, and its concomitant use with drugs primarily metabolised via this enzyme should be considered only when clearly necessary (see section 4.5).

HMG-CoA Reductase Inhibitors (statins): Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised when prescribing clarithromycin with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin and statins. Patients should be monitored for signs and symptoms of myopathy.

In situations where the concomitant use of clarithromycin with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. Use of a statin that is not dependent on CYP3A metabolism (e.g. fluvastatin) can be considered (see section 4.5).

Clarithromycin inhibits the metabolism of some HMG-CoA reductase inhibitors, which results in increased plasma concentrations of these drugs (see section 4.5). Exacerbation of symptoms of myasthenia gravis has been reported in patients receiving clarithromycin therapy.

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

Oral anticoagulants: There is a risk of serious haemorrhage and significant elevations in International Normalized Ratio (INR) and prothrombin time when clarithromycin is co-administered with warfarin (see section 4.5). INR and prothrombin times should be frequently monitored while patients are receiving clarithromycin and oral anticoagulants concurrently.

Excipients

Clarithromycin Extended-Release Tablets USP 500mg 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:

Clarithromycin has been reported to elevate plasma levels of cisapride, pimozide, astemizole, and terfenadine. Increased levels of these drugs may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Concomitant administration of clarithromycin and any of these medicinal products is contraindicated (see section 4.3).

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 (see section 4.3).

Oral Midazolam

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

HMG-CoA Reductase Inhibitors (statins)

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

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

Effect of other medicinal products on clarithromycin

Clarithromycin is metabolised via enzyme CYP3A4. Therefore, strong inhibitors of this enzyme may inhibit Clarithromycin metabolism, this results in increased plasma concentrations of Clarithromycin.

CYP3A4 inducers (such as rifampicin, phenytoin, carbamazepine, phenobarbital, products containing St. John Wort) may induce clarithromycin metabolism. This may result in sub-therapeutic levels of clarithromycin which; decrease the product's efficacy. If clarithromycin is clearly indicated, it may be necessary to increase the dose of clarithromycin, and closely monitor its efficacy and safety. Further monitoring of plasma levels of the CYP3A4 inducer may be necessary, because the levels may be increased due to CYP3A4 inhibition by clarithromycin (see also relevant Summary of Product Characteristics of the administered CYP3A4 inducer). Concomitant administration of rifabutin and clarithromycin has resulted in increased rifabutin levels and decreased clarithromycin levels in serum, and in an increased risk of uveitis. A 39% reduction in AUC for clarithromycin and a 34% increase in AUC for the active 14-hydroxy metabolite have been seen when clarithromycin was used concomitantly with the CYP3A4 inducer efavirenz.

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. 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, such as clarithromycin immediate release tablets, sachet or paediatric suspensions (not all presentations may be marketed). Doses of clarithromycin greater than 1000 mg per day should not be coadministered with protease inhibitors.

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 pharmacokinetic interactions).

Effect of clarithromycin on other medicinal products

CYP3A-based Interactions

Co-administration of clarithromycin, known to inhibit CYP3A, and a drug primarily metabolized by CYP3A may be associated with elevations in drug concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant drug.

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 (see sections 4.3 and 4.4).

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 (see section 4.3).

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 post-marketing reports of torsade de pointes occurring with concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QTc prolongation during Co-administration of clarithromycin with these drugs. Serum levels of 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.

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.

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.

There are no in-vivo human data available describing an interaction between clarithromycin and the following drugs: aprepitant, eletriptan, halofantrine, and ziprasidone. However, because in vitro data suggest these drugs are CYP3A substrates, caution should be used when they are co-administered with clarithromycin.

Eletriptan should not be coadministered with CYP3A inhibitors such as clarithromycin.

There have been spontaneous or published reports of drug interactions of CYP3A inhibitors, including clarithromycin, with cyclosporine, tacrolimus, methylprednisolone, vinblastine, and cilostazol.

Ciclosporin, tacrolimus and sirolimus

Concomitant administration of the oral form of Clarithromycin with ciclosporin or tacrolimus results in a more than two-fold increase of Cmin plasma concentrations of ciclosporin and tacrolimus. Similar effects can also be expected with sirolimus.

Plasma levels of ciclosporin, tacrolimus or sirolimus should be thoroughly monitored when commencing treatment with Clarithromycin in patients on the above mentioned immunosuppressants, and their doss should be decreased if necessary.

Clarithromycin discontinuation in those patients also requires a thorough monitoring of ciclosporin, tacrolimus or sirolimus plasma levels to guide dose adjustment.

There have been spontaneous or published reports of drug interactions of CYP3A inhibitors including Clarithromycin with ciclosporin, tacrolimus, methylprednisolone, vinblastine and cilostazol.

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. Patients should be monitored for clinical symptoms of colchicine toxicity (see section 4.4).

Digoxin

Digoxin is a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When clarithromycin and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving clarithromycin and digoxin concomitantly have also been reported in post marketing surveillance. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and clarithromycin simultaneously.

Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of clarithromycin and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with drugs not thought to be 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.

Bidirectional pharmacokinetic interactions

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bidirectional 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 bidirectional 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 co-administered for a limited time at the doses/formulations studied. Observations from drug interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule. Observations from drug interaction studies performed with saquinavir alone may not be representative of the effects seen with saquinavir/ritonavir therapy. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on clarithromycin (see section 4.5: Ritonavir).

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

4.6 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 embryofoetal development cannot be excluded. Therefore, use during pregnancy is not advised without carefully weighing the benefits against risk (see section 5.3).

Breast-feeding

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

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 available on the effect of clarithromycin on the ability to drive or use machines. When performing these activities the possible occurrence of the adverse reactions dizziness, vertigo, confusion and disorientation should be taken into account.

4.8 Undesirable effects

The most frequent and common adverse reactions related to clarithromycin therapy for both adult and paediatric populations are abdominal pain, diarrhoea, nausea,

vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics.

The following table displays adverse reactions reported in clinical trials and from post- marketing experience with clarithromycin extended-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).

System Organ Class	**Very common ≥1/10**	**Common ≥1/100 to < 1/10**	**Uncommon ≥ 1/1,000 to < 1/100**	**Not Known* (cannot be estimated from the available data)**
Infections and infestations			Candidiasis, gastroenteritis, vaginal infection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system			Leukopenia	Agranulocytosis, thrombocytopenia
Immune system disorders			Hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders			Anorexia, decreased appetite	
Psychiatric disorders		Insomnia	Anxiety	Psychotic disorder, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders		Dysgeusia, headache	Dizziness, Tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders			Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders			Electrocardiogram	Torsades de

			QT prolonged, palpitations	pointes, ventricular tachycardia, Ventricular fibrillation
Respiratory, thoracic and mediastinal disorder			Epistaxis	
Gastrointestinal disorders		Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Gastrooesophageal reflux disease, gastritis, proctalgia, stomatitis, glossitis, constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discolouration, tooth discolouration
Hepatobiliary disorders		Liver function test abnormal	Alanine aminotransferase increased, aspartate aminotransferase increased	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders		Rash, hyperhidrosis	Pruritus, urticaria,	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			Myalgia	Rhabdomyolysis, myopathy
Renal and urinary disorders				Renal failure, nephritis interstitial
General disorders and administration site conditions			Asthenia	

Investigations				International normalised ratio increased, prothrombin time prolonged, urine colour abnormal

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 marketing authorization holder.

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, hypokalaemia and hypoxaemia.

Adverse reactions accompanying overdosage 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

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

Mode of Action

Clarithromycin is an antibiotic belonging to the macrolide antibiotics group. It exerts its antibacterial action by inhibiting the intracellular protein synthesis of susceptible bacteria. It selectively binds to the 50S subunit of bacterial ribosomes and thus prevents the translocation of activated amino acids.

The 14(R)-hydroxy metabolite of clarithromycin, a product of parent drug metabolism in humans, also has antimicrobial activity. The metabolite is less active than the parent compound for most organisms, including Mycobacterium spp. An exception is *Haemophilus influenzae* against which the metabolite is 1 to 2 times more active than the parent compound. Clarithromycin combined with the metabolite showed a strain-dependent additive or synergistic effect both *in vitro* and *in vivo*.

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 influenza; Haemophilus parainfluenza; Moraxella (Branhamella) catarrhalis; Neisseria gonorrhoeae; Legionella pneumophila; Bordetella pertussis; Campylobacter jejuni.*

Mycoplasma: *Mycoplasma pneumoniae; Ureaplasma urealyticum.*
Other Organisms: *Chlamydia trachomatis; Mycobacterium avium; Mycobacterium leprae; Mycobacterium kansasii; Mycobacterium chelonae; Mycobacterium fortuitum; Mycobacterium intracellularis; Chlamydia pneumoniae.*
Anaerobes: *Clostridium perfringens*; Peptococcus species; Peptostreptococcus species; *Propionibacterium acnes*.
Clarithromycin has relevant bactericidal activity against several bacterial strains. The organisms include *H. influenzae, S. pneumoniae, S. pyogenes, Streptococcus agalactiae; Moraxella (Branhamella) catarrhalis; Neisseria gonorrhoeae and Campylobacter spp.*

PK/PD Relationship

Clarithromycin is extensively distributed in body tissues and fluids. Because of high tissue penetration, intracellular concentrations are higher than serum concentrations.

Clarithromycin concentrations in tonsil and whole lung tissue are 2 to 6 fold higher than those observed in the serum. Tissue and serum concentrations observed in Abbott studies with immediate-release (IR) tablets are presented below.

Mean Clarithromycin Concentration [250mg BID]		
Tissue Type	Tissue	Serum
Tonsil	1.6 µg/g	0.8 µg/ml
Lung	8.8 µg/g	1.7 µg/ml

The pharmacokinetics of orally administered modified-release (MR) clarithromycin tablets have been studied in adult humans (refer to section 5.2) and compared with clarithromycin 250 mg and 500 mg IR tablets. The extent of absorption – area under curve (AUC) – was found to be equivalent when equal total daily doses were administered. The equivalent AUCs would be expected to drive tissue levels equivalent to those observed for clarithromycin IR tablets.

Mechanism of Resistance

Acquired macrolide resistance in *S. pneumoniae*, *S. pyogenes*, and *S. aureus* is mediated primarily by the presence of one of two mechanisms (i.e. *erm* and *mef* or *msr*).

Ribosomal binding of the antimicrobial is prevented through methylation of the ribosome by an enzyme (*erm*). Alternatively an efflux mechanism (*mef* or *msr*) can prevent the antimicrobial from reaching its ribosomal target by pumping the antimicrobial out of the cell. No acquired resistance mechanisms have been identified in Moraxella or Haemophilus spp. Macrolide resistance mechanisms are equally effective against 14- and 15-membered macrolides includingerythromycin, clarithromycin, roxithromycin, and azithromycin. The mechanisms for penicillin resistance and macrolide resistance are unrelated.

Attention should be paid to the erm-mediated cross-resistance between macrolides such as clarithromycin and lincosamides such as lincomycin and clindamycin.

Clarithromycin antagonises the bacterial effects of beta-lactam antibiotics. Also the effects of lincomycin and clindamycin are antagonised, at least *in vitro*.

Breakpoints

The following breakpoints for clarithromycin, separating susceptible organisms from resistant organisms, 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	0.5 mg/L [1]
[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		

Clarithromycin is used for the eradication of *H. pylori*; minimum inhibitory concentration (MIC) ≤ 0.25 µg/ml which has been established as the susceptible breakpoint by the Clinical and Laboratory Standards Institute (CLSI).

*The correlation between H. Influenzae macrolides MICs and clinical outcome is weak. Therefore, breakpoints for macrolides and related antibiotics were set to categorise wild type

H. Influenzae as intermediate.

The activity of 14(R)-hydroxy-clarithromycin is greater than that of clarithromycin against *Haemophilus influenzae*. Studies done *in vitro* have suggested an additive activity of the 14(R) hydroxy clarithromycin and the parent molecule against *H. influenzae*.

Susceptibility

The prevalence of acquired resistance rates may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when the local prevalence of resistance is such that the utility of an agent in at least some types of infections is questionable.

Commonly susceptible species
Aerobic Gram-positive micro-organisms Streptococcus group F **Aerobic Gram-negative micro-organisms** Legionella pneumophila Moraxella catarrhalis Legionella spp **Anaerobic micro-organisms** Clostridium perfringens **"Other"** Chlamydia pneumoniae Chlamydia trachomatis Mycoplasma pneumoniae
Species for which acquired resistance may be a problem# Aerobic Gram-positive micro-organisms Staphylococcus aureus (resistant or susceptible* to methicillin)+ staphylococcus coagulase negative + Streptococcus group B, C, G Streptococcus pneumoniae* + Streptococcus pyogenes* Streptococcus spp **Aerobic Gram-negative micro-organisms** H. Influenzae§

Inherently resistant organisms
Aerobic Gram-positive micro-organisms Enterococcus spp **Aerobic Gram-negative micro-organisms** Enterobacteriaceae Pseudomonas aeruginosa

* Species against which efficacy has been demonstrated in clinical investigations (if susceptible)

+ Indicates species for which a high rate of resistance (i.e. greater than 50%) has been observed in one or more area/country/regions(s) of the EU

§species with intermediate natural susceptibility

≥10% resistance in at least one country of the European Union

5.2 Pharmacokinetic properties

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%. Little or no unpredicted accumulation was found and the metabolic disposition did not change in any species following multiple dosing.

Based upon the finding of equivalent absorption the following in vitro and in vivo data are applicable to the extended -release formulation.

In vitro: Results of in vitro studies showed that the protein binding of clarithromycin in human plasma averaged about 70 % at concentrations of 0.45 - 4.5µg/mL A decrease in binding to 41% at 45.0µg/mL suggested that the binding sites might become saturated, but this only occurred at concentrations far in excess of therapeutic drug levels.

In vivo: Clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were found in the liver and lung tissue, where the tissue to plasma ratios reached 10 to 20.

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, Reproduction and Teratogenicity

Studies performed in rats at oral doses up to 500 mg/kg/day (highest dose associated with overt renal toxicity) demonstrated no evidence for clarithromycin-related adverse effects on male fertility. This dose corresponds to a human equivalent dose (HED) of approximately 5 times the maximum recommended human dose (MRHD) on a mg/m^2 basis for a 60-kg individual.

Fertility and reproduction studies in female rats have shown that a daily dosage of 150mg/kg/day (highest dose tested) caused no adverse effects on the oestrus cycle, fertility, parturition and number and viability of offspring. Oral teratogenicity studies in rats (Wistar and Sprague-Dawley), rabbits (New Zealand White) and cynomolgous monkeys failed to demonstrate any teratogenicity from clarithromycin at the highest doses tested up to 1.5, 2.4 and 1.5 times the MRHD on a mg/m^2 basis in the respective species. However, a 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 at 5 times the MRHD on a mg/m^2 basis for a 60-kg individual. Embryonic loss was seen in monkeys 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
- Hypromellose
- Hypromellose Phthalate
- Talc
- Magnesium Stearate

Film Coat

- Hypromellose
- Lactose Monohydrate
- Macrogol
- Quinoline Yellow Aluminium Lake (E104)
- Talc
- Titanium Dioxide (E171)

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 Primary Packaging

Blister pack of 7 tablets packed using Rigid PVC film coated with PVdC Pharma Grade (Clear, 90gsm coated) and Printed Aluminium foil.

Secondary Packaging

Such one blister of 7 tablets is packed in a carton along with insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. MARKETING AUTHORISATION HOLDER

8. MARKETING AUTHORISATION NUMBER

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT

06/2024