1.3.1.1 PROFESSIONAL INFORMATION FOR MEDICINES FOR HUMAN USE

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

CLARIDE XL 500 mg modified release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet of CLARIDE XL contains 500 mg clarithromycin as clarithromycin citrate.

Contains sugar: Each tablet of CLARIDE XL contains lactose monohydrate 298 mg.

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Modified release tablets

CLARIDE XL is a yellow coloured film coated, oblong shaped, and biconvex tablet with both sides plain.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CLARIDE XL is indicated for:

- Lower respiratory tract infections e.g. bronchitis, pneumonia;
- Upper respiratory tract infections e.g. pharyngitis, sinusitis;
- Skin and soft tissue infections e.g. folliculitis, cellulitis, erysipelas.

4.2 Posology and method of administration

Posology

Adults

The recommended dosage of CLARIDE XL in adults is 500 mg (one CLARIDE XL 500 mg tablet) once daily with food.

In more severe infections, the dosage can be increased to 1 000 mg once daily (two CLARIDE XL 500 mg tablets).

Special populations

Renal impairment

CLARIDE XL tablets should not be used in patients with significant renal impairment (creatinine clearance less than 30 mL / min) as appropriate CLARIDE XL dosage reduction is not possible when administering this medicine. 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 CLARIDE XL tablet per day (see section 4.3).

Paediatric population

CLARIDE XL is not suitable for children younger than 12 years.

Method of administration

For oral administration.

CLARIDE XL tablets should be swallowed whole.

4.3 Contraindications

CLARIDE XL is contraindicated in:

- Patients with hypersensitivity to clarithromycin, macrolide antibiotic medicines or to any of the excipients in CLARIDE XL (see section 6.1);
- Patients with creatinine clearance less than 30 mL/min (see section 4.2; Renal impairment);
- Patients with a history of QT prolongation or ventricular cardiac dysrhythmia, including torsades de pointes (see sections 4.4 and 4.5);
- Patients who suffer from severe hepatic failure in combination with renal impairment.
- Patients with hypokalaemia (risk of prolongation of QT-time);
- Concomitant administration of CLARIDE XL and any of the following medicines is contraindicated: astemizole, cisapride, pimozide, terfenadine and ergotamine or dihydroergotamine (see section 4.5) .
- Concomitant administration of CLARIDE XL and oral midazolam is contraindicated (see section 4.5).
- Concomitant administration with ticagrelor or ranolazine is contraindicated.
- Concomitant use 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);
- Colchicine is contraindicated in patients with renal or hepatic impairment who are taking P-glycoprotein or a strong CYP3A4 inhibitor.

4.4 Special warnings and precautions for use

Hypersensitivity

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 (SJS), Toxic Epidermal Necrolysis (TEN) and Drug Rash with Eosinophilia and Systemic Symptoms (DRESS), CLARIDE XL therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Cardiovascular disorders

There is an increased risk of death in patients with heart disease and health care providers should consider using other antibiotics in such patients.

Hepatic disorders

CLARIDE XL 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 CLARIDE XL to patients with moderate to severe renal impairment (see section 4.3).

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.

Clostridium difficile-associated diarrhoea (CDAD)

Pseudomembranous colitis has been reported with nearly all antibacterial medicines, including clarithromycin, and may range in severity from mild to life threatening. CDAD has been reported with use of nearly all antibacterial medicines including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial medicines alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*. Therefore, it is important to consider this diagnosis in

patients who present with diarrhoea subsequent to the administration of antibacterial medicines.

Prolonged or repeated use 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. Microbial testing should be performed and adequate treatment initiated. Medicines inhibiting peristalsis should be avoided.

Myasthenia gravis

Exacerbation of symptoms of myasthenia gravis has been reported in patients receiving clarithromycin therapy (see section4.8).

Colchicine

Colchicine toxicity has been reported with the concomitant use of clarithromycin, as contained in CLARIDE XL, and colchicine, especially in the elderly, or in patients with renal insufficiency. Deaths have occurred. Concomitant administration of clarithromycin, as contained in CLARIDE XL, and colchicine is contraindicated (see sections 4.3 and 4.5).

Benzodiazepines

Caution is advised regarding concomitant administration of CLARIDE XL and triazolo benzodiazepines, such as triazolam, and intravenous or oromucosal midazolam (see sections 4.3 and 4.5).

Ototoxic medicines

Caution is advised regarding concomitant administration of clarithromycin with other ototoxic medicines, especially with aminoglycosides. Monitoring of

vestibular and auditory function should be carried out during and after treatment.

Prolongation of the QT interval

Due to the risk for QT prolongation, clarithromycin should be used with caution in patients with coronary artery disease, severe cardiac insufficiency, hypomagnesaemia, bradycardia (< 50 bpm), or when co-administered with other medicinal products associated with QT prolongation (see section 4.5). Clarithromycin must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular arrhythmia (see section 4.3).

Pneumonia

It is important that sensitivity testing be performed when prescribing CLARIDE XL for community-acquired pneumonia. In hospital-acquired pneumonia, CLARIDE XL 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 medicine 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. CLARIDE XL should be used with caution when administered concurrently with medications that induce the cytochrome CYP3A4 enzyme (see section 4.5).

HMG-CoA reductase inhibitors (statins)

Concomitant use of CLARIDE XL with lovastatin or simvastatin is contraindicated (see section 4.3).

Caution should be exercised when prescribing CLARIDE XL with other statins. Rhabdomyolysis has been reported in patients taking clarithromycin, as contained in CLARIDE XL, and statins. Patients should be monitored for signs and symptoms of myopathy.

In situations where the concomitant use of CLARIDE XL 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).

Oral hypoglycaemic medicines/insulin

Oral hypoglycaemic medicines/insulin: The concomitant use of clarithromycin and oral hypoglycaemic medicines and/or insulin can result in significant hypoglycaemia. With certain hypoglycaemic medicines such as nateglinide, pioglitazone, repaglinide and rosiglitazone, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia when used concomitantly. 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 (PT) when CLARIDE XL is co-administered with warfarin (see section 4.5).

INR and prothrombin times should be frequently monitored while patients are receiving CLARIDE XL and oral anticoagulants concurrently.

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

Attention should also be paid to the possibility of cross resistance between clarithromycin, as contained in CLARIDE XL, and other macrolide medicines, as well as lincomycin and clindamycin.

Excipients

CLARIDE XL contains lactose monohydrate. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take CLARIDE XL. Lactose may influence the glycaemic control of patients with diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

The use of the following medicines is strictly contraindicated due to the potential for severe medicine interaction effects

Cisapride, pimozide, astemizole and terfenadine

Elevated cisapride levels have been reported in patients receiving clarithromycin, as contained in CLARIDE XL, and cisapride concomitantly. This may result in QT prolongation and cardiac dysrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects have been reported in patients taking clarithromycin, as contained in CLARIDE XL, and pimozide concomitantly (see section 4.3).

Macrolides have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac arrhythmias such as QT prolongation, ventricular tachycardia, ventricular fibrillation and torsades de pointes (see section 4.3). In one study in 14 healthy volunteers, the concomitant administration of clarithromycin and terfenadine resulted in a two to three

fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergotamine/dihydroergotamine

Co-administration of clarithromycin with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterized by vasospasm, and ischemia of the extremities and other tissues including the central nervous system. Concomitant administration of clarithromycin and these medicinal products is contraindicated (see section 4.3).

HMG-CoA reductase inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3 and section 4.4).

Effect of other medicinal products on clarithromycin

Products that are inducers of CYP3A4 (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 a reduced efficacy. Furthermore it might be necessary to monitor the plasma levels of the CYP3A4 inducer, which could be increased owing to the inhibition of CYP3A4 by clarithromycin (see also the relevant product information for the CYP3A4 inducer administered). Concomitant administration of rifabutin and clarithromycin resulted in an increase in rifabutin, and decrease in clarithromycin serum levels together with an increased risk of uveitis.

The following medicines 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, as contained in CLARIDE XL, 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 CLARIDE XL should be considered for the treatment of MAC.

Fluconazole

Concomitant administration of fluconazole 200 mg daily and clarithromycin, as contained in CLARIDE XL, 500 mg twice daily increases the mean steady-state minimum clarithromycin concentration (C_{min}) and area under the curve (AUC) of 33 % and 18 % respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin were not affected by concomitant administration of fluconazole. No CLARIDE XL dose adjustment is necessary.

Ritonavir

Concomitant administration of ritonavir 200 mg every eight hours and clarithromycin, as contained in CLARIDE XL, 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 31 %, C_{min} increased 182 % and AUC increased by 77 % with concomitant administration of ritonavir.

Because of the large therapeutic window for clarithromycin, as contained in CLARIDE XL, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: for patients with CL_{CR} 30 to 60 mL/min the dose of CLARIDE XL should be reduced by 50 % (see section 4.3).

For patients with CL_{CR} <30 mL/min the dose of clarithromycin should be decreased by 75 %. Doses of CLARIDE XL greater than 1 g/day should not be co-administered with ritonavir (see section 4.3).

Similar dose adjustments should be considered in patients with reduced renal function when ritonavir is used as a pharmacokinetic enhancer with other HIV protease inhibitors including atazanavir and saquinavir.

Effect of clarithromycin on other medicines

CYP3A-based interactions

Co-administration of CLARIDE XL, known to inhibit CYP3A, and medicines primarily metabolised by CYP3A may be associated with elevations in medicines concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant medicines.

CLARIDE XL should be used with caution in patients receiving treatment with other medicines 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 medicines primarily metabolised by CYP3A should be monitored closely in patients concurrently receiving CLARIDE XL (see section 4.2).

The following medicine or medicine classes are known or suspected to be metabolised by the same CYP3A isozyme: alprazolam, astemizole, carbamazepine, cilostazol, cisapride, ciclosporin, ibrutinib, disopyramide, ergot alkaloids, lovastatin, methylprednisolone, midazolam, omeprazole, oral anticoagulants (e.g. warfarin, see section 4.4), atypical antipsychotics (e.g. quetiapine), pimozide, quinidine, rifabutin, sildenafil, simvastatin, sirolimus, tacrolimus, terfenadine, triazolam and vinblastine but this list is not exhaustive.

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

Antidysrhythmics

Torsades de pointes occurring with the concurrent use of clarithromycin, as contained in CLARIDE XL, and quinidine or disopyramide have been reported.

Electrocardiograms (ECG) should be monitored for QT prolongation during co-administration of clarithromycin, as contained in CLARIDE XL, with these medicines.

Serum concentrations of these medications should also be monitored during CLARIDE XL therapy.

Omeprazole

Clarithromycin (500 mg every 8 hours) was given in combination with omeprazole (40 mg daily) to healthy adult subjects. The steady-state plasma concentrations of omeprazole were increased (C_{max}, AUC0-24, and $t_{1/2}$ increased by 30 %, 89 % and 34

% respectively, when administered concomitantly with clarithromycin for H. pylori eradication; however the change in the mean 24-hour gastric pH value from 5,2 (omeprazole alone) to 5,7 (omeprazole + clarithromycin) is not considered clinically significant.

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 CLARIDE XL.

Co-administration of CLARIDE XL 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 medicines are co-administered with CLARIDE XL.

Theophylline, carbamazepine

Results of clinical studies indicate there was a modest but statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either of these medicines 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). A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as CLARIDE XL in the CYP2D6 poor metaboliser population.

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

When midazolam was co-administered with clarithromycin, as contained in CLARIDE XL, (500 mg twice daily), midazolam AUC was increased 2,7 fold after intravenous administration of midazolam. If intravenous midazolam is co-administered with

CLARIDE XL, the patient must be closely monitored to allow dose adjustment. Medicines delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the medicines, will likely result in a similar interaction to that reported 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 CLARIDE XL is unlikely.

There have been reports of medicines interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin, as contained in CLARIDE XL, and triazolam. Monitoring the patient for increased CNS pharmacological effects is recommended.

Other medicine interactions

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). CLARIDE XL and other macrolides are known to inhibit CYP3A and Pgp. When CLARIDE XL and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin, as contained in CLARIDE XL, may lead to increased exposure to colchicine (see section 4.3 and section 4.4).

Digoxin

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin, as contained in CLARIDE XL, is known to inhibit Pgp. When clarithromycin, as contained in CLARIDE XL, 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, as

contained in CLARIDE XL, and digoxin concomitantly have also been reported. Some patients have shown clinical signs consistent with digoxin toxicity, including potentially fatal dysrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and CLARIDE XL simultaneously.

Zidovudine

Due to reduced gastrointestinal absorption of zidovudine in the presence of clarithromycin, reduced serum levels of zidovudine were observed in adults during concomitant therapy with clarithromycin and zidovudine. Because clarithromycin appears to interfere with the absorption of simultaneously administered oral zidovudine, patients should observe a 4-hour interval between taking these two medicines. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and valproate

There have been reports of interactions of CYP3A inhibitors, including clarithromycin, as contained in CLARIDE XL, with medicines not thought to be metabolised by CYP3A (e.g. phenytoin and valproate). Serum level determinations are recommended for these medicines when administered concomitantly with clarithromycin, as contained in CLARIDE XL, as increased serum levels have been reported.

Bi-directional medicines interactions

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional medicine 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(R)-hydroxy-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 CLARIDE XL greater than 1 000 mg per day should not be co-administered with protease inhibitors (see section 4.2).

Itraconazole

Both clarithromycin, as contained in CLARIDE XL, and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional medicines interaction. CLARIDE XL may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of CLARIDE XL. Patients taking itraconazole and CLARIDE XL 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 medicine interaction. Concomitant administration of clarithromycin (500 mg bid) and saquinavir (soft gelatin capsules, 1200 mg tid) to 12 healthy volunteers resulted in steady-state area under the curve (AUC) and maximum concentration (C_{max}) values of saquinavir which were 177 % and 187 % higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40 % higher than those seen with clarithromycin alone. No dose adjustment is required when the two medicines are co-administered for a limited time at the doses/formulations studied. Observations from medicine interaction studies using the soft gelatin capsule formulation may not be representative of the effects seen using the saquinavir hard gelatin capsule (see section 4.5: Ritonavir).

Observations from medicine interaction studies done with unboosted saquinavir 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 above, effect of other medicinal products on clarithromycin).

Calcium channel blockers

Caution is advised regarding the concomitant administration of CLARIDE XL and calcium channel blockers metabolized by CYP3A4 (e.g. verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of CLARIDE XL as well as calcium channel blockers may increase due to the interaction.

Verapamil

Hypotension, bradydysrhythmias and lactic acidosis have been observed in patients taking CLARIDE XL and verapamil concomitantly.

Oral contraceptives

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 as contained in CLARIDE XL during pregnancy and not been established. The medical practitioner should not prescribe CLARIDE XL to pregnant women, particularly in the first trimester of pregnancy.

Breastfeeding

CLARIDE XL is excreted into breast milk. The safety of clarithromycin as contained in CLARIDE XL during breastfeeding of infants has not been established.

Fertility

There is no data available

4.7 Effects on ability to drive and use machines

Since adverse reactions such as vertigo, dizziness and somnolence have been reported in patients receiving CLARIDE XL, patients should not drive, use machinery or perform any tasks that require concentration, until they are certain that CLARIDE XL does not adversely affect their ability to do so (see section 4.8).

4.8 Undesirable effects

a) Summary of the safety profile

The most frequent and common adverse reactions related to clarithromycin as contained in CLARIDE XL are abdominal pain, nausea, vomiting and taste perversion.

b) Tabulated list of adverse reactions

Table 1: Side effects reported for this formulation of clarithromycin containing medicines such as CLARIDE XL

System Organ Class	Frequent	Less Frequent	Frequency unknown
Infections and infestations	Oral candidiasis	Candidiasis, vaginal infection, gastroenteritis	Pseudomembranous colitis, erysipelas
Blood and lymphatic system		Leukopenia, thrombocythaemia	Agranulocytosis, thrombocytopenia
Immune system disorders		Hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders		Anorexia, decreased appetite	Hypoglycaemia
Psychiatric disorders	Insomnia	Anxiety	Psychotic disorder, depersonalisation, depression, disorientation, hallucination,

			abnormal dreams, mania, confusional state
Nervous system disorders	Dysgeusia, headache, taste perversion	Dizziness, tremor, somnolence	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders		Vertigo, impaired hearing, tinnitus	Deafness
Cardiac disorders		Palpitations	Torsades de pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders	Vasodilation		Haemorrhage
Respiratory, thoracic and mediastinal disorder		Epistaxis	
Gastrointestinal disorders	Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Gastroesophageal reflux disease, gastritis, proctalgia, stomatitis, glossitis, constipation, dry mouth, eructation, flatulence, gastrointestinal haemorrhage	Acute Pancreatitis, tongue discolouration, tooth discolouration
Hepatobiliary disorders		Alanine aminotransferase increased, aspartate aminotransferase increased	Hepatic failure, hepatocellular jaundice, hepatitis, cholestatic jaundice, cholestatic hepatitis, abnormal hepatic function
Skin and subcutaneous tissue disorders	Rash, hyperhidrosis	Pruritus, urticaria, dry skin	Severe Cutaneous Adverse Reactions (SCAR) (e.g. Acute Generalised Exanthemata's Pustulosis (AGEP), Stevens-Johnson Syndrome (SJS), Toxic Epidermal Necrolysis (TEN), 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, abnormal urine colour
General disorders and administration site conditions		Asthenia	
Investigations	Abnormal liver function test	Increased alanine aminotransferase, increased aspartate aminotransferase, electrocardiogram QT prolonged	Increased international normalised ratio, prolonged prothrombin time, increased blood creatinine, Serum Glutamic Oxaloacetic Transaminase (SGOT), Serum Glutamic Pyruvate Transaminase (SGPT), abnormally low white blood cell and platelet counts, elevated blood urea nitrogen levels

c) Description of selected adverse reactions

In some instances, hepatic failure with fatal outcome has been reported and generally has been associated with serious underlying diseases and/or concomitant medications (see section 4.4).

A special attention to diarrhoea should be paid as *Clostridium difficile*-associated diarrhoea (CDAD) has been reported with use of antibacterial medicines including clarithromycin and may range in severity from mild diarrhoea to fatal colitis (see section 4.4).

In the event of severe acute hypersensitivity reactions, such as anaphylaxis, Stevens-Johnson Syndrome and toxic epidermal necrolysis, clarithromycin

therapy should be discontinued immediately and appropriate treatment should be urgently initiated (see section 4.4).

As with other macrolides, QT prolongation, ventricular tachycardia, and torsade de pointes have rarely been reported with clarithromycin (see section 4.4 and 4.5).

Pseudomembranous colitis has been reported with antibacterial medicines, including clarithromycin, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of antibacterial medicines (see section 4.4).

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

There have been post-marketing reports of colchicine toxicity with concomitant use of clarithromycin and colchicine, especially in elderly and/or patients with renal insufficiency, some with a fatal outcome (see sections 4.3, 4.4 and 4.5).

There have been reports of hypoglycaemia, some of which have occurred in patients on concomitant oral hypoglycaemic medicines or insulin (see section 4.4 and 4.5).

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

There is a risk of serious haemorrhage and significant elevations in 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 (see section 4.4 and 4.5).

There have been rare reports of clarithromycin ER (extended release) 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.

e) Other special populations

Immunocompromised patients

In AIDS and other immunocompromised patients treated with the higher doses of clarithromycin over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with clarithromycin administration from underlying signs of Human Immunodeficiency Virus (HIV) disease or intercurrent illness.

In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 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 Glutamic Pyruvate 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 to 4 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 outside the seriously abnormal level (i.e. the extreme high or low limit) for the specified test. On the basis of these criteria, about 2 % to 3 % of

those patients who received 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 incidences 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 medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare providers are asked to report any suspected adverse reactions to:

SAHPRA:

Med Safety APP (Medsafety X SAHPRA) and eReporting platform (who-umc.org) found on SAHPRA website.

Aspen Pharmacare:

E-mail: Drugsafety@aspenpharma.com

Tel: 0800 118 088

4.9 Overdose

Symptoms

Ingestion of large amounts of CLARIDE XL can be expected to produce gastrointestinal symptoms. Ingesting 8 grams of clarithromycin, as contained in CLARIDE XL, can cause altered mental status, paranoid behaviour, hypokalaemia and hypoxaemia.

Treatment

Adverse reactions accompanying over dosage should be treated by the prompt elimination of the unabsorbed CLARIDE XL and supportive measures. CLARIDE XL

serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Category and class: A 20.1.1-Medium and broad spectrum antibiotics

Pharmacotherapeutic group: Macrolides

ATC code : J01FA09

Mechanism of action

Clarithromycin is a macrolide antibiotic which exerts its antibacterial action by binding to the 5OS ribosomal sub-units of susceptible bacteria and suppresses protein synthesis.

The *in-vitro* antibacterial spectrum of pathogens usually sensitive to clarithromycin is as follows *(in-vitro* sensitivity does not necessarily imply *in vivo* efficacy):

Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus pneumoniae, Legionella pneumophila, Mycoplasma pneumoniae, Chlamydia trachomatis, Branhamella catarrhalis, Certain strains of *Staphylococcus aureus, Haemophilus influenzae, Helicobacter (Campylobacter) pylori, Mycobacterium avium, Mycobacterium kansasii, Mycobacterium chelonae , Mycobacterium intracel/ulare*

Clarithromycin is bactericidal to *Helicobacter pylori,* this activity being greater at neutral pH than at acid pH.

The principal metabolite of clarithromycin in man and other primates is the 14-hydroxy-clarithromycin metabolite, which also has antibacterial activity. This metabolite is as active or 1-to-2 fold less active than the parent compound for most organisms, except for *H. influenzae* against which it is twice as active. The parent

compound and the 14-0H metabolite exert either an additive or synergistic effect on *H. influenzae in vitro* and *in vivo,* depending on bacterial strains.

5.2 Pharmacokinetic properties

Absorption and Biotransformation

The kinetics of orally administered clarithromycin modified release tablets have been studied in adult humans and compared with clarithromycin 250 mg and 500 mg immediate release tablets. The extent of absorption was found to be equivalent when equal 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 humans following multiple dosing. Based upon the finding of equivalent extent of absorption, the following *in vitro* and *in vivo* data is applicable to the modified release tablet.

In vitro studies showed the protein binding of clarithromycin in human plasma averaged about 70 % at concentrations of 0,45 to 4,5 mcg/mL. A decrease in binding to 41 % at 45,0 mcg/mL suggested that the binding sites might become saturated, but this occurred at concentrations far in excess of the therapeutic drug levels.

This non-linear pharmacokinetic behaviour of clarithromycin, coupled with the overall decrease in the formation of 14-hydroxylation and N-demethylation products at the higher doses, indicates the non-linear metabolism of clarithromycin becomes more pronounced at high doses.

Distribution

Results of animal studies showed clarithromycin levels in all tissues, except the central nervous system, were several times higher than the circulating drug levels. The highest concentrations were usually found in the liver and lung where the tissue to plasma (T/P) ratios reached 10 to 20.

Clarithromycin and its 14-0H-metabolite distribute readily into body tissues and

fluids. Limited data from a small number of patients suggests that clarithromycin does not achieve significant levels in cerebrospinal fluid after oral doses (i.e. only 1 to 2 % of serum levels in CFS in patients with normal blood-cerebrospinal fluid barriers). Concentrations in tissues are usually several fold higher than serum concentrations.

Elimination

In fed patients given 500 mg clarithromycin modified release tablets once daily, the peak steady state plasma concentration of clarithromycin and 14-hydroxy-clarithromycin were 1,3 and 0,48 mcg /mL, respectively. Elimination half-lives of the parent drug and metabolite were approximately 5,3 hours and 7,7 hours respectively. When clarithromycin modified release tablets were administered at a dose of 1000 mg once daily (2 x 500 mg), the steady state C_{max} for clarithromycin and its hydroxylated metabolite averaged 2,4 mcg/ml and 0,67 mcg/mL, respectively. The half-life of the parent drug at the 1000 mg dose level was approximately 5,8 hours, while that of the 14-hydroxy-clarithromycin was approximately 8,9 hours. The T_{max} for both the 500 mg and 1000 mg doses was approximately 6 hours. At steady state the 14-hydroxy-clarithromycin levels did not increase proportionately with the clarithromycin dose, and the apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at the higher doses.

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

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Lactose Monohydrate, Hypromellose, Hypromellose Phthalate, Purified Talc, Magnesium Stearate, Purified Water.

Coating Material: Opadry II Yellow 31G52300 (Hypromellose, Lactose Monohydrate, Titanium Dioxide E171, Macrogol / PEG 4000, Talc, Quinoline Yellow Aluminium Lake E104, Macrogol / PEG 400)

6.2. Incompatibilities

Not applicable

6.3. Shelf life

48 months

6.4. Special precautions for storage

Store at or below 30 °C. Protect from light and moisture.

Keep in original packaging until required for use.

6.5. Nature and contents of container

An outer cardboard carton containing a PVC film coated with PVDC–Aluminium blister strip containing 7 tablets.

6.6. Special precautions for disposal and other handling

No special requirements

7. HOLDER OF THE CERTIFICATE OF REGISTRATION

PHARMACARE LIMITED

Healthcare Park

Woodlands Drive

Woodmead 2191

8. REGISTRATION NUMBER

53/20.1.1/0648

9. DATE OF FIRST AUTHORISATION

08 October 2024

10. DATE OF REVISION OF TEXT

08 October 2024

Die Afrikaanse Professionele Inligting is op versoek beskikbaar. Mediese Blitslyn: 0800 118 088.

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