SCHEDULING STATUS **S4**

1 NAME OF THE MEDICINE

CLARITHROMYCIN UNIMED 500 Film-coated tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 500 mg clarithromycin.

Preservative: Sorbic Acid 1.5 % w/w

Sugar free.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablets

Light yellow coloured, oval shaped, biconvex film-coated tablets, with D debossed on one side and 63 on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

CLARITHROMYCIN UNIMED 500 is indicated for the treatment of:

- 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
- Eradication of *H.pylori*, resulting in decreased recurrence of duodenal ulcer when used in combination with a proton-pump inhibitor to suppress acid secretion and another antibiotic . Clarithromycin has been used in treatment regimens which include clarithromycin plus amoxycillin and omeprazole; clarithromycin plus tinidazole and omeprazole; and clarithromycin plus tetracycline and bismuth subsalicylate .
- There is some evidence that disseminated and localised mycobacterial infections in HIV-positive adults, due to *Mycobacterium avium* or *Mycobacterium intracellulare* respond to

clarithromycin. Based on bacteriological results, clarithromycin should be used in conjunction with other antimycobacterials. Localised infections due to *Mycobacterium chelonae* and *Mycobacterium kansasii* have responded to clarithromycin to a lesser extent.

4.2 Posology and Method of Administration

The recommended dosage of CLARITHROMYCIN UNIMED 500 is 500 mg (one tablet) twice daily orally.

Eradication of H. pylori

To decrease recurrence of duodenal ulcer in combination with a proton-pump inhibitor and another antibiotic: 500 mg twice daily in combination with amoxycillin 1000 mg twice daily and omeprazole 20 mg daily for 7 - 10 days .

Dosage in HIV patients with mycobacterial infections

The recommended treatment for adults with disseminated or localised mycobacterium infections (*M. avium, M. intracellulare , M. chelonae, M. kansasii*) is 500 mg twice daily.

Treatment of disseminated MAC infections in AIDS patients

Treatment should continue as long as clinical and microbiological benefit is demonstrated . A decrease in efficacy has been noted in patients on treatment exceeding 12 weeks . CLARITHROMYCIN UNIMED 500 should be used in conjunction with other antimycobacterial agents

Treatment of other non-tuberculous mycobacterial infections should continue at the discretion of the physician.

Renal impairment

CLARITHROMYCIN UNIMED 500 is not suitable for patients with renal impairment with creatinine clearance of less than 30 ml/min.

Paediatric population

CLARITHROMYCIN UNIMED 500 should not be used in children younger than 12 years.

4.3 Contraindications

- Hypersensitivity to macrolide antibiotic medicines or to any of the excipients listed in section 6.1.
- Concomitant administration of clarithromycin and ergot alkaloids (e.g. ergotamine or dihydroergotamine), as this may result in ergot toxicity (see section 4.5).
- Concomitant administration of clarithromycin and oral midazolam (see section 4.5).
- Concomitant administration of clarithromycin and any of the following drugs: astemizole, cisapride, domperidone, pimozide and terfenadine as this may result in QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsade's de pointes (see section 4.4 and 4.5).
- Concomitant administration with ticagrelor or ranolazine.
- Concomitant administration 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).
- Clarithromycin should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsade's de pointes (see sections 4.4 and 4.5).
- 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 atypical antipsychotics that are predominantly metabolised through the CYP3A4 pathway, for example quetiapine, cariprazine, and aripiprazole.

4.4 Special warnings and precautions for use

Hypersensitivity reactions

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.

Hepatic dysfunction

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.

Renal impairment

CLARITHROMYCIN UNIMED 500 should not be administered to patients with moderate to severe renal impairment (see section 4.2).

Cardiovascular Events

Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac arrhythmia and torsade's 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 torsade's 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).

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 UNIMED 500.

Pseudomembranous colitis

This has been reported with nearly all antibacterial agents, including macrolides, 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 agents. *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 UNIMED 500 therapy should be considered regardless of the indication. Microbial testing should be performed, and adequate treatment initiated. Drugs inhibiting peristalsis should be avoided.

Pneumonia

In view of the emerging resistance of *Streptococcus pneumoniae* to macrolides, it is important that sensitivity testing be performed when prescribing CLARITHROMYCIN UNIMED 500 for community-acquired pneumonia. In hospital acquired pneumonia, CLARITHROMYCIN UNIMED 500 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.

Long-term use

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.

Cross resistance

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

Helicobacter *pylori* infections

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

Colchicine toxicity

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).

Triazolobenzodiazepines

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

Cytochrome CYP3A4 enzyme

Clarithromycin 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 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).

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

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicines 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 torsade's de pointes. Similar effects have been observed in patients taking clarithromycin 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 torsade's de pointes (see section 4.3). 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 (see section 4.3).

Oral Midazolam

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam area under the curve (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.

Effects of Other Medicinal Products on Clarithromycin

Medicines that are inducers of CYP3A

(e.g. rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort)

These may induce the metabolism of clarithromycin resulting in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the

plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 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;

Dosage adjustment or consideration of alternative treatments may be required.

Efavirenz, nevirapine, rifampicin, rifabutin and rifapentine

Strong inducers of the cytochrome P450 metabolism system such as efavirenz, nevirapine, rifampicin, rifabutin, and rifapentine may accelerate the metabolism of clarithromycin and thus lower the plasma levels of clarithromycin, while increasing those of 14-OH-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-OH-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of clarithromycin and enzyme inducers.

Etravirine

Clarithromycin exposure was decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, were increased. Because 14-OH-clarithromycin has reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered; therefore, alternatives to clarithromycin should be considered for the treatment of MAC.

Fluconazole

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

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax increased by 31 %, Cmin increased 182 % and AUC increased by 77 % with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CLCR 30 to 60 mL/min the dose of clarithromycin should be reduced by 50 %. For patients with CLCR <30 mL/min the dose of clarithromycin should be decreased by 75 %. Doses of clarithromycin greater than 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 UNIMED 500 is contraindicated in patients receiving the CYP3A substrates astemizole, cisapride, 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.

Concomitant administration of clarithromycin and atypical antipsychotics that are predominantly metabolised through the CYP3A4 pathway, for example quetiapine, cariprazine, and aripiprazole may result in an increase in plasma levels of these antipsychotics as a result of inhibition which may present a potential for serious adverse reactions.

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

Antiarrhythmics

There have been post-marketed reports of torsade's de pointes occurring with the concurrent use of clarithromycin and quinidine or disopyramide. Electrocardiograms should be monitored for QT prolongation during coadministration of CLARITHROMYCIN UNIMED 500 with these drugs. Serum levels of quinidine and disopyramide should be monitored during CLARITHROMYCIN UNIMED 500 therapy. There have been post marketing reports of hypoglycaemia with the concomitant administration of CLARITHROMYCIN UNIMED 500 and disopyramide. Therefore, blood glucose levels should be monitored during concomitant administration of disopyramide.

Oral hypoglycaemic agents/Insulin

With certain hypoglycaemic drugs such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia 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 UNIMED 500.

Theophylline, carbamazepine

Results of clinical studies indicate that there was a modest but statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels when either of these drugs were administered concomitantly with clarithromycin. Dose reduction may need to be considered.

Tolterodine

The primary route of metabolism for tolterodine is via the 2D6 isoform of cytochrome P450 (CYP2D6). However, in a subset of the population devoid of CYP2D6, the identified pathway of metabolism is via CYP3A. In this population subset, inhibition of CYP3A results in significantly higher serum concentrations of tolterodine. A reduction in tolterodine dosage may be necessary in the presence of CYP3A inhibitors, such as clarithromycin in the CYP2D6 poor metaboliser

population.

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

When midazolam was co-administered with clarithromycin tablets (500 mg twice daily), midazolam AUC was increased 2.7-fold after intravenous administration of midazolam. If intravenous midazolam is co-administered with clarithromycin, the patient must be closely monitored to allow dose adjustment. Drug delivery of midazolam via oromucosal route, which could bypass pre-systemic elimination of the drug, will likely result in a similar interaction to that observed after intravenous midazolam rather than oral administration. The same precautions should also apply to other benzodiazepines that are metabolised by CYP3A, including triazolam and alprazolam. For benzodiazepines which are not dependent on CYP3A for their elimination (temazepam, nitrazepam, lorazepam), a clinically important interaction with clarithromycin is unlikely. There have been post-marketing reports of drug interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) with the concomitant use of clarithromycin and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other drug interactions

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, Pglycoprotein (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 (see section 4.4).

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 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 UNIMED 500 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.

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 UNIMED 500. 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 UNIMED 500 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 UNIMED 500 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 gelatine 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 gelatine capsule formulation may not be representative of the effects seen using the saquinavir hard gelatine 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).

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

Women of childbearing potential / Contraception in males and females

Concurrent use of CLARITHROMYCIN UNIMED 500 and oral contraceptives decreases the efficacy of the oral contraceptive. Patients should be strongly advised to use an alternative or additional method of contraception while taking this medicine (see section 4.5).

Pregnancy

The safety of CLARITHROMYCIN UNIMED 500 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 (see section 5.3).

Breastfeeding

The safety of CLARITHROMYCIN UNIMED 500 for using during breast-feeding of infants has not been established.

Clarithromycin is excreted into human breast milk.

Fertility

No evidence of harmful effects observed in animal studies (see section 5.3).

4.7 Effects on ability to drive and use machines

There are no data on the effect of CLARITHROMYCIN UNIMED 500 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 most frequent and common adverse reactions related to CLARITHROMYCIN UNIMED 500 are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics. There was no significant difference in the incidence of these gastrointestinal adverse reactions during clinical trials between the patient population with or without pre-existing mycobacterial infections.

System Organ Class	Frequent	Less Frequent	Frequency unknown
Infections and infestations		candidiasis, gastroenteritis, vaginal infection	Pseudomembranous colitis, erysipelas
Blood and lymphatic system		Leukopenia, neutropenia, thrombocythemia, eosinophilia	Agranulocytosis, thrombocytopenia
Immune system disorders		Hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders		Anorexia, decreased appetite, Hypoglycaemia	
Psychiatric disorders	Insomnia	Anxiety, nervousness	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders	Dysgeusia, headache, taste perversion	dizziness, somnolence, tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders		Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders		electrocardiogram QT prolonged, palpitations	Torsade de pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders			Hemorrhage
Respiratory, thoracic and mediastinal disorder		epistaxis	
Gastrointestinal disorders	Diarrhea, vomiting, dyspepsia, nausea, abdominal pain	gastrooesophageal reflux disease, gastritis, proctalgia, stomatitis, glossitis, abdominal distension, constipation, dry mouth, eructation,	Pancreatitis acute, tongue discolouration, tooth discoloration

System Organ Class	Frequent	Less Frequent	Frequency unknown
		flatulence	
Hepatobiliary disorders	Liver function test abnormal	Cholestasis, hepatitis, alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders	Rash, hyperhidrosis	pruritus, urticaria, rash maculo-papular	Stevens-Johnson syndrome, toxic epidermal necrolysis, drug rash with eosinophilia and systemic symptoms (DRESS), acne, acute generalised exanthematous pustulosis (AGEP)
Musculoskeletal and connective tissue disorders		Muscle spasms, myalgia	Rhabdomyolysis, myopathy
Renal and urinary disorders			Renal failure, nephritis interstitial
General disorders and administration site conditions		Malaise, pyrexia, asthenia, chest pain, chills, fatigue	
Investigations		blood alkaline phosphatase increased, blood lactate dehydrogenase increased	International normalised ratio increased, prothrombin time prolonged, urine color abnormal

Description of selected adverse reactions

Paediatric population

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 1000 mg and 2000 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 1000 mg and 2000 mg but were generally about 3 to 4 times as frequent for those patients who received total daily doses of 4000 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 1000 mg or 2000 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 4000 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. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the “6.04 Adverse Drug Reactions Reporting Form”, found online under SAHPRA’s publications:
https://www.sahpra.org.za/Publications/Index/8

4.9 Overdose

Reports indicate that the ingestion of large amounts of CLARITHROMYCIN UNIMED 500 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 UNIMED 500 serum levels are not expected to be appreciably affected by

haemodialysis or peritoneal dialysis.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacological Classification

A 20.1.1 - Medium and broad-spectrum antibiotics

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide

ATC-Code: J01FA09

Mechanism of action

Clarithromycin is an antibiotic belonging to the macrolide antibiotic group. It exerts its antibacterial action by selectively binding to the 50s ribosomal subunit of susceptible bacteria preventing translocation of amino acids. It inhibits the intracellular protein synthesis of susceptible bacteria.

The principal metabolite of clarithromycin in man and other primates is a microbiologically active metabolite 14-hydroxyclarithromycin, a product of parent drug metabolism also has antimicrobial activity. The metabolite is less active than the parent compound for most organisms, including mycobacterium spp. An exception is *Haemophilus influenza* where the 14-hydroxyclarithromycin metabolite is twofold more active than the parent compound. 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.

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.

5.2 Pharmacokinetic properties

Absorption

Clarithromycin is rapidly and well absorbed from the gastro-intestinal tract after oral administration of clarithromycin. The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first-pass metabolism.

Results of a study of the effects of food on absorption indicated that food taken shortly before dosing somewhat delayed the onset of absorption of clarithromycin. However, food intake did not affect the overall bioavailability of the drug.

Mean peak plasma levels after a single oral dose of clarithromycin occurred approximately 2 hours after administration and ranged from 0,35 mcg/ml after a 100 mg dose to 3,97 mcg/ml after a 1200 mg dose. Mean half-life appeared to be dose-dependent and ranged from 2,27 hours after a 100 mg dose to 5,98 hours after the 1200 mg dose.

Distribution

Protein binding decreased with increasing drug concentration in plasma.

Clarithromycin is 80 % bound to plasma proteins at therapeutic levels.

Thus 14-hydroxyclarithromycin is not extensively bound to plasma proteins and its binding sites appeared to be readily saturated at high drug concentrations. Clarithromycin and its 14-OH-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 (CSF) after oral doses (i.e. only 1 to 2 % of serum levels in CSF in patients with normal blood-cerebrospinal fluid barriers).

Clarithromycin provides tissue concentrations that are several times higher than the circulating drug levels. Increased levels have been found in both tonsillar and lung tissue.

Clarithromycin also penetrates the gastric mucus. Levels of clarithromycin in gastric mucus and gastric tissue are higher when clarithromycin is co-administered with omeprazole than when clarithromycin is administered alone.

Biotransformation

A metabolism study in human males given 14C-clarithromycin showed peak plasma levels of radioactivity and parent drug occurred 2-4 hours after administration of a 200 mg or 1 200 mg total dose. The major metabolite in plasma after either dose was the 14-hydroxy (R) epimer of clarithromycin, with peak levels of 0,5 mcg/ml and 1,2 mcg/ml after doses of 250 mg and 1200 mg respectively. Low levels of descladinosyl-clarithromycin were seen in the plasma only after the 1200 mg dose. The 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, indicate that metabolism of clarithromycin approaches saturation at high doses.

Elimination

At 250 mg b.i.d. 15-20 % of unchanged drug is excreted in the urine. With 500 mg b.i.d. daily dosing urinary excretion is greater (approximately 36 %). 14-hydroxyclarithromycin is the major urinary metabolite and accounts for 10-15 % of the dose. Most of the remainder of the dose is eliminated in the faeces, primarily via the bile. 5-10 % of the parent drug is recovered from the faeces.

Linearity/non-linearity

The pharmacokinetics of clarithromycin are non-linear; however, steady state is attained within 2 days of dosing.

Pharmacokinetics in patients with *Mycobacterium avium* infections

Steady-state concentrations of clarithromycin and 14-0H-clarithromycin observed following administration of 500 mg doses of clarithromycin every 12 hours to adult patients with HIV infection were similar to those observed in normal subjects. However, at the higher doses which may be required to treat *Mycobacterium avium* infections, clarithromycin concentrations were much higher than those observed at the usual doses. In adult HIV-infected patients taking 1000 and 2000 mg/day in two divided doses, steady-state clarithromycin Cmax values ranged from 2-4 mcg/ml and 5-10 mcg/ml respectively. Elimination half-lives appeared to be lengthened at these higher doses as compared to those seen with usual doses in normal subjects. The higher plasma

concentrations and longer elimination half-lives observed at these doses are consistent with the known non-linearity in clarithromycin pharmacokinetics.

Pharmacokinetics in patients with *Helicobacter pylori* infections

H. pylori is associated with acid peptic disease including duodenal ulcer and gastric ulcer in which about 95 % and 80 % of patients respectively are infected with the agent.

H. pylori is also implicated as a major contribution factor in the development of gastritis and ulcer recurrence in such patients. Clarithromycin has been used in small numbers of patients in other treatment regimens. Possible kinetic interactions have not been fully investigated. These regimens include: Clarithromycin plus tinidazole and omeprazole; clarithromycin plus tetracycline, bismuth subsalicylate and ranitidine; clarithromycin plus ranitidine alone.

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

5.3 Preclinical safety data

In acute mouse and rat studies, the median lethal dose was greater than the highest feasible dose for administration (5g/kg). In repeated dose studies, toxicity was related to dose, duration of treatment and species. Dogs were more sensitive than primates or rats. The major clinical signs at toxic doses included emesis, weakness, reduced food consumption and weight gain, salivation, dehydration and hyperactivity. In all species the liver was the primary target organ at toxic doses. Hepatotoxicity was detectable by early elevations of liver function tests. Discontinuation of the drug generally resulted in a return to or toward normal results. Other tissues less commonly affected included the stomach, thymus and other lymphoid tissues and the kidneys. At near therapeutic doses, conjunctival injection and lacrimation occurred only in dogs. At a massive dose of 400mg/kg/day, some dogs and monkeys developed corneal opacities and/or oedema.

Fertility, 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/m2 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 cynomolgus 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/m2 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/m2 basis for a 60-kg individual. Embryonic loss was seen in monkeys but only at dose levels which were clearly toxic to the mothers.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core:

Microcrystalline Cellulose

Croscarmellose Sodium

Povidone

Colloidal anhydrous silica

Magnesium Stearate

Tablet film coating:

Purified Water

Opadry Yellow (Hypromellose, Propylene Glycol, Titanium Dioxide, Hydroxypropyl Cellulose, Vanillin, Sorbic Acid, Iron Oxide Yellow)

6.2 Incompatibilities

None known

6.3 Shelf life

36 Months

6.4 Special precautions for storage

Store at or below 25 °C.

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Clear PVC film coated with PVdC - Aluminium foil blister pack containing 10 tablets.

6.6 Special precautions for disposal and other handling

No special requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

UNIMED HEALTHCARE (PTY) LTD

Corner Birch Road & Bluegum Avenue,

Anchorville,

Lenasia, 1827

South Africa

8 REGISTRATION NUMBER

50/20.1.1/0585

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 August 2021

10 DATE OF REVISION OF THE TEXT

14 May 2024