SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

KLARIZON 250 Tablets

KLARIZON 500 Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

KLARIZON 250: Each film-coated tablet contains clarithromycin 250 mg as active ingredient.

KLARIZON 500: Each film-coated tablet contains clarithromycin 500 mg as active ingredient.

Sugar free.

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets.

KLARIZON 250: Yellow, film-coated, oval-shaped, biconvex tablets, scored on one side (14,5 mm).

KLARIZON 500: Yellow, film-coated, oval-shaped, biconvex tablets, scored on one side (19,0 mm).

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KLARIZON is indicated for the treatment of the following mild to moderate severe infections caused by susceptible organisms:

- Lower respiratory tract infections such as bronchitis and pneumonia.
- Upper respiratory tract infections such as pharyngitis and sinusitis.

- Mild to moderately severe acute otitis media due to *S. pneumoniae*, *M. catarrhalis* and *H. influenzae*.
- Skin and soft tissue infections such as folliculitis, cellulitis or erysipelas.
- Eradication of *Helicobacter pylori* when used in combination with a proton pump inhibitor and another antibiotic to decrease recurrence of duodenal ulcer.

4.2 Posology and method of administration

Posology

Adults: 250 mg twice daily.

In more severe infections, the dosage may be increased to 500 mg twice daily.

Renal impairment

Creatinine clearance (< 30 mL/min): Reduce dose by half i.e., 250 mg once daily or 250 twice daily for severe infections. Limit the duration of treatment to 14 days.

Eradication of *H.pylori*

Adults: 500 mg twice daily, in combination with an appropriate antibiotic and an acid lowering agent, for 7 to 10 days.

The safety and efficacy of KLARIZON in combination with proton-pump inhibitors other than omeprazole has not been established.

Atypical mycobacterial infections (MAC) in HIV patients

Adults: 500 mg twice daily

Treatment of disseminated MAC infections in AIDS patients should continue as long as clinical and microbiological benefit is demonstrated. A decrease in efficacy has been noted in patients taking KLARIZON for more than 12 weeks. KLARIZON should be used in conjunction with other antimycobacterial medicines.

Method of administration

For oral administration.

KLARIZON may be taken with or without meals.

4.3 Contraindications

- Hypersensitivity to clarithromycin or the macrolide antibiotics or to any of the excipients of KLARIZON listed in section 6.1.
- Concomitant administration of KLARIZON with astemizole, cisapride, pimozide, domperidone and terfenadine as this may result in QT prolongation and cardiac dysrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see section 4.4 and 4.5).
- Concomitant administration of KLARIZON and ergot alkaloids (e.g., ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity (see sections 4.4 and 4.5).
- Concomitant administration of KLARIZON and oral midazolam is contraindicated (see section 4.5).
- KLARIZON should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac dysrhythmia, including torsades de pointes. (See section 4.4 and 4.5).
- Concomitant administration with ticagrelor or ranolazine is contraindicated.
- KLARIZON should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolised by CYP3A4, (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis (see section 4.5).
- Concomitant administration of clarithromycin (e.g., KLARIZON) 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 (see section 4.5)

- As with other strong CYP3A4 inhibitors, KLARIZON should not be used in patients taking colchicine (see sections 4.4 and 4.5).
- KLARIZON should not be given to patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of the QT interval).
- KLARIZON should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
- Porphyria.
- Safety and efficacy in infants less than 6 months of age have not been established.

4.4 Special warnings and precautions for use

KLARIZON should be used with caution in:

- Clarithromycin as contained in KLARIZON 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 KLARIZON to patients with moderate to severe renal impairment (see section 4.2).
- Renal function impairment (severe) - The elimination of KLARIZON is reduced in patients with renal function impairment, especially those with a creatinine clearance of < 30 mL/min. The dose of KLARIZON should be halved or the dosing interval doubled in patients with a creatinine clearance of < 30 mL/min.
- Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with clarithromycin. Treatment with KLARIZON should be discontinued if any signs of hepatic dysfunction develop. Hepatic dysfunction is usually reversible but may be severe. In rare instances, hepatic failure with fatal outcome has been reported, usually associated with other serious underlying diseases and/or concomitant medicines. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicines. 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. Cases of increased serum creatinine have been reported but an association with KLARIZON has not been established.

- Rhabdomyolysis has been reported with concomitant use of KLARIZON and the HMGCoA reductase inhibitors e.g., simvastatin and lovastatin (see section 4.3 and 4.5).
- Rifabutin and rifampicin - May decrease serum concentration of KLARIZON by > 50 %. Co-administration has been reported to cause a higher incidence of uveitis compared to rifabutin alone (see section 4.5).
- Theophylline – The area under the plasma concentration-time curve is increased. Monitoring of theophylline serum concentrations is recommended (see section 4.5).
- Cross-resistance between KLARIZON and other macrolides, lincomycin and clindamycin have been reported.
- Pseudomembranous colitis has been reported with KLARIZON and it may range in severity from mild to life-threatening. *Clostridioides difficile- associated diarrhoea* (CDAD) has been reported with use of nearly all antibacterial medicines including KLARIZION 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*.
- 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 medicines.
- Therefore, discontinuation of KLARIZON therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated. Medicines inhibiting peristalsis should be avoided.
- Colchicine toxicity with concomitant use of KLARIZON and colchicine have been reported during post-marketing experience, especially in the elderly, some of which occurred in patients with renal insufficiency. Fatalities have been reported in such patients (see section 4.5). Concomitant administration of KLARIZON and colchicine is contraindicated (see section 4.3).

- Caution is advised regarding concomitant administration of KLARIZON and triazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam (see section 4.5). Concomitant administration of KLARIZON and midazolam is contraindicated (see section 4.3).

Cardiovascular Events

- Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac dysrhythmia and torsades de pointes, have been seen in patients treated with macrolides including KLARIZON (see section 4.8). Due to increased risk of QT prolongation and ventricular dysrhythmias (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 electrolyte disturbances such as hypomagnesaemia or hypokalaemia; and in patients with a history of QT prolongation or ventricular cardiac dysrhythmia (see section 4.3).
- Furthermore, KLARIZON should be used with caution in the following:

– Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia.

– Patients concomitantly taking other medicines 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 dysrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including clarithromycin as contained in KLARIZON. Consideration of these findings should be balanced with treatment benefits when prescribing KLARIZON.

Pneumonia

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

hospital-acquired pneumonia, KLARIZON 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 e.g., KLARIZON should be discontinued immediately and appropriate treatment should be urgently initiated.
- KLARIZON 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 KLARIZON with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised when prescribing KLARIZON 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 KLARIZON 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

- There have been less frequent reports of hypoglycaemia, some of which occurred in patients on concomitant oral hypoglycaemics (such as sulphonylurias) or insulin. 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 KLARIZON is co-administered with warfarin (see section 4.5). INR and prothrombin times should be frequently monitored while patients are receiving KLARIZON and oral anticoagulants concurrently.
- Caution should be exercised when KLARIZON is co-administered with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk of bleeding (see section 4.5).
- 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 between KLARIZON and other macrolides, lincomycin and clindamycin has been reported.
- Adverse effects in immunocompromised patients treated with higher doses of KLARIZON over long periods include nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, hearing disturbance, AST and ALT elevations, elevated BUN levels and abnormally low white blood cell and platelet counts. Additional low-frequency events included dyspnoea, insomnia and dry mouth.

KLARIZON contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially ‘sodium-free’.

4.5 Interaction with other medicines and other forms of interaction

Concomitant use of KLARIZON with:

Astemizole, cisapride, domperidone, pimozide and terfenadine

Elevated cisapride levels have been reported in patients receiving clarithromycin and cisapride concomitantly. Similar effects have been observed in patients taking clarithromycin and pimozide concomitantly (see section 4.3). Have resulted in cardiac dysrhythmias, including QTc-interval prolongation, ventricular dysrhythmia, ventricular tachycardia, ventricular fibrillation and torsades de pointes. Fatalities have occurred. The most likely cause is the inhibition of metabolism of these medicines by KLARIZON. Concurrent use is contraindicated. See section 4.3.

Macrolides such as KLARIZON have been reported to alter the metabolism of terfenadine resulting in increased levels of terfenadine which has occasionally been associated with cardiac dysrhythmias, 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 2- to 3-fold increase in the serum level of the acid metabolite of terfenadine and in prolongation of the QT interval which did not lead to any clinically detectable effect. Similar effects have been observed with concomitant administration of astemizole and other macrolides.

Ergot alkaloids

Post-marketing reports indicate that concomitant use of KLARIZON with ergotamine or dihydroergotamine has been associated with acute ergot toxicity characterised by vasospasm, and ischaemia of the extremities and other tissues including the central nervous system. Permanent tissue damage may result.

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 KLARIZON is contraindicated (see section 4.3).

HMG-CoA Reductase Inhibitors (statins)

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

Caution should be exercised when prescribing KLARIZON with statins. In situations where the concomitant use of KLARIZON 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 medicines on KLARIZON

Medicines that are inducers of CYP3A (e.g., rifampicin, phenytoin, carbamazepine, phenobarbital, St John's wort) may induce the metabolism of clarithromycin. This may result in sub-therapeutic levels of clarithromycin leading to reduced efficacy. Furthermore, it might be necessary to monitor the plasma levels of the CYP3A inducer, which could be increased owing to the inhibition of CYP3A by clarithromycin (see also the relevant product information for the CYP3A4 inducer administered). Concomitant administration of rifabutin and KLARIZON 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; KLARIZON 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 KLARIZON 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 KLARIZON should be considered for the treatment of MAC.

Fluconazole

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

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and clarithromycin 500 mg every 12 hours resulted in a marked inhibition of the metabolism of clarithromycin. The clarithromycin C_{max} increased by 31 %, C_{min} increased 182 % and AUC increased by

77 % with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin was noted.

Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with 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 KLARIZON 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, Bi- directional drug interactions).

Effect of KLARIZON on other medicines

CYP3A-based interactions

Co-administration of clarithromycin as contained in KLARIZON, which is known to inhibit CYP3A, and a medicine 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 medicine.

The use of KLARIZON is contraindicated in patients receiving the CYP3A substrates astemizole, cisapride, domperidone, pimozide and terfenadine due to the risk of QT prolongation and cardiac dysrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see sections 4.3 and 4.4).

The use of KLARIZON is also contraindicated with ergot alkaloids, oral midazolam, HMGCoA reductase inhibitors metabolised mainly by CYP3A4 (e.g., lovastatin and simvastatin), colchicine, ticagrelor and ranolazine (see section 4.3).

Caution is required if KLARIZON is co-administered 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 KLARIZON. Medicines or medicine 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, methadone, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g., warfarin, rivaroxaban, apixaban), quinidine, rifabutin, sildenafil, sirolimus, tacrolimus, triazolam and vinblastine.

Concomitant administration of clarithromycin as contained in KLARIZON 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 (see section 4.3).

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

Antidysrhythmics

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

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

Oral hypoglycaemic medicines/insulin:

With certain hypoglycemic medicines such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by KLARIZON 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 (C_{max}, AUC_{0-24}, and $t_{1/2}$ increased by 30 %, 89 %, and 34 %, respectively), by the concomitant administration of KLARIZON. 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.

Direct acting oral anticoagulants (DOACs)

The DOAC dabigatran is a substrate for the efflux transporter P-gp. Rivaroxaban and apixaban are metabolised via CYP3A4 and are also substrates for P-gp. Caution should be exercised when KLARIZON is co-administered with these medicines particularly to patients at high risk of bleeding (see section 4.4).

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 KLARIZON 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 KLARIZON.

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 medicines were administered concomitantly with KLARIZON. 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 contained in KLARIZON 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 KLARIZON, 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 medicine, 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 KLARIZON is unlikely.

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 KLARIZON and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other medicine 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 as contained in KLARIZON and colchicine are administered together, inhibition of Pgp and/or CYP3A by clarithromycin may lead to increased exposure to colchicine (see section 4.3 and 4.4).

Digoxin

Digoxin is thought to be a substrate for the efflux transporter, P-glycoprotein (Pgp). Clarithromycin is known to inhibit Pgp. When KLARIZON and digoxin are administered together, inhibition of Pgp by clarithromycin may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving KLARIZON and digoxin concomitantly have also been reported in post marketing surveillance. 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 KLARIZON simultaneously.

Zidovudine

Simultaneous oral administration of KLARIZON 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 KLARIZON 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 KLARIZON 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 KLARIZON. Increased serum levels have been reported.

Bi-directional medicine 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-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 KLARIZON should be decreased by 50 %. For patients with creatinine clearance < 30 ml/min, the dose of KLARIZON should be decreased by 75 % using an appropriate clarithromycin formulation. Doses of KLARIZON greater than 1 000 mg per day should not be co-administered with protease inhibitors.

Calcium Channel Blockers

Caution is advised regarding the concomitant administration of KLARIZON, and calcium channel blockers metabolised 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, bradydysrhythmias and lactic acidosis have been observed in patients taking KLARIZON and verapamil concomitantly.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional drug interaction. KLARIZON may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and KLARIZON 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 medicine interaction. Concomitant administration of clarithromycin (500 mg twice daily) and saquinavir (soft gelatin capsules, 1 200 mg three times daily) to 12 healthy volunteers resulted in steady-state AUC and C_{max} values of saquinavir which were 177 % and 187 % higher than those seen with saquinavir alone. Clarithromycin AUC and C_{max} values were approximately 40 % higher than 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. Observations from medicine 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 KLARIZON (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

Safety and efficacy in pregnancy has not been established.

Breastfeeding

Safety and efficacy for using during breastfeeding of infants has not been established.

KLARIZON is excreted into human breast milk in small amounts.

Fertility

In the rat, fertility studies have not shown any evidence of harmful effects.

4.7 Effects on ability to drive and use machines

KLARIZON could have a minor influence on the patient's ability to drive and use machines and the effect on the individual should be established before driving or using machinery.

4.8 Undesirable effects

Tabulated list of adverse reactions

Blood and lymphatic system disorders

Less frequent:	Leukopenia, neutropenia, eosinophilia.
Frequency unknown:	Agranulocytosis, thrombocytopenia.

Infections and infestations

Less frequent:	Candidiasis, gastroenteritis, infection (fever and chills, cough or hoarseness, lower back or side pain, painful or difficult urination), vaginal infection.

Frequency unknown: Pseudomembranous colitis (abdominal cramps or pain, tenderness, severe, watery diarrhoea which may also be bloody, fever), erysipelas, oral candidiasis.

Immune system disorders

Less frequent: Hypersensitivity reactions, anaphylaxis.

Frequency unknown: Anaphylactic reaction, angioedema.

Metabolism and nutrition disorders

Less frequent: Anorexia, decreased appetite.

Psychiatric disorders

Frequent: Insomnia.

Less frequent: Anxiety, nervousness.

Frequency unknown: Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania.

Nervous system disorders

Frequent: Headache, dysgeusia.

Less frequent: Dizziness, somnolence, tremor.

Frequency unknown: Convulsions, ageusia, parosmia, anosmia, paraesthesia.

Ear and labyrinth disorders

Less frequent: Vertigo, tinnitus, impaired hearing.

Frequency unknown: Deafness.

Eye disorders

Frequency unknown: Visual impairment, blurred vision.

Cardiac disorders

Less frequent: QT prolongation, palpitations.

Frequency unknown: Torsades de pointes, ventricular tachycardia, ventricular fibrillation and dysrhythmias.

Vascular disorders

Frequency unknown: Haemorrhage.

Endocrine disorders

Frequency unknown: Hypoglycaemia.

Respiratory, thoracic and mediastinal disorders

Less frequent: Epistaxis.

Gastrointestinal disorders

Frequent: Nausea, vomiting, abdominal pain, diarrhoea, dyspepsia.

Less frequent: Abnormal taste sensation, flatulence, gastrointestinal disturbances, gastroesophageal reflux disease, gastritis, proctalgia, glossitis, stomatitis, abdominal distension, constipation, dry mouth, eructation.

Frequency unknown: Tongue discolouration, tooth discolouration, pancreatitis acute.

Hepato-biliary disorders

Frequent: Abnormal liver function test.

Less frequent: Cholestasis, hepatitis, increased alanine aminotransferase, increased aspartate aminotransferase, increased gamma glutamyltransferase.

Frequency unknown: Hepatic failure, jaundice hepatocellular.

Skin and subcutaneous tissue disorders

Frequent: Rash, hyperhidrosis.

Less frequent: Pruritus, rash maculo-papular, urticaria.

Frequency unknown: Mild skin eruptions, Stevens-Johnson syndrome, toxic epidermal necrolysis, severe cutaneous adverse reactions (SCAR) (e.g., acute generalised exanthematous pustulosis (AGEP), drug rash with eosinophilia and systemic symptoms (DRESS), acne.

Musculoskeletal and connective tissue disorders

Less frequent: Muscle spasms, myalgia.

Frequency unknown: Rhabdomyolysis, myopathy.

Renal and urinary disorders

Frequency unknown: Nephritis interstitial, renal failure.

General disorders and administration site conditions

Less frequent: Malaise, asthenia, chest pain, chills, fatigue.

Investigations

Less frequent: Increased blood alkaline phosphatase, increased blood lactate dehydrogenase.

Frequency unknown: Increased international normalised ratio, prothrombin time prolonged, abnormal urine colour.

Description of selected adverse reactions

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 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 have been rare reports of clarithromycin ER tablets in the stool, many of which have occurred in patients with anatomic (including ileostomy or colostomy) or functional gastrointestinal disorders with shortened GI transit times. In several reports, tablet residues have occurred in the context of diarrhoea. It is recommended that patients who experience tablet residue in the stool and no improvement in their condition should be switched to a different clarithromycin formulation (e.g., suspension) or another antibiotic.

Special population: Adverse Reactions in immunocompromised patients (see section *Other special populations*).

Paediatric population

Clinical trials have been conducted using clarithromycin paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use clarithromycin paediatric suspension. Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

Other special populations

Immunocompromised patients

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

In adult patients, the most frequently reported adverse reactions by patients treated with total daily doses of 1 000 mg and 2 000 mg of clarithromycin were: nausea, vomiting, taste perversion, abdominal pain, diarrhoea, rash, flatulence, headache, constipation, hearing disturbance, serum glutamic oxaloacetic transaminase (SGOT) and serum 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 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

(See section 4.4)

Symptoms of overdose

Ingestion of large amounts of KLARIZON can be expected to produce gastrointestinal symptoms.

Allergic reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed medicine and supportive measures.

Treatment of overdose

Treatment is symptomatic and supportive. KLARIZON serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

A 20.1.1: Medium and broad spectrum antibiotics

ATC Classification: Pharmacotherapeutic group: Antibacterial for systemic use, macrolide

ATC-Code: J01FA09

Mechanism of action

Clarithromycin is a macrolide antibiotic. It exerts its antibacterial action by binding reversibly to the 50S ribosomal subunit of the 70S ribosome of sensitive microorganisms, thereby inhibiting bacterial RNA-dependent protein synthesis. The *in vitro* antibacterial spectrum of pathogens sensitive to clarithromycin includes:

(*in vitro* sensitivity does not necessarily imply *in vivo* efficacy)

Streptococcus agalactiae, Streptococcus pyogenes, Streptococcus pneumoniae

Legionella pneumophilia

Mycoplasma pneumoniae

Chlamydia trachomatis

Moraxella (Branhamella) catarrhalis

Haemophilus influenzae

Staphylococcus aureus (methicillin sensitive)

Helicobacter (Campylobacter) pylori

Mycobacterium avium, Mycobacterium kansasii, Mycobacterium chelonae, Mycobacterium intracellulare

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

The incidence of bacterial resistance to clarithromycin is higher in penicillin-resistant strains than among penicillin-sensitive strains. Therefore methicillin-resistant and oxacillin-resistant Staphylococcus and Streptococcus are also resistant to clarithromycin and cross-resistant to other macrolide antibiotics. Isolated cases of *Helicobacter pylori* and *Mycobacterium avium* with clarithromycin resistance caused by genetic mutations have been reported.

5.2 Pharmacokinetic properties

Absorption:

Clarithromycin is absorbed rapidly from the gastrointestinal tract after oral administration, but its bioavailability is reduced to 50 – 55 % because of rapid first-past metabolism.

Distribution:

Peak plasma concentration occurs approximately 2 hours after administration. Clarithromycin may be given with or without food. Both clarithromycin and 14-hydroxyclarithromycin distribute widely throughout the body and achieve high intracellular concentrations. Tissue concentrations generally exceed serum concentrations. Clarithromycin does not achieve significant levels in the cerebrospinal fluid. Protein binding of clarithromycin ranges from 40 to 70 % and is concentration dependent.

Biotransformation:

Clarithromycin is metabolised by the liver to the active metabolite, 14-hydroxyclarithromycin, as well as to several other metabolites.

Elimination:

The elimination half-lives of clarithromycin and 14-hydroxyclarithromycin are approximately 3 to 7 and 5 to 9 hours respectively. Longer half-lives are observed after larger doses. Clarithromycin is eliminated by renal and nonrenal routes. The amount of clarithromycin excreted unchanged in the urine ranges from 20 to 40 %, depending on the dose administered and the formulation. Between 10 and 15 % of the dose is excreted in the urine as the 14-hydroxy metabolite. Although the pharmacokinetics of clarithromycin is altered in patients with hepatic or renal dysfunction, dosage adjustment is not necessary unless a patient has severe renal dysfunction (creatinine clearance of < 30 ml/minute). At higher doses in HIV-infected patients clarithromycin and 14-hydroxyclarithromycin concentrations are much higher when compared with usual doses in non-infected patients. The elimination half-lives also appear to be lengthened.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Uncoated tablets

Colloidal anhydrous silica

Croscarmellose sodium

Magnesium stearate

Microcrystalline cellulose

Povidone K25

Stearic acid

Talc

Film-coating

Hydroxypropyl cellulose

Hydroxypropylmethyl cellulose

Propylene glycol

Sorbic acid

Sorbitan mono-oleate

Titanium dioxide

Quinoline yellow lake

Vanilla dry flavour

6.2 Incompatibilities

Not applicable

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store at or below 25 °C and protect from light.

Keep the blisters in the carton until required for use.

6.5 Nature and contents of container

KLARIZON 250: PVC/PVDC blister packs containing 10 or 14 tablets, packed into an outer carton together with a package insert.

KLARIZON 500: PVC/PVDC blister packs containing 10 or 14 tablets, packed into an outer carton together with a package insert.

6.6 Special precautions for disposal and other handling

No special requirements.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Biotech Laboratories (Pty) Ltd.

Block K West, Central Park

400 16th Road, Halfway House

Midrand, 1685

8. REGISTRATION NUMBER(S)

KLARIZON 250: A38/20.1.1/0724

KLARIZON 500: A38/20.1.1/0725

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of registration: 11 August 2006

10. DATE OF REVISION OF THE TEXT

21 November 2023