1.3.1 SOUTH AFRICAN PACKAGE INSERT

1.3.1.1 PACKAGE INSERT HUMAN MEDICINE

SCHEDULING STATUS: S4

1. NAME OF MEDICINE

CLARICULE (powder for injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION POSITION

Each vial contains 500 mg Clarithromycin. For the full list of excipients, see section 6.1.

Sugar free

3 PHARMACEUTICAL FORM

Powder for solution for Infusion

White to off white lyophilized powder for infusion

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

CLARICULE is indicated in the treatment of infections due to susceptible organisms whenever parenteral therapy is required;

- Lower respiratory tract infections for example, acute and chronic bronchitis, and pneumonia
- Upper respiratory tract infections for example, pharyngitis and tonsillitis due to *S. pyrogenes*, sinusitis
- Skin and soft tissue infections due to *S.aureus*
- There is some evidence that disseminated and localised infections in HIV-positive adults, due to *Mycobacterium avium* or *Mycobacterium intracellulare* respond to CLARICULE. Based on bacteriological results; CLARICULE should be used in conjunction with other antimycobacterials. To a lesser extent, localised infections due to *Mycobacterium kansasil* have responded to CLARICULE.

4.2 Posology and method of administration

Posology

Adults: The recommended dosage of CLARICULE is 1.0 gram daily, divided into two equal doses, each infused after dilution with an appropriate I.V diluent, over a 60 minute period.

Dosage in patients with Mycobacterial infections:

In disseminated or localised mycobacterial infections (*M.avium; M. intracellulare; M.cheloane; M.kansasi*) the recommended treatment in adults is 1000 mg/day in two divided doses. 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 on treatment exceeding 12 weeks. CLARICULE should be used in conjunction with other antimycobacterial medicines.

CLARICULE should not be given as a bolus or an lntra-muscular Injection.

Intravenous therapy may be limited for up to 2 to 5 days in the very ill patient and should be changed to oral therapy whenever possible as determined by the medical practitioner.

Special populations

Renal impairment

In patients with renal impairment who have creatinine clearance of less than 30 mL / min, the dosage of CLARICULE should be reduced to one-half of the normal recommended dose.

Paediatric population

The safety of CLARICULE for use in children has not been established.

Method of administration

For intravenous administration only.

For preparation or reconstitution instructions, refer to section 6.6.

4.3 Contraindications

Hypersensitivity to macrolide antibiotic medicines or to any of the excipients listed in section 6.1.

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

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

Concomitant administration of CLARICULE and any of the following medicines is contraindicated: astemizole, cisapride, domperidone, pimozide 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).

CLARICULE 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 sections 4.4 and 4.5).

Concomitant administration with ticagrelor or ranolazine is contraindicated.

CLARICULE should not be used concomitantly with HMG-CoA reductase inhibitors (statins) that are extensively metabolized by CYP3A4, (lovastatin or simvastatin), due to the increased risk of myopathy, including rhabdomyolysis.

CLARICULE should not be used in patients taking colchicine (see sections 4.4 and 4.5).

CLARICULE should not be given to patients with hypokalaemia (risk of prolongation of QT-time).

CLARICULE should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.

4.4 Special warnings and precautions for use

The medical practitioner should not prescribe CLARICULE to pregnant women without carefully weighing the benefits against risk, particularly during the first three months of pregnancy (see section 4.6).

CLARICULE 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 CLARICULE to patients with moderate to severe renal impairment (see section 4.2).

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, has been reported with CLARICULE. 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.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including macrolides, and may range in severity from mild to life-threatening. Clostridium difficile-associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial agents including CLARICULE 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 CLARICULE therapy should be considered regardless of the indication. Microbial testing should be performed and adequate treatment initiated.
Medicines inhibiting peristalsis should be avoided. 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 CLARICULE and colchicine is contraindicated (see section 4.3).
Caution is advised regarding concomitant administration of CLARICULE and triazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam (see section 4.5).
Cardiovascular Events:
Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac dysrhythmia and torsades de pointes, have been seen in patients treated with macrolides including clarithromycin (see section 4.8). Due to increased risk of QT prolongation and ventricular 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 hypokalaemia; and in patients with a history of QT prolongation or ventricular cardiac dysrhythmia (see section 4.3).
Furthermore, CLARICULE 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 dysrhythmia, myocardial infarction and cardiovascular mortality associated with macrolides including CLARICULE. Consideration of these findings should bebalanced with treatment benefits when prescribing CLARICULE.

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

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

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 medicine rash with eosinophilia and systemic symptoms (DRESS)), CLARICULE therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

CLARICULE 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 CLARICULE with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised when prescribing CLARICULE with other statins.

Rhabdomyolysis has been reported in patients taking CLARICULE and statins. Patients should be monitored for signs and symptoms of myopathy.

In situations where the concomitant use of CLARICULE 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 CLARICULE 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 CLARICULE is co-administered with warfarin (see section 4.5). INR and prothrombin times should be frequently monitored while patients are receiving CLARICULE and oral anticoagulants concurrently.

Long-term use may, as with other antibiotics, result in colonisation with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be instituted.

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

4.5 Interaction with other medicines and other forms of interaction

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

Astemizole, cisapride, domperidone, pimozide, and terfenadine:

Elevated cisapride levels have been reported in patients receiving CLARICULE and cisapride concomitantly. This may result in QT prolongation and cardiac dysrhythmias including

ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects have been observed in patients taking CLARICULE 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 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 CLARICULE 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 co-administration of CLARICULE 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 CLARICULE and ergot alkaloids is contraindicated (see section 4.3).

Oral Midazolam

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

HMG-CoA Reductase Inhibitors (statins)

Concomitant use of CLARICULE with lovastatin or simvastatin is contraindicated (see 4.3) as these statins are extensively metabolized by CYP3A4 and concomitant treatment with CLARICULE increases their plasma concentration, which increases the risk of myopathy,

including rhabdomyolysis. Reports of rhabdomyolysis have been received for patients taking CLARICULE 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 CLARICULE with statins. In situations where the concomitant use of CLARICULE 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.

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.

Effects of Other Medicinal Products on CLARICULE

Medicines that are inducers of CYP3A (e.g. rifampicin, phenytoin, carbamazepine, phenobarbitone, St John's wort) may induce the metabolism of CLARICULE. This may result in sub-therapeutic levels of CLARICULE 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 CLARICULE (see also the relevant product information for the CYP3A4 inducer administered). Concomitant administration of rifabutin and CLARICULE 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; CLARICULE 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 CLARICULE 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 CLARICULE and enzyme inducers.

Etravirine

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

Fluconazole

Concomitant administration of fluconazole 200 mg daily and CLARICULE 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 CLARICULE dose adjustment is necessary.

Ritonavir

A pharmacokinetic study demonstrated that the concomitant administration of ritonavir 200 mg every eight hours and CLARICULE 500 mg every 12 hours resulted in a marked inhibition of the metabolism of CLARICULE. 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 CLARICULE, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, the following dosage adjustments should be considered: For patients with CL_{CR} 30 to 60 mL/min the dose of CLARICULE should be reduced by 50%. For patients with CL_{CR} <30 mL/min the dose of CLARICULE should be decreased by 75%. Doses of CLARICULE 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 medicine interactions).

Effect of CLARICULE on Other Medicinal Products

CYP3A-based interactions

Co-administration of CLARICULE, which is to inhibit CYP3A, and a medicine primarily metabolised by CYP3A may be associated with elevations in medicine concentrations that could increase or prolong both therapeutic and adverse effects of the concomitant medicine.
The use of CLARICULE 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 CLARICULE 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 CLARICULE 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 CLARICULE.

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, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g. warfarin), atypical antipsychotics (e.g. quetiapine), quinidine, rifabutin, sildenafil, sirolimus, tacrolimus, triazolam and vinblastine.

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

Antidysrhythmics

There have been post-marketed reports of torsades de pointes occurring with the concurrent use of CLARICULE and quinidine or disopyramide. Electrocardiograms should be monitored for QT prolongation during co-administration of CLARICULE with these medicines. Serum levels of quinidine and disopyramide should be monitored during CLARICULE therapy. There have been post marketing reports of hypoglycemia with the concomitant administration of CLARICULE and disopyramide. Therefore blood glucose levels should be monitored during concomitant administration of CLARICULE and disopyramide.

Oral hypoglycemic agents/Insulin

With certain hypoglycemic medicines such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by CLARICULE may be involved and could cause hypolgycemia when used concomitantly. Careful monitoring of glucose is recommended.

Omeprazole

CLARICULE (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 CLARICULE. The mean 24-hour gastric pH value was 5.2 when omeprazole was administered alone and 5.7 when omeprazole was co-administered with CLARICULE.

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 CLARICULE. Co-administration of CLARICULE 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 CLARICULE.

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 CLARICULE. 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 CLARICULE 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 CLARICULE, the patient must be closely monitored to allow dose adjustment. Medicine 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 CLARICULE 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 CLARICULE 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). CLARICULE and other macrolides are known to inhibit CYP3A and Pgp. When CLARICULE and colchicine are administered together, inhibition of Pgp and/or CYP3A by CLARICULE 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). CLARICULE is known to inhibit Pgp. When CLARICULE and digoxin are administered together, inhibition of Pgp by CLARICULE may lead to increased exposure to digoxin.

Elevated digoxin serum concentrations in patients receiving CLARICULE 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 CLARICULE simultaneously.

Zidovudine

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

Phenytoin and Valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including CLARICULE 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 CLARICULE. Increased serum levels have been reported.

Bi-directional medicine interactions

Atazanavir

Both CLARICULE 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 CLARICULE 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 CLARICULE, 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 CLARICULE should be decreased by 50%. For patients with creatinine clearance <30 mL/min, the dose of CLARICULE should be decreased by 75% using an appropriate clarithromycin formulation. Doses of CLARICULE 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 CLARICULE and calcium channel blockers metabolized by CYP3A4 (e.g. verapamil, amlodipine, diltiazem) due to the risk of hypotension. Plasma concentrations of CLARICULE as well as calcium channel blockers may increase due to the interaction. Hypotension, bradydysrhythmias and lactic acidosis have been observed in patients taking CLARICULE and verapamil concomitantly.

Itraconazole

Both CLARICULE and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional medicine interaction.

CLARICULE may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of CLARICULE. Patients taking itraconazole and CLARICULE concomitantly should be monitored closely for signs or symptoms of increased or prolonged pharmacologic effect.

Saquinavir

Both CLARICULE and saquinavir are substrates and inhibitors of CYP3A, and there is evidence of a bi-directional medicine interaction. Concomitant administration of CLARICULE (500 mg twice daily) and saquinavir (soft gelatin capsules, 1200 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 CLARICULE (see section 4.5: Ritonavir).

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

4.6 Fertility, pregnancy and lactation

Pregnancy

The safety of CLARICULE for use during pregnancy has not been established. The medical practitioner should not prescribe CLARICULE to pregnant women, particularly in the first trimester of pregnancy.

Breastfeeding

The safety of clarithromycin during lactation has not been established. CLARICULE is excreted into human breast milk.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

The most frequent and common adverse reactions related to CLARICULE therapy for both adult and paediatric populations are abdominal pain, diarrhoea, nausea, vomiting and taste perversion.

The reactions considered at least possibly related to CLARICULE are displayed by system organ class and frequency.

.

System Organ Class	Frequent	Less Frequent	Frequency unknown
Infections and infestations		Cellulitis, candidiasis, gastroenteritis	Pseudomembranous colitis, erysipelas,
Blood and lymphatic system		Leukopenia,	Agranulocytosis, thrombocytopenia
Immune system disorders		Anaphylactoid reaction, hypersensitivity	Anaphylactic reaction. angioedema
Metabolism and nutrition disorders		Anorexia, decreased appetite	
Psychiatric disorders	Insomnia	Anxiety	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders	Dysgeusia, headache	Loss of consciousness, dyskinesia, dizziness, tremor	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders		Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders		Cardiac arrest, atrial fibrillation, electrocardiogram QT prolonged, extrasystoles, palpitations	Torsades de pointes,
Vascular disorders	Vasodilation		Haemorrhage
Respiratory, thoracic and mediastinal disorder		Asthma, pulmonary embolism	
Gastrointestinal disorders	Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Oesophagitis, gastrooesophageal reflux disease, constipation, dry mouth, eructation, flatulence.	Pancreatitis acute, tongue discolouration, tooth discolouration

Hepatobiliary disorders	Liver function test abnormal	alanine aminotransferase increased, aspartate aminotransferase increased, gamma-glutamyltransferase increased	Hepatic failure, jaundice hepatocellular
Skin and subcutaneous tissue disorders	Rash, hyperhidrosis	Dermatitis bullous, pruritus, urticaria,	Severe cutaneous adverse reactions (SCAR) (e.g. Acute generalised exanthematous pustulosis (AGEP),Stevens-Johnson syndrome, toxic epidermal necrolysis, medicine rash with eosinophilia and systemic symptoms (DRESS)), acne
Musculoskeletal and connective tissue disorders		musculoskeletal stiffness,	
Renal and urinary disorders		Blood creatinine increased, blood urea increased	Renal failure, nephritis interstitial
General disorders and administration site conditions	Injection site phlebitis Injection site pain		
Investigations		Albumin globulin ratio abnormal,	International normalised ratio increased, prothrombin time prolonged, urine colour abnormal

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Medicine Reaction 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 orally 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 medicine and supportive measures. As with other macrolides, CLARICULE serum levels are not expected to be appreciably affected by haemodialysis or peritoneal dialysis.

In the case of overdosage, CLARICULE should be discontinued and all other appropriate supportive measures should be instituted.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide

ATC-Code: J01FA09

Pharmacological classification

A 20.1.1 – Medium and broad spectrum antibiotics

CLARICULE is an antibiotic belonging to the macrolide antibiotic group. It exerts its antibacterial action by selectively binding to the 50s ribosomal sub-unit of susceptible bacteria preventing translocation of activated amino acids. It inhibits the intracellular protein synthesis of susceptible bacteria. The 14-hydroxy metabolite of clarithromycin, a product of parent medicine metabolism also has anti-microbial activity. The metabolite is less active than the parent compound for most organisms, including *mycobacterium spp*. An exception is

Haemophilus influenza where the 14-hydroxy metabolite is two-fold more active than the parent compound.

CLARICULE has bactericidal activity against several bacterial strains. These organisms include *H. influenzae, Streptococcus pneumoniae, Streptococcus pyogenes, Streptococcus agalactiae, Morazella (Brahamella) catarrhalis, Neisseria gonorrhoeae, Helicobacter pylori* and *Campylobacter spp*. The activity of CLARICULE against *H. pylori* is greater at neutral pH than at acid pH

5.2 Pharmacokinetic properties

The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism as indicated by lower biovailability of the metabolite following IV administration. Following IV administration the blood levels of clarithromycin achieved are well in excess of the MIC 90s for the common pathogens and the levels of 14-hydroxyclarithromycin exceed the necessary concentrations for important pathogens, e.g. *H. influenzae*.

The pharmacokinetics of clarithromycin and the 14-hydroxy metabolite are non-linear; steady state is achieved by day 3 of IV dosing. Following a single 500mg IV dose over 60 minutes, about 33% clarithromycin and 11% 14-hydroxyclarithromycin is excreted in the urine at 24 hours.

CLARICULE does not contain tartrazine or other azo dyes, lactose or gluten.

5.3 Preclinical safety data

No fertility studies with intravenous (I.V.) administration of CLARICULE have been conducted. Oral fertility and reproduction studies in rats have shown no adverse effects.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

sodium Hydroxide,

lactobionic acid

6.2 Incompatibilities

None known. However, CLARICULE should only be diluted with the diluents recommended.

6.3 Shelf life

2 years

6.4 Special precautions for storage

Store below 30º C. Do not freeze.

Storage condition for reconstituted solution: 20° C - 25° C

Shelf life of the reconstituted solution: 6 hours at 25°C. Keep out of reach of children.

6.5 Nature and contents of container

White to off white lyophilized powder for infusion in 15 ml, USP Type I, clear glass vial. Vials are stoppered with grey bromo butyl double slotted rubber stoppers along with blue aluminium seals.

The primary packs are then packed in carton along with leaflet. Pack size of 1, 5, 10, 20

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution (Step 1)

Prepare the initial solution of CLARICULE by adding 10 ml of sterile Water for Injection to the 500 mg vial. Shake until the vial contents have dissolved. Use only sterile Water for Injection, as other diluents may cause precipitation during reconstitution. Do not use diluents containing preservatives or inorganic salts. Each ml contains 50 mg clarithromycin.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

Dilution (Step 2)

The reconstituted product (500 mg in 10 ml Water for Injection) should be added to a minimum of 250 ml of one of the following diluents before administration: 5% dextrose in Lactated Ringer's solution, 5% dextrose, Lactated Ringer's, 5% dextrose in 0.3% sodium chloride, Normosol-M in 5% dextrose, Normosol-R in 5% dextrose, 5% dextrose in 0.45% sodium chloride, and 0.9% sodium chloride.

1ml of the infusion solution prepared in this way contains 2mg clarithromycin.

The final diluted product should be used within 6 hours if stored at room temperature (25^0 C) or within 48 hours if stored at 5^0 C.

The product is for single use only. Any unused medicinal product or waste material should be disposed.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Ruby Pharmaceuticals (PTY) LTD

Unit 1, 96 Hartley Road

Durban, 4091

8 REGISTRATION NUMBER(S)

55/20.1.1/0075

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

30 November 2021

10 DATE OF REVISION OF THE TEXT

15 November 2023