Approved Professional Information for Medicines for Human Use:

KLARISTELL IV

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

KLARISTELL IV 500 mg lyophilised powder for solution for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

KLARISTELL IV 500 mg lyophilised powder for solution for injection

Each vial contains clarithromycin 500 mg and lactobionic acid as a solubilising agent.

Sugar free

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

KLARISTELL IV 500 mg lyophilised powder for solution for injection

KLARISTELL IV is a homogenous uniform white-coloured freeze-dried powder which on reconstitution with water for injection produces a clear, colourless solution free of particulate matter.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

KLARISTELL IV is indicated in the treatment of infections due to susceptible organisms in the following conditions whenever parenteral therapy is required:

- Lower respiratory tract infections, e.g. bronchitis, pneumonia.
- Upper respiratory tract infections, e.g. pharyngitis and tonsillitis due to *S.pyogenes*, 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 clarithromycin. Based on bacteriological results, KLARISTELL IV should be used in conjuction with other antimycobacterials. To a lesser extent localised infections due to *Mycobacterium kansasii* have responded to clarithromycin.

4.2 Posology and method of administration

Posology

Adults

The recommended dosage of KLARISTELL IV is 1,0 gram daily, divided into 2 equal doses, each infused, following further dilution with an appropriate I.V. diluent, over a 60 minute period. Clarithromycin should not be given as a bolus or an intra-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 physician.

Special populations

Renal impairment

If the patient has creatinine clearance of less than 30 mL/min, the dosage of KLARISTELL IV should be reduced to one-half of the normal recommended dose.

Dosage in HIV patients with atypical mycobacterial infections

There is currently no data regarding use of KLARISTELL IV in immunocompromised patients. However, data is available regarding the use of oral clarithromycin in HIV-infected patients. In disseminated or localised mycobacterium infections (*M.avium, M.intracellulare, M.chelonae, M. Kansasii*) an oral dosage of 1000 mg/day in two divided doses has been used. Treatment of disseminated Mycobacterium avium complex infections in AIDS patients should continue as long as clinical and microbiological benefit is demonstrated.

In patients on treatment exceeding 12 weeks, a decrease in efficacy has been noted.

KLARISTELL IV should be used in conjunction with other antimycobacterial medicines.

Treatment of other nontuberculous mycobacterial infections should continue at the discretion of the physician.

Paediatric population

Children older than 12 years

As for adults.

Children under 12 years

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

Method of administration

KLARISTELL IV is for intravenous administration.

Preparation for use

The final solution for infusion is prepared as follows:

Prepare the initial solution of KLARISTELL IV by adding 10 mL of sterile water for injection to the 500 mg vial and shake vigorously until the entire contents are dissolved.

4.3 Contraindications

- Hypersensitivity to clarithromycin, macrolide antibiotic medicines or any of the excipients listed in section 6.1.
- Concomitant administration with 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 with oral midazolam is contraindicated (see section 4.5).
- Concomitant administration with lomitapide is contraindicated see section 4.5).
- Concomitant administration with any of the following medicines is contraindicated: certain antihistamines (e.g. astemizole and terfenadine), domperidone, cisapride and pimozide as this may result in QT prolongation and cardiac dysrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see sections 4.4 and 4.5).
- 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.
- Concomitant administration 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).
- Patients taking colchicine (see section 4.4 and 4.5).
- Patients with electrolyte disturbances (hypokalaemia or hypomagnesaemia, due to the risk of prolongation of QT time).
- Patients who suffer from severe hepatic failure in combination with renal impairment.

- Safety in pregnancy and lactation has not been established.

4.4 Special warnings and precautions for use

Pregnancy

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

Hepatic impairment

KLARISTELL IV is extensively metabolised in the liver and caution should be exercised in administration to patients with impaired hepatic function.

Renal impairment

Caution should also be exercised when administering to patients with moderate to severe renal impairment (see section 4.2).

Fatal hepatic failure

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 medicines. If signs and symptoms of hepatic disease develop, such as anorexia,

jaundice, dark urine, pruritus, or tender abdomen, treatment with KLARISTELL IV must be stopped.

Pseudomembranous colitis

Pseudomembranous colitis has been reported with nearly all antibacterial medicines, including macrolides, such as KLARISTELL IV and may range in severity from mild to life-threatening. *Clostridium difficile*- associated diarrhoea (CDAD) has been reported with use of nearly all antibacterial medicines including clarithromycin, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial medicines alters the normal flora of the colon, which may lead to overgrowth of *C. difficile*. 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 clarithromycin 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

Colchicine toxicity with concomitant use of KLARISTELL IV, a strong CYP3A4 inhibitor, 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 KLARISTELL IV, 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). Concomitant administration of oral midazolam and KLARISTELL IV is contraindicated (see section 4.3).

Cardiovascular Events

Prolonged cardiac repolarisation and QT interval, imparting a risk of developing cardiac dysrhythmia and torsades de pointes, have been seen in treatment with macrolides including clarithromycin (see section 4.8).

Carefully consider the balance of benefits and risks before prescribing clarithromycin for any patients taking hydroxychloroquine or chloroquine, because of the potential for an increased risk of cardiovascular events and cardiovascular mortality (see section 4.5).

Therefore, as the following situations may lead to an increased risk for ventricular dysrhythmias (including torsades de pointes), KLARISTELL IV should be used with caution in the following patients:

- Patients with coronary artery disease, severe cardiac insufficiency, conduction disturbances or clinically relevant bradycardia.
- Patients with electrolyte disturbances such as hypomagnesaemia. KLARISTELL IV must not be given to patients with hypokalaemia (see section 4.3).
- Patients concomitantly taking other medicines associated with QT prolongation (see section 4.5).
- Concomitant administration of KLARISTELL IV with astemizole, cisapride, pimozide and terfenadine is contraindicated (see section 4.3).
- KLARISTELL IV must not be used in patients with congenital or documented acquired QT prolongation or history of ventricular dysrhythmia (see section 4.3).

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. Consideration of these findings should be balanced with treatment benefits when prescribing KLARISTELL IV

Pneumonia

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

Skin and soft tissue conditions

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, such as KLARISTELL IV 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.

Severe acute 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)), KLARISTELL IV therapy should be discontinued immediately and appropriate treatment should be urgently initiated.

Cytochrome CYP3A4 inducers

KLARISTELL IV 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 KLARISTELL IV 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 KLARISTELL IV 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

The concomitant use of KLARISTELL IV and oral hypoglycaemic medicines (such as sulphonylureas e.g. gliclazide or glimepiride) 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 KLARISTELL IV and oral anticoagulants concurrently.

Caution should be exercised when KLARISTELL IV is co-administration with direct acting oral anticoagulants such as dabigatran, rivaroxaban and apixaban, particularly to patients at high risk of bleeding (see section 4.5)

Superinfections

Prolonged or repeated use of clarithromycin may result in colonisation with increased numbers of non-susceptible bacteria and fungi. If superinfections occur, KLARISTELL IV should be discontinued and appropriate therapy instituted.

Cross resistance

Attention should be paid to the possibility of cross resistance between KLARISTELL IV 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 clarithromycin 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 clarithromycin and pimozide concomitantly (see section 4.3).

Macrolides, such as KLARISTELL IV, 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). 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 KLARISTELL IV with ergotamine or dihydroergotamine may be 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 occur. Concomitant administration of KLARISTELL IV and ergot alkaloids is contraindicated (see section 4.3).

Oral midazolam

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

HMG-CoA reductase inhibitors (statins)

Concomitant use of clarithromycin with lovastatin or simvastatin is contraindicated (see section 4.3) as these statins are extensively metabolised by CYP3A4 and concomitant treatment with KLARISTELL IV 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 KLARISTELL IV cannot be avoided, therapy with lovastatin or simvastatin must be suspended during the course of treatment.

Caution should be exercised when prescribing KLARISTELL IV with statins. In situations where the concomitant use of KLARISTELL IV with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of a 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 KLARISTELL IV.

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 clarithromycin resulted in an increase in rifabutin, and a 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 of KLARISTELL IV 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 KLARISTELL IV and thus lower the plasma levels of clarithromycin, while increasing those of 14-hydroxy-clarithromycin, a metabolite that is also microbiologically active. Since the microbiological activities of clarithromycin and 14-hydroxy-clarithromycin are different for different bacteria, the intended therapeutic effect could be impaired during concomitant administration of KLARISTELL IV and enzyme inducers.

Etravirine

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

Fluconazole

Concomitant administration of fluconazole 200 mg daily and clarithromycin 500 mg twice daily 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-hydroxy-clarithromycin were not significantly affected by concomitant administration of fluconazole. No KLARISTELL IV dose adjustment is necessary.

Ritonavir

Marked inhibition of the metabolism of clarithromycin has been reported during concomitant administration of ritonavir 200 mg every 8 hours and clarithromycin 500 mg every 12 hours. 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-hydroxy-clarithromycin was noted. Because of the large therapeutic window for clarithromycin, no dosage reduction of KLARISTELL IV 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 creatinine clearance 30 to 60 mL/min the dose of KLARISTELL IV should be reduced by 50 %. For patients with creatinine clearance < 30 mL/min the dose of KLARISTELL IV 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, Bi-directional medicine interactions).

CYP3A-based interactions

Co-administration of clarithromycin, known to be a potent inhibitor of 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 KLARISTELL IV is contraindicated in patients receiving the CYP3A substrates astemizole, cisapride, domperidone, pimozide and terfenadine due to the

risk of QT prolongation and cardiac arrhythmias, including ventricular tachycardia, ventricular fibrillation, and torsades de pointes (see section 4.3 and 4.4).

The use of KLARISTELL IV 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 (se section 4.3).

Concomitant administration of KLARISTELL IV with lomitapide is contraindicated due to the potential for markedly increased transaminases (see section 4.3).

KLARISTELL IV should be used with caution in patients receiving treatment with other medicines known to be CYP3A enzyme substrates, especially if the CYP3A substrate has a narrow safety margin (e.g. carbamazepine) and/or the substrate is extensively metabolised by this enzyme.

Dosage adjustments may be considered, and when possible, serum concentrations of medicines primarily metabolised by CYP3A should be monitored closely in patients concurrently receiving KLARISTELL IV.

The following medicines or medicine classes are known or suspected to be metabolised by the same CYP3A isozyme (but this list is not comprehensive) alprazolam, carbamazepine, cilostazol, ciclosporin, disopyramide, ibrutinib, methadone, methylprednisolone, midazolam (intravenous), omeprazole, oral anticoagulants (e.g. warfarin, rivaroxaban, apixaban), 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-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 KLARISTELL IV with these medicines. Serum levels of quinidine and disopyramide should be monitored during KLARISTELL IV therapy.

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

Oral hypoglycaemic medicines/Insulin

With certain hypoglycaemic medicines such as nateglinide, and repaglinide, inhibition of CYP3A enzyme by clarithromycin may be involved and could cause hypoglycaemia when used concomitantly with KLARISTELL IV 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 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, such as KLARISTELL IV.

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 KLARISTELL IV is co-administered with these agents 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 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 medicines are co-administered with KLARISTELL IV.

Theophylline and carbamazepine

A modest but statistically significant ($p \leq 0,05$) increase of circulating theophylline or carbamazepine levels occurred when either of these medicines were administered concomitantly with clarithromycin, such as KLARISTELL IV 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 KLARISTELL IV 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 KLARISTELL IV, the patient must be closely monitored to allow dose adjustment. 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 clarithromycin 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 clarithromycin, such as KLARISTELL IV 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). KLARISTELL IV and other macrolides are known to inhibit CYP3A and Pgp. When KLARISTELL IV and colchicine are administered together, inhibition of Pgp

and/or CYP3A by KLARISTELL IV 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 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 dysrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and KLARISTELL IV simultaneously.

Zidovudine

Simultaneous oral administration of clarithromycin 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 KLARISTELL IV and zidovudine to allow for a 4-hour interval between each medication. This interaction does not appear to occur in paediatric HIV-infected patients taking clarithromycin suspension with zidovudine or dideoxyinosine. This interaction is unlikely when clarithromycin is administered via intravenous infusion.

Phenytoin and Valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including clarithromycin with 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 **KLARISTELL IV**

Increased serum levels have been reported.

Hydroxychloroquine and Chloroquine

Observational data have shown that co-administration of azithromycin with hydroxychloroquine in patients with rheumatoid arthritis is associated with an increased risk of cardiovascular events and cardiovascular mortality. Because of the potential for a similar risk with other macrolides when used in combination with hydroxychloroquine or chloroquine, careful consideration should be given to the balance of benefits and risks before prescribing KLARISTELL IV for any patients taking hydroxychloroquine or chloroquine.

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-hydroxy-clarithromycin, with a 28 % increase in the AUC of atazanavir. Because of the large therapeutic window for clarithromycin, no dosage reduction should be necessary in patients with normal renal function. For patients with moderate renal function (creatinine clearance 30 to 60 mL/min), the dose of KLARISTELL IV should be decreased by 50 %. For patients with creatinine clearance < 30 mL/min, the dose of KLARISTELL IV should be decreased by 75 %. Doses of KLARISTELL IV greater than 1000 mg per day should not be co-administered with protease inhibitors.

Calcium Channel Blockers

Caution is advised regarding the concomitant administration of clarithromycin and calcium channel blockers 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 clarithromycin, such as KLARISTELL IV and verapamil concomitantly.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, leading to a bidirectional medicine interaction. Clarithromycin may increase the plasma levels of itraconazole, while itraconazole may increase the plasma levels of clarithromycin. Patients taking itraconazole and KLARISTELL IV 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, 1200 mg three times daily) 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 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

Pregnancy

Safety of KLARISTELL IV during pregnancy and lactation has not been established.

Based on variable results obtained from animal studies and experience in humans, the possibility of adverse effects on embryofoetal development cannot be excluded. Some observational studies evaluating exposure to KLARISTELL IV during the first and second trimester have reported an increased risk of miscarriage compared to no antibiotic use or other antibiotic use during the same period. The available epidemiological studies on the risk of major congenital malformations with use of macrolides including KLARISTELL IV during pregnancy provide conflicting results. Therefore, use during pregnancy is not advised without carefully weighing the benefit against risks (see section 5.3).

Breastfeeding

The safety of clarithromycin for using during breast-feeding of infants has not been established**.** Clarithromycin is excreted into human breast milk in small amounts. It has been estimated that an exclusively breastfed infant would receive about 1,7 % of the maternal weight-adjusted dose of KLARISTELL IV.

Fertility

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

a) **Summary of the safety profile**

The most frequent and common adverse reactions related to KLARISTELL IV therapy for both adult and paediatric populations are abdominal pain, diarrhoea, nausea, vomiting and taste perversion. These adverse reactions are usually mild in intensity and are consistent with the known safety profile of macrolide antibiotics (see section b of section 4.8).

b) Tabulated list of adverse reactions

The table below shows all adverse drug reactions (ADRs) observed during clinical trials and postmarket spontaneous reports with clarithromycin

System Organ Class	**Frequency**		
	Frequent	**Less Frequent**	**Not known**

Infections and infestations		Cellulitis[1], candidiasis, gastroenteritis[2] , infection[3], vaginal infection	Pseudomembranous colitis, erysipelas,
Blood and lymphatic system disorders		Leucopenia, neutropenia[4], thrombocythaemia[3], eosinophilia[4]	Agranulocytosis, thrombocytopenia
Immune system disorders		Anaphylactoid reactions[1], hypersensitivity	Anaphylactic reaction, angioedema
Metabolism and nutrition disorders		Anorexia, decreased appetite	
Psychiatric disorders	Insomnia	Anxiety, nervousness[3]	Psychotic disorder, confusional state[5], depersonalisation,

			depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders	Dysgeusia, headache	Loss of consciousness[1], dyskinesia[1], dizziness, somnolence[5], tremor	Convulsions, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders		Vertigo, hearing impaired, tinnitus	Deafness
Cardiac disorders		Cardiac arrest[1], atrial fibrillation[1], electrocardiogram QT prolonged, extrasystoles[1], palpitations	Torsades de pointes, ventricular tachycardia, ventricular fibrillation
Vascular disorders	Vasodilatation		Haemorrhage

Respiratory, thoracic and mediastinal disorders		Asthma[1], epistaxis[2], pulmonary embolism[1]	
Gastrointestinal disorders	Diarrhoea, vomiting, dyspepsia, nausea, abdominal pain	Oesophagitis[1], gastro-esophageal reflux disease[2], gastritis, proctalgia[2], stomatitis, glossitis, abdominal distension[4], constipation, dry mouth, eructation, flatulence	Pancreatitis acute, tongue discolouration, tooth discolouration
Hepatobiliary disorders	Liver function test	Cholestasis[4], hepatitis[4], alanine aminotransferase increased, aspartate aminotransferase increased, gamma glutamyltransferase increased[4]	Hepatic failure, jaundice, hepatocellular
Skin and subcutaneous tissue disorders	Rash, hyperhidrosis	Dermatitis bullous[1], pruritus, urticaria, rash maculo-papular[3]	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		Muscle spasms[3], musculoskeletal stiffness[1], myalgia[2]	Rhabdomyolysis[2,6], myopathy
Renal and urinary disorders		Blood creatinine increased[1], blood urea increased[1]	Renal failure, nephritis interstitial

General disorders and administration site conditions	Injection site phlebitis[1], Injection site pain[1], injection site inflammation[1]	Malaise[4], pyrexia[3], asthenia, chest pain[4], chills[4], fatigue4	
Investigations		Albumin globulin ratio abnormal[1], blood alkaline phosphatase increased[4], blood lactate dehydrogenase increased[4]	International normalised ratio increased, prothrombin time prolonged, urine colour abnormal

1 ADRs reported only for the Powder for Concentrate for Solution for Infusion formulation

2ADRs reported only for the Extended-Release Tablets formulation

3 ADRs reported only for the Granules for Oral Suspension formulation

4 ADRs reported only for the Immediate-Release Tablets formulation

5,6 See section c)

** Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliablyestimate their frequency or establish a causal relationship to drug exposure. Patient exposure is estimated to be greater than 1 billion patient treatment days for clarithromycin.*

c. Description of selected adverse reactions

Injection site phlebitis, injection site pain, and injection site inflammation are specific to the KLARISTELL IV intravenous formulation.

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

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 KLARISTELL IV and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested (see section 4.5).

There have been rare reports of KLARISTELL IV 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 KLARISTELL IV formulation (e.g. suspension) or another antibiotic.

Special population: Adverse Reactions in Immunocompromised Patients (see section e).

d. Paediatric population

Clinical trials have been conducted using different KLARISTELL IV paediatric suspension in children 6 months to 12 years of age. Therefore, children under 12 years of age should use different KLARISTELL IV paediatric suspension.

Frequency, type and severity of adverse reactions in children are expected to be the same as in adults.

e. Other special populations

Immunocompromised patients

In AIDS and other immunocompromised patients treated with the higher doses of KLARISTELL IV over long periods of time for mycobacterial infections, it was often difficult to distinguish adverse events possibly associated with KLARISTELL IV 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 KLARISTELL IV 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 KLARISTELL IV.

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 KLARISTELL IV 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. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via the "**6.04 Adverse Drug Reaction Reporting Form**", found online under SAHPRA's publications:

https://www.sahpra.org.za/Publications/Index/8

Suspected adverse reactions can also be reported directly to the HCR via medsafety@austell.co.za

4.9 Overdose

Signs and symptoms

Ingestion of large amounts of KLARISTELL IV have been reported to produce gastro-intestinal symptoms. A patient with a history of bipolar disorder who ingested 8 g of KLARISTELL IV tablets showed altered mental status, paranoic behaviour, hypokalaemia and hypoxaemia.

Treatment

In the case of over-dosage, KLARISTELL IV should be discontinued and all other appropriate supportive measures should be instituted.

Allergic reactions accompanying overdosage should be treated by the prompt elimination of unabsorbed medicine and supportive measures. Like other macrolides, haemodialysis or peritoneal dialysis are not expected to appreciably affect clarithromycin serum levels.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Pharmacotherapeutic group: Antibacterial for systemic use, macrolide

ATC Code: J01FA09

Pharmacodynamics properties

Clarithromycin is a macrolide antibiotic. It causes suppression of protein synthesis in susceptible bacteria by binding to the 50S ribosomal sub-units of these bacteria.

The 14-hydroxy-clarithromycin metabolite, a product of parent medicine metabolism also has antibacterial 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.

Susceptibility

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

1. Commonly susceptible species
Aerobic Gram-negative micro-organisms
Haemophilic influenzae[$]
Moraxella catarrhalis
Other micro-organisms
Chlamydophila pneumoniae°
Legionella pneumophila°
Mycoplasma pneumoniae°
2. Species for which acquired resistance may be a problem
Aerobic Gram-positive micro-organisms
Staphylococcus aureus (methicillin-sensitive)
Staphylococcus aureus (methicillin-resistant)[+]
Streptococcus pneumoniae
Streptococcus pyogenes[1]
3. Inherently resistant organisms
Aerobic Gram-negative micro-organisms
Escherichia coli
Klebsiella spp.

Pseudomonas aeruginosa

° No actual data were available when the tables were published. Sensitivity is assumed in the primary literature, reference works and treatment recommendations.

$ The natural sensitivity of most isolates lies in the intermediate range.

+ The rate of resistance is above 50 % in at least one region.

1 Rate of resistance in some studies ≥ 10 %

5.2 Pharmacokinetic properties

Absorption

The pharmacokinetics of clarithromycin and the 14-hydroxy metabolite are non-linear due to saturation of hepatic metabolism at high doses; steady state is achieved by day 3 of IV dosing.

Distribution

Clarithromycin and its active metabolite are widely distributed with tissue concentrations exceeding serum levels partly due to intracellular uptake. Plasma protein binding is variable and concentration dependent.

Biotransformation

Clarithromycin is extensively metabolised in the liver. The microbiologically active metabolite 14-hydroxy-clarithromycin is formed by first pass metabolism as indicated by lower bioavailability of the metabolite following IV administration.

Following IV administration the blood levels of clarithromycin achieved are well in excess of the MIC_{90} for the common pathogens and the levels of 14-hydroxy-clarithromycin exceed the necessary concentrations for important pathogens, e.g. *H. influenzae.*

The metabolism of clarithromycin approaches saturation at high doses resulting in the non-linear pharmacokinetic behaviour of clarithromycin and the 14-hydroxy metabolite and an overall decrease in the formation of 14-hydroxylation and N-demethylation products.

Elimination

Clarithromycin is eliminated by renal and non-renal mechanisms. At steady state the 14-hydroxy-clarithromycin levels did not increase proportionately with the clarithromycin dose, and the apparent half-lives of both clarithromycin and its hydroxylated metabolite tended to be longer at the higher doses. The elimination half-lives are 3 – 7 hours for clarithromycin and 5 – 9 hours for 14-hydroxy-clarithromycin.

Following a single 500 mg IV dose over 60 minutes, about 33 % clarithromycin and 11 % 14-hydroxy-clarithromycin is excreted in the urine at 24 hours.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

lactobionic acid

water for injection

6.2 Incompatibilities

There is no data addressing the compatibility of KLARISTELL IV with other intravenous admixtures.

No medicine or chemical agent should be added to KLARISTELL IV fluid admixture unless its effect on the chemical and physical stability of the solution has first been determined.

KLARISTELL IV should only be diluted with the diluents recommended (see section 6.6 below).

6.3 Shelf life

36 months

6.4 Special precautions for storage

Store in the original packaging until required for use. Store at or below 25 °C.

The reconstituted product can be stored at 25 ºC for 6 hours or at 2 - 8 ºC for 48 hours.

6.5 Nature and contents of container

KLARISTELL IV is supplied in 20 mL transparent type I glass vials with grey chlorobutyl cap and green flip-off aluminium capsule.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

1. When the product is reconstituted as directed above, each mL contains 50 mg of clarithromycin. Only sterile water for injection is to be used, other diluents may cause precipitation during reconstitution. Do not use diluents containing preservatives or inorganic salts.

The reconstituted product should be used within 6 hours if stored at room temperature (25 °C) or within 48 hours if stored at 5 °C.

2. The reconstituted product (500 mg in 10 mL water for injection) should be added to 250 mL of one of the following diluents before administration:

- Ringer's lactate
- 5 % dextrose in Ringer's lactate solution
- 3,3 % dextrose and 0,3 % sodium chloride
- 5 % dextrose solution in 0,45 % sodium chloride solution.

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

7. HOLDER OF CERTIFICATE OF REGISTRATION

Camox Pharmaceuticals (Pty) Ltd

1 Sherborne Road

Parktown,

Johannesburg

2193, South Africa

8. REGISTRATION NUMBER(S)

KLARISTELL IV: 49/20.1.1/0680

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25 September 2018

10. DATE OF REVISION OF THE TEXT

29 June 2023