PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1 NAME OF THE MEDICINE

KLANBICID (Powder for solution for infusion)

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

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

The concentration of the final reconstituted and diluted solution for infusion is 2 mg/ml of clarithromycin.

Sugar free

For full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

White to off white lyophilized powder.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

KLANBICID 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 and pneumonia;
- Upper respiratory tract infections, e.g. pharyngitis, tonsillitis due to *Streptococcus pyogenes* and sinusitis;
- Skin and soft tissue infections due to *Staphylococcus 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, KLANBICID should be used in conjunction with other antimycobacterials. To a lesser extent localised infection due to *Mycobacterium kansasii* may respond to KLANBICID.

KLANBICID is indicated in adults and children 12 years and older.

4.2 Posology and method of administration

Posology

Adults and children older than 12 years

Recommended dosage

The recommended dosage of KLANBICID is 1000 mg daily, divided into two 500 mg doses, each infused and appropriately diluted with an intravenous diluent, over a 60-minute period. For preparation for use, see section 6.6.

Duration of therapy

Intravenous therapy may be given for 2 to 5 days in the very ill patient and should be changed to oral clarithromycin therapy whenever possible as determined by the doctor.

Dosage in patients with Mycobacterium infections

Although there currently are no data regarding the use of KLANBICID in immunocompromised patients, data are 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*), the recommended treatment in adults is 1000 mg/day, in two divided doses. Treatment of disseminated Mycobacterium avium complex (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. KLANBICID should be used in conjunction with other antimycobacterial agents.

Treatment of other non-tuberculous mycobacterium infections should continue at the discretion of the doctor.

Special populations

Elderly

As for adults.

Renal impairment

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

Paediatric population

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

Method of administration

For intravenous (IV) administration only.

KLANBICID should be administered into one of the larger proximal veins as an IV infusion over 60 minutes, using a diluted solution concentration of about 2 mg/ml. KLANBICID should not be given as a bolus or an intramuscular injection.

For preparation for use, see section 6.6.

4.3 Contraindications

- Hypersensitivity to clarithromycin, macrolide antibiotic medicines, or to any of the excipients listed in section 6.1;
- Concomitant administration of KLANBICID 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);
- Concomitant administration of KLANBICID and ergot alkaloids (e.g. ergotamine or dihydroergotamine) is contraindicated, as this may result in ergot toxicity (see section 4.5);

- Concomitant administration of KLANBICID and oral midazolam is contraindicated (see section 4.5);
- KLANBICID should not be given to patients with history of QT prolongation (congenital or documented acquired QT prolongation) or ventricular cardiac arrhythmia, including torsades de pointes (see sections 4.4 and 4.5);
- Concomitant administration with ticagrelor or ranolazine is contraindicated;
- KLANBICID 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 (see section 4.5);
- As with other strong CYP3A4 inhibitors, clarithromycin should not be used in patients taking colchicine (see sections 4.4 and 4.5);
- KLANBICID should not be given to patients with hypokalaemia (risk of prolongation of QT-time);
- KLANBICID should not be used in patients who suffer from severe hepatic failure in combination with renal impairment.
- Concomitant administration of KLANBICID with the atypical antipsychotics cariprazine, quetiapine and aripiprazole.

4.4 Special warnings and precautions for use

Prescribers must adhere to the principles of antibiotic stewardship.

Liver impairment

Clarithromycin is principally metabolised by the liver. Therefore, caution should be exercised in administering KLANBICID to patients with impaired hepatic function.

Hepatic dysfunction, including increased liver enzymes, and hepatocellular and/or cholestatic hepatitis, with or without jaundice, may occur during the use of with clarithromycin antibiotics. 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 pre-existing hepatic disease or may be taking other hepatotoxic medicines. Treatment with KLANBICID should be stopped

immediately and the prescribing medical practitioner should be contacted if signs and symptoms of hepatic disease develop, such as anorexia, jaundice, dark urine, pruritus, or tender abdomen.

Renal impairment

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

Pseudomembranous colitis

Pseudomembranous colitis may occur when using antibacterial agents, including KLANBICID a macrolide, and may range in severity from mild to life-threatening. *Clostridium difficile*-associated diarrhoea (CDAD) 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 KLANBICID use. Careful medical history is necessary since CDAD may occur over two months after the administration of KLANBICID. 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 therefore be avoided.

Colchicine

Colchicine toxicity may occur during concomitant use of clarithromycin and colchicine, especially in elderly patients and those suffering from renal insufficiency. Deaths may occur in such patients (see section 4.5). Concomitant administration of KLANBICID and colchicine is therefore contraindicated (see section 4.3).

Triazolobenzodiazepines

Caution is advised regarding concomitant administration of KLANBICID and

triazolobenzodiazepines, such as triazolam, and intravenous or oromucosal midazolam (see section 4.5).

Cardiac events

Prolongation of the QT interval, reflecting effects on cardiac repolarisation imparting a risk of developing cardiac dysrhythmia and torsades de pointes, may occur in patients treated with macrolides including KLANBICID (see section 4.8). Due to increased risk of QT prolongation and ventricular dysrhythmias (including torsades de pointes), the use of KLANBICID is contraindicated based on the following conditions:

- Patients taking astemizole, cisapride, domperidone, pimozide and terfenadine
- Patients who have hypokalaemia
- Patients with a history of QT prolongation or ventricular cardiac dysrhythmia (see section 4.3).

Furthermore, KLANBICID 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 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. Consideration of these findings should be balanced with treatment benefits when prescribing KLANBICID.

Pneumonia

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

pneumonia. In hospital-acquired pneumonia, KLANBICID 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.

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

Cytochrome CYP3A4 inducers

KLANBICID 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 KLANBICID with lovastatin or simvastatin is contraindicated (see section 4.3). Caution should be exercised when prescribing KLANBICID with other statins. Rhabdomyolysis may occur in patients taking KLANBICID and statins. Patients should be monitored for signs and symptoms of myopathy.

In situations where the concomitant use of KLANBICID with statins cannot be avoided, it is recommended to prescribe the lowest registered dose of the statin. The 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 KLANBICID 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 the International Normalized Ratio (INR) and prothrombin time when KLANBICID is co-administered with warfarin (see section 4.5). INR and prothrombin times should be frequently monitored while patients are receiving KLANBICID and oral anticoagulants concurrently.

Long-term use

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

Cross resistance

Attention should also be paid to the possibility of cross resistance between KLANBICID and other macrolide antibiotics, this includes lincomycin and clindamycin.

Paediatric population

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

4.5 Interaction with other medicines and other forms of interaction

Medicines strictly contraindicated due to the potential for severe medicine interactions:

Cisapride, domperidone, pimozide, and terfenadine

Elevated cisapride levels may occur in patients receiving clarithromycin and cisapride concomitantly. This may result in QT prolongation and cardiac arrhythmias including ventricular tachycardia, ventricular fibrillation and torsades de pointes. Similar effects may be observed in patients taking KLANBICID and pimozide concomitantly (see section 4.3).

Ergot alkaloids

Co-administration of KLANBICID with ergotamine or dihydroergotamine may be associated with acute ergot toxicity characterized by vasospasm, and ischaemia of the extremities and other tissues including the central nervous system. Concomitant administration of KLANBICID and ergot alkaloids is contraindicated (see section 4.3).

Oral midazolam

Co-administration of oral midazolam with clarithromycin tablets (500 mg twice daily), may cause midazolam AUC to increase 7-fold after oral administration of midazolam. Concomitant administration of oral midazolam and KLANBICID is contraindicated (see section 4.3).

HMG-CoA Reductase Inhibitors (Statins)

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

Caution should be exercised when prescribing KLANBICID with other statins. In situations where the concomitant use of KLANBICID 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 KLANBICID

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

Etravirine

Clarithromycin exposure may be decreased by etravirine; however, concentrations of the active metabolite, 14-OH-clarithromycin, may increase. Because 14-OH-clarithromycin has

reduced activity against Mycobacterium avium complex (MAC), overall activity against this pathogen may be altered; therefore, alternatives to KLANBICID should be considered for the treatment of MAC.

Fluconazole

Concomitant administration of fluconazole and KLANBICID may lead to increases in the mean steady-state minimum clarithromycin concentration (Cmin) and area under the curve (AUC) of 33 % and 18 % respectively. Steady state concentrations of the active metabolite 14-OH-clarithromycin are not significantly affected by concomitant administration of fluconazole. No KLANBICID dose adjustment is necessary.

Ritonavir

The concomitant administration of ritonavir and KLANBICID may result in a marked inhibition of the metabolism of clarithromycin. The clarithromycin Cmax may increase by 31 %, Cmin by 182 % and AUC by 77 % with concomitant administration of ritonavir. An essentially complete inhibition of the formation of 14-OH-clarithromycin may be noted.

Because of the large therapeutic window for KLANBICID, no dosage reduction should be necessary in patients with normal renal function. However, for patients with renal impairment, dosage adjustments should be considered.

Effect of KLANBICID on other medicines

CYP3A-based interactions

Co-administration of KLANBICID, which is an inhibitor of 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 KLANBICID 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 KLANBICID 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 KLANBICID. 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, 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.

Concomitant administration of KLANBICID 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.

Antidysrhythmics

Torsades de pointes may occur with the concurrent use of KLANBICID and quinidine or disopyramide. Electrocardiograms should be monitored for QT prolongation during co-administration of KLANBICID with these medicines. Serum levels of quinidine and disopyramide should be monitored during KLANBICID therapy.
Hypoglycaemia may occur with the concomitant administration of KLANBICID and disopyramide. Therefore, blood glucose levels should be monitored during concomitant administration of KLANBICID and disopyramide.

Oral hypoglycaemic agents / Insulin

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

Omeprazole

KLANBICID given in combination with omeprazole may cause the steady-state plasma concentrations of omeprazole to increase (Cmax, AUC0-24, and t1/2 may show an increase by up to 30 %, 89 %, and 34 %, respectively). Gastric pH may increase when omeprazole is co-administered with KLANBICID.

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 KLANBICID. Co-administration of KLANBICID 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 KLANBICID.

Theophylline, carbamazepine

A modest but statistically significant ($p \leq 0.05$) increase of circulating theophylline or carbamazepine levels may occur when either of these medicines were administered concomitantly with KLANBICID. 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 KLANBICID in the CYP2D6 poor metaboliser population.

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

When midazolam is co-administered with clarithromycin tablets, midazolam AUC may increase up to 2,7-fold after intravenous administration of midazolam. If intravenous midazolam is co-administered with KLANBICID, 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 KLANBICID is unlikely.

Medicine interactions and central nervous system (CNS) effects (e.g., somnolence and confusion) may be experienced with the concomitant use of KLANBICID and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested.

Other interactions

Colchicine

Colchicine is a substrate for both CYP3A and the efflux transporter, P-glycoprotein (Pgp). KLANBICID and other macrolides are known to inhibit CYP3A and Pgp. When KLANBICID 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). KLANBICID is known to inhibit Pgp. When KLANBICID and digoxin are administered together,

inhibition of Pgp by KLANBICID may lead to increased exposure to digoxin. Elevated digoxin serum concentrations in patients receiving KLANBICID and digoxin concomitantly may occur. Some patients may show clinical signs consistent with digoxin toxicity, including potentially fatal arrhythmias. Serum digoxin concentrations should be carefully monitored while patients are receiving digoxin and KLANBICID simultaneously.

Zidovudine

Simultaneous oral administration of clarithromycin tablets and zidovudine to HIV-infected adult patients may result in decreased steady-state zidovudine concentrations. Because KLANBICID appears to interfere with the absorption of simultaneously administered oral zidovudine, this interaction can be largely avoided by staggering the doses of KLANBICID 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 KLANBICID is administered via intravenous infusion.

Phenytoin and Valproate

There have been spontaneous or published reports of interactions of CYP3A inhibitors, including KLANBICID 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 KLANBICID. Increased serum levels may occur.

Bi-directional interactions

Bi-directional medicine interactions are likely to occur with KLANBICID and some medicines because both medicines are substrates and inhibitors of CYP3A. The following medicines are examples thereof:

Atazanavir

Both clarithromycin and atazanavir are substrates and inhibitors of CYP3A, and a bi-directional medicine interaction is likely to occur. Co-administration of KLANBICID with atazanavir may result in a 2-fold increase in exposure to KLANBICID, approximately 70 % decrease in exposure to 14-OH-clarithromycin and a 28 % increase in the AUC of atazanavir.

Because of the large therapeutic window for KLANBICID, 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 KLANBICID should be decreased by 50 %.

For patients with creatinine clearance < 30 ml/min, the dose of KLANBICID should be decreased by 75 % using an appropriate clarithromycin formulation.

Doses of KLANBICID 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 KLANBICID 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, brady-dysrhythmias, and lactic acidosis may occur in patients taking KLANBICID and verapamil concomitantly.

Itraconazole

Both clarithromycin and itraconazole are substrates and inhibitors of CYP3A, which may lead 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 KLANBICID 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 a bi-directional medicine interaction is likely to occur. Concomitant administration of clarithromycin and saquinavir may result in steady-state AUC and Cmax value increases up to 177 % and 187 % respectively. Clarithromycin AUC and Cmax values may increase about 40 % higher than those taking clarithromycin alone. No dose adjustment is required when the two medicines are co-administered for a limited time. When saquinavir is co-administered with ritonavir, consideration should be given to the potential effects of ritonavir on KLANBICID (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

The safety of KLANBICID for use during pregnancy and lactation has not been established.

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

Clarithromycin in KLANBICID is excreted in human breast milk.

4.7 Effects on ability to drive and use machines

The potential for dizziness, vertigo, confusion and disorientation may occur during the use of KLANBICID and should be considered before patients drive or use machines.

4.8 Undesirable effects

a. Summary of the safety profile

The most frequent side effects related to KLANBICID therapy are abdominal pain, diarrhoea, nausea, vomiting and taste perversion.

b. Tabulated summary of adverse reactions

System Organ Class	Frequency	Undesirable effect
Infections and infestations	*Less frequent*	Cellulitis, candidiasis, vaginal infection
	Frequency unknown	Pseudomembranous colitis, erysipelas
Blood and lymphatic system disorders	*Less frequent*	Leukopenia
	Frequency unknown	Agranulocytosis, thrombocytopenia
Immune system disorders	*Less frequent*	Anaphylactic reaction, hypersensitivity
	Frequency unknown	Angioedema
Metabolism and nutrition disorders	*Less frequent*	Anorexia, decreased appetite
	Frequency unknown	Hypoglycaemia
Psychiatric disorders	*Frequent*	Insomnia
	Less frequent	Anxiety
	Frequency unknown	Psychotic disorder, confusional state, depersonalisation, depression, disorientation, hallucination, abnormal dreams, mania
Nervous system disorders	*Frequent*	Dysgeusia, headache

	Less frequent	Loss of consciousness, dyskinesia, dizziness, somnolence, tremor
	Frequency unknown	Convulsion, ageusia, parosmia, anosmia, paraesthesia
Ear and labyrinth disorders	*Less frequent*	Vertigo, hearing impaired, tinnitus
	Frequency unknown	Deafness
Cardiac disorders	*Less frequent*	Cardiac arrest, atrial fibrillation, electrocardiogram QT prolonged, extrasystoles, palpitations
	Frequency unknown	*Torsades de pointes*, ventricular tachycardia, ventricular fibrillation
Vascular disorders	*Frequent*	Vasodilation, phlebitis, thrombophlebitis
	Frequency unknown	Haemorrhage
Respiratory, thoracic and mediastinal disorders	*Less frequent*	Asthma, pulmonary embolism
Gastrointestinal disorders	*Frequent*	Diarrhoea, gastrointestinal upset, vomiting, dyspepsia, nausea, abdominal pain
	Less frequent	Oesophagitis, gastritis, stomatitis, glossitis, constipation, dry mouth, eructation, flatulence
	Frequency unknown	Pancreatitis acute, tongue discolouration, tooth discolouration
Hepato-biliary disorders	*Frequent*	Liver function test abnormal

	Less frequent	Alanine aminotransferase increased, aspartate aminotransferase increased, hepatitis
	Frequency unknown	Hepatic failure, jaundice hepatocellular, hepatitis cholestatic
Skin and subcutaneous disorders	*Frequent*	Rash, hyperhidrosis
	Less frequent	Dermatitis bullous, pruritus, urticaria
	Frequency unknown	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	*Less frequent*	Musculoskeletal stiffness
	Frequency unknown	Rhabdomyolysis, myopathy
Renal and urinary disorders	*Less frequent*	Blood creatinine increased; blood urea increased
	Frequency unknown	Renal failure, nephritis interstitial
General disorders and administration site conditions	*Frequent*	Injection site phlebitis, injection site pain, injection site inflammation, venepuncture site plan

	Less frequent	Asthenia
Investigations	*Less frequent*	Albumin globulin ratio abnormal
	Frequency unknown	International normalised ratio increased, prothrombin time prolonged, urine colour abnormal, blood creatinine increased, hepatic enzymes increased

c. Description of selected adverse reactions

Long-term use may result in colonisation with increased number of non-susceptible bacteria and fungi. If superinfections occur, appropriate therapy should be initiated.

Pseudomembranous colitis may occur during the use of KLANBICID and may range in severity from mild to life threatening. Therefore, it is very important to consider this diagnosis if patients who present with diarrhoea subsequent to the administration of antibacterial agents.

Colchicine toxicity with concomitant use of KLANBICID may occur, especially in the elderly, some of which may occur in patients with renal insufficiency (see section 4.5 and 4.3).

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

Rhabdomyolysis may occur when KLANBICID is administered concomitantly with statins, fibrates, colchicine or allopurinol (see section 4.3 and 4.4).

Medicine interactions and central nervous system (CNS) effects (e.g. somnolence and confusion) with the concomitant use of KLANBICID and triazolam. Monitoring the patient for increased CNS pharmacological effects is suggested (see section 4.5).

d. Paediatric population

Undesirable effects in paediatrics:

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

Use of KLANBICID is not recommended for children younger than 12 years. Children under 12 years of age should use clarithromycin paediatric suspension.

e. Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Health care providers are asked to report any suspected adverse reactions to SAHPRA via the **"6.04 Adverse Drug Reactions Reporting Form",** found online under SAHPRA's publications:

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

4.9 Overdose

Symptoms may be an exacerbation of the adverse reactions. It may include altered mental status, paranoid behaviour, hypokalaemia, and hypoxaemia.

Treatment

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

As with other macrolides, clarithromycin 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-code: J01FA09

Mechanism of action

Clarithromycin is an antibiotic belonging to the macrolide antibiotic group. It exerts its antibacterial action by selectively binding to the 50s ribosomal 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 drug metabolism, also has anti-microbial activity. The metabolite is less active than the parent clarithromycin for most organisms, with the exception of Haemophilus influenza, where the 14-hydroxy metabolite is two-fold more active than the parent clarithromycin.

Resistance

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, clarithromycin should be used in combination with additional appropriate antibiotics.

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

5.2 Pharmacokinetic properties

The microbiologically active metabolite 14-hydroxyclarithromycin is formed by first pass metabolism as indicated by lower bioavailability of the metabolite following IV administration. Following intravenous 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 both non-linear.

Steady state is achieved by Day 3 of IV dosing. Following a single 500 mg IV dose over 60 minutes, approximately 33 % clarithromycin and 11 % 14-hydroxyclarithromycin are excreted in the urine, after 24 hours.

Pharmacokinetics in patients with Mycobacterial infections

Steady-state concentrations of clarithromycin and 14-OH-clarithromycin observed following oral administration of usual doses of adult patients with HIV infection appear to be similar to those observed in healthy patients. However, at the higher doses which may be required to treat mycobacterial infections, clarithromycin concentrations can be much high than those observed at the usual doses. In adult HIV-infected patients taking 1000 and 2000 mg/day in two divided doses, steady-state clarithromycin Cmax values can range from 2 – 4 µg/ml and 5 – 10 µg/ml respectively. Elimination half-lives may be lengthened at these higher doses when compared with usual doses in healthy subjects. The higher the clarithromycin concentrations and longer elimination half-lives observed at these doses are consistent with the known non-linearity in clarithromycin pharmacokinetics.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lactobionic acid

6.2 Incompatibilities

Unknown. KLANBICID should only be diluted with the diluents recommended in section 6.6.

6.3 Shelf life

Unopened vial

A shelf life of 36 months is approved for Clarithromycin lyophilised powder for solution for infusion 500mg/vial manufactured by Anfarm Hellas S.A. Clarithromycin manufactured by Ind-Swift Laboratories when packed in Type I clear glass vial of 15 ml sealed with a grey

bromobutyl rubber stopper and sealed with a with a dark grey aluminium cap with orange plastic flip-off seal and stored at or below 25 °C.

Do not freeze.

Reconstituted solution with water for injection

(See section 6.6 – Step 1)

From a microbiological point of view, the product should be used immediately.

If not used immediately, in-use storage times and conditions are the responsibility of the user. Chemical and physical in-use stability has been demonstrated for 24 hours when stored at or below 25 °C or for 48 hours in the refrigerator in a refrigerator (2 - 8 °C) prior to the preparation of the patient's infusion solution.

Do not freeze.

Final dilution for infusion with specified diluents

(See section 6.6 – Step 2)

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user. Chemical and physical in-use stability has been demonstrated for 6 hours when stored at room temperature (at or below 25°C) or 48 hours when stored in the refrigerator (2 to 8 °C) in the intravenous bag or bottle. Do not freeze.

From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user. And would normally not be longer than 24 hours at 2 to 8°C, unless reconstitution / dilution has taken place in controlled and validated aseptic conditions (CPMP/QWP/159/96)

6.4 Special precautions for storage

Store the unopened vial at room temperature (at or below 25 °C) in its original container. For storage conditions during reconstitution and dilution, see section 6.3.

6.5 Nature and contents of container

KLANBICID is presented in an uncoloured, clear glass vial (type I), with a nominal capacity of 15 ml, sealed with a grey bromobutyl rubber stopper and sealed with a dark grey aluminium cap with orange plastic flip-off seal. Each 500 mg vial are packed in units of 1 vial per carton box.

6.6 Special precautions for disposal and other handling

KLANBICID should be administered into one of the larger proximal veins as an IV infusion over 60 minutes, using a solution concentration of 2 mg/ml. Clarithromycin should not be given as a bolus or an intramuscular injection.

Preparation for use

Step 1 - Reconstitution

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

The concentration of the reconstituted solution as directed in Step 1, is 50 mg/ml. For storage conditions after reconstitution of the medicinal product, see section 6.3.

Step 2 - Dilution

The reconstituted product (500 mg in 10 ml Water for Injection) should be added to a cumulative minimum of 250 ml to one of the following diluents before it can be administered to a patient:

0.9 % Sodium chloride;

5 % Dextrose;

5 % Dextrose in 0,3 % sodium chloride

5 % Dextrose in 0,45 % sodium chloride

5 % Dextrose in Ringer's lactated solution

Ringer's lactated solution

The concentration final dilution for infusion as directed in Step 2, is 2 mg/ml. For storage conditions after dilution of the medicinal product, see section 6.3.

Important notification before the administration of final diluted product to patients

Both the reconstitution and dilution steps (1 and 2) should be fully completed before KLANBICID can be administered to a patient. No other medicine or chemical agent should be added to the final diluted product, unless its effect on the chemical and physical stability of the solution has first been determined.

Disposal

KLANBICID is for single use only. The vial and any other unused solution should be adequately disposed of in accordance with local requirements.

7 HOLDER OF CERTIFICATE OF REGISTRATION

Juno Pharma SA (Pty) Ltd

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1686

8 REGISTRATION NUMBER

52/20.1.1/0243

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

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