1.3.1.1 PROFESSIONAL INFORMATION

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

LINOBACT IV, 600 mg/300 ml solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 300 ml infusion bag of LINOBACT IV contains 600 mg linezolid; providing 2 mg linezolid per ml.

Excipients with known effect

Contains sugar (15,072 g glucose monohydrate per 300 ml solution).

Contains sodium (131,49 mg sodium per 300 ml solution).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.

A clear, colourless to yellowish solution, free from visible particles.

pH range 4,6 – 5,0

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LINOBACT IV is indicated for the treatment of patients with the following infections, caused by susceptible strains of the designated microorganisms. LINOBACT IV is

not indicated for the treatment of Gram-negative infections. It is critical that specific Gram-negative therapy must be initiated immediately if a concomitant Gram-negative pathogen is documented or suspected (see section 4.4).

- **Vancomycin-resistant** *Enterococcus faecium* infections, including cases with concurrent bacteraemia.
- **Nosocomial pneumonia** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), or *Streptococcus pneumonia*e (including multi-medicine resistant *S. pneumoniae* (MDRSP) strains).
- **Complicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible and methicillin-resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. LINOBACT IV has not been studies in the treatment of decubitus ulcers.
- **Uncomplicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*.
- **Community-acquired pneumonia** caused by *Streptococcus pneumoniae* (including multi-medicine resistant *S. pneumoniae* (MDRSP) strains), including cases with concurrent bacteraemia, or *Staphylococcus aureus* (methicillin-susceptible and -resistant strains).

Due to concern about inappropriate use of antibiotics leading to an increase in resistant organisms, prescribers should carefully consider alternatives before initiating treatment with LINOBACT IV in the outpatient setting.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to linezolid. Therapy may be instituted empirically while awaiting results of these

tests. Once these results become available, antimicrobial therapy should be adjusted accordingly.

4.2 Posology and method of administration

Posology

Patients who commence treatment on the parenteral formulation should be switched to an oral presentation when clinically indicated.

LINOBACT IV solution for infusion should be administered over a period of 30 to 120 minutes. The recommended intravenous (IV) dosage schedule for LINOBACT IV is as follows:

Adult and adolescent (12 years and older) patients:

<table>
<tr><th>Infections (including those associated with concurrent bacteraemia)</th><th>Dosage and route of administration</th><th>Duration of treatment</th></tr>
<tr><td>Community-acquired pneumonia, including concurrent bacteraemia</td><td rowspan="2">600 mg IV every 12 hours</td><td rowspan="3">10 – 14 consecutive days</td></tr>
<tr><td>Nosocomial pneumonia, including concurrent bacteraemia</td></tr>
<tr><td>Skin and soft tissue infections, including concurrent bacteraemia</td><td>600 mg IV every 12 hours depending on clinical severity</td></tr>
</table>

Infections *(including those associated with concurrent bacteraemia)*	**Dosage and route of administration**	**Duration of treatment**
Enterococcal infections, including vancomycin-resistant infections, and those with concurrent bacteraemia	600 mg IV every 12 hours	14 – 28 consecutive days

Special populations

Paediatric patients (birth* through to 11 years):

Infections *(including those associated with concurrent bacteraemia)*	**Dosage and route of administration**	**Duration of treatment**
Community-acquired pneumonia, including concurrent bacteraemia	10 mg/kg IV every 8 hours	10 – 14 consecutive days
Nosocomial pneumonia, including concurrent bacteraemia		
Skin and soft tissue infections, including concurrent bacteraemia		
Enterococcal infections, including vancomycin-resistant infections, and those with concurrent bacteraemia	10 mg/kg IV every 8 hours	14 – 28 consecutive days

***** Pre-term neonates less than 7 days of age (gestational age less than 34 weeks) have

lower systemic LINOBACT IV clearance values and larger AUC values than many full-term neonates and older infants. By day 7 of age, LINOBACT IV clearance and AUC values are like those of full-term neonates and older infants.

Elderly patients:

No dose adjustment is necessary.

Patients with renal impairment:

- *Patients with renal insufficiency:* No dosage adjustment is required.
- *Patients with severe renal insufficiency* (CL_{CR} **<** 30 ml/min.):

  No dose adjustment is required. Due to the unknown clinical significance of higher exposure (up to 10-fold) to the two primary metabolites of LINOBACT IV in patients with severe renal insufficiency, LINOBACT IV should be used with special caution in these patients and only when the anticipated benefit is considered to outweigh the theoretical risk.

Haemodialysis:

As about 30 % of a LINOBACT IV dose is removed during 3 hours of haemodialysis, LINOBACT IV should be given after dialysis in patients receiving such treatment. The primary metabolites of LINOBACT IV are removed to some extent by haemodialysis, but the concentrations of these metabolites are still considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

Therefore LINOBACT IV should be used with special caution in patients with severe renal insufficiency who are undergoing dialysis and only when the anticipated benefit is considered to outweigh the theoretical risk.

There is no experience of LINOBACT IV administration to patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or alternative treatments for renal failure (other than haemodialysis).

Patients with hepatic insufficiency:

No dose adjustment is required. However, there are limited clinical data and it is recommended that LINOBACT IV should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk.

Method of administration

LINOBACT IV should be administered intravenously twelve-hourly.

Route of administration: Intravenous use.

Administer LINOBACT IV solution for infusion over a period of 30 to 120 minutes.

See section 6.6 for special precautions on handling.

4.3 Contraindications

LINOBACT IV is contraindicated for use in patients who have known hypersensitivity to linezolid or any excipients in LINOBACT IV, listed in section 6.1.

Monoamine oxidase inhibitors

LINOBACT IV should not be used in patients taking any medicine which inhibits monoamine oxidases A or B (e.g. phenelzine, isocarboxazid), or within two weeks of taking any such medicine.

Relative contraindications:

Potential interactions producing elevation of blood pressure

Unless patients are monitored for potential increases in blood pressure, LINOBACT IV should not be administered to patients with uncontrolled hypertension, pheochromocytoma, hyperthyroidism and/or patients taking any of the following types of medicines: directly and indirectly acting sympathomimetic medicines (e.g., pseudoephedrine, phenylpropanolamine), vasopressive

medicines (e.g., epinephrine, norepinephrine), dopaminergic medicines (e.g., dopamine, dobutamine) (see section 4.5).

Potential serotonergic interactions

Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, LINOBACT IV should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medicines: serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), meperidine, pethidine or buspirone (see section 4.5).

4.4 Special warnings and precautions for use

Prescribers should adhere to the principles of antibiotic stewardship.

Pseudomembranous colitis, *Clostridium difficile* associated diarrhoea (CDAD)

Pseudomembranous colitis has been reported with linezolid as in LINOBACT IV and may range in severity from mild to life-threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhoea subsequent to the administration of LINOBACT IV.

CDAD has been reported with linezolid as in LINOBACT IV and may range in severity from mild diarrhoea to fatal colitis. Treatment with LINOBACT IV alters the normal flora of the colon leading to overgrowth of *Clostridium difficile.*

C. difficile produces toxins A and B which contribute to the development of CDAD. Hypertoxin-producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD should 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.

Myelosuppression

Reversible myelosuppression (including anaemia, leukopenia, pancytopenia and thrombocytopenia) that may be dependent on duration of therapy has been reported in some patients receiving linezolid (as in LINOBACT IV). Monitoring of complete blood counts should be considered for patients who are at increased risk for bleeding, who have pre-existing myelosuppression, who receive concomitant medicines that may decrease haemoglobin levels or platelet count or function, or who receive LINOBACT IV for more than 2 weeks.

If significant myelosuppression occurs during LINOBACT IV therapy, treatment should be stopped unless it is considered absolutely necessary to continue therapy.

Cases of sideroblastic anaemia have been reported (see section 4.8). Where time of onset was known, most patients had received linezolid therapy for more than 28 days. Most patients fully or partially recovered following discontinuation of linezolid with or without treatment for their anaemia.

Peripheral and optic neuropathy

Peripheral neuropathy, optic neuropathy and optic neuritis have been reported in patients treated with linezolid (as in LINOBACT IV). In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration. Visual blurring has been reported in some patients treated with linezolid for less than 28 days.

If symptoms of visual impairment appear, such as changes in visual acuity, changes in colour vision, blurred vision, or visual field defect, prompt ophthalmic

evaluation is recommended. Visual function should be monitored in all patients receiving LINOBACT IV for extended periods (≥ 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with LINOBACT IV. If peripheral or optic neuropathy occurs, the continued use of LINOBACT IV in these patients should be weighed against the potential risks.

There may be an increased risk of neuropathies when LINOBACT IV is used in patients currently taking or who have recently taken antimycobacterial medicines for the treatment of tuberculosis.

Lactic acidosis

Lactic acidosis has been reported with the use of linezolid as in LINOBACT IV. Patients who develop recurrent nausea or vomiting, unexplained acidosis, or a low bicarbonate level while receiving LINOBACT IV should receive immediate medical attention.

Mitochondrial dysfunction

Linezolid, contained in LINOBACT IV, inhibits mitochondrial protein synthesis. Adverse events, such as lactic acidosis, anaemia and neuropathy (optic and peripheral), may occur as a result of this inhibition; these events are more common when LINOBACT IV is used longer than 28 days.

Convulsions

Convulsions have been reported in patients treated with linezolid as in LINOBACT IV (see section 4.8). In some of these cases a history of seizures or risk factors for seizures were reported.

Gram-negative pathogens

LINOBACT IV has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections (see sections 5.1 and 4.1). Specific Gram-negative therapy is required if a concomitant Gram-negative pathogen is documented or suspected.

LINOBACT IV should be used with special caution in patients at high risk for life-threatening systemic infections, such as those with infections related to central venous catheters in intensive care units. LINOBACT IV is **not** approved for the treatment of patients with catheter-related bloodstream infections.

Superinfection

The use of antibiotics (including LINOBACT IV) may result in an overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate treatment should be instituted.

Treatment period

The safety and efficacy of LINOBACT IV when administered for periods longer than 28 days have not been established.

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid as in LINOBACT IV and serotonergic medicines, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported. Co-administration of LINOBACT IV and serotonergic medicines is therefore contraindicated (see section 4.3), except where administration of LINOBACT IV and concomitant serotonergic medicines is essential. In those cases, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and

incoordination. If signs or symptoms occur medical practitioners should consider discontinuing either one or both medicines; if the concomitant serotonergic medicine is withdrawn, discontinuation symptoms can occur.

Patient populations

Underlying clinical conditions

LINOBACT IV has not been studied in patients with uncontrolled hypertension, phaeochromocytoma, carcinoid syndrome or untreated hyperthyroidism.

Renal impairment

LINOBACT IV should be used with special care in patients with severe renal impairment and only when the expected benefit is considered to exceed the theoretical risk.

Hepatic impairment

It is recommended that LINOBACT IV should be used in patients with severe hepatic insufficiency only when the anticipated benefit is considered to outweigh the theoretical risk.

Excipients with known effect

LINOBACT IV contains 50,24 mg/ml glucose monohydrate (15,072 g per 300 ml) solution. This should be taken into account in patients with diabetes mellitus or other conditions associated with glucose intolerance.

LINOBACT IV contains 0,44 mg sodium/ml (131,49 mg sodium per 300 ml solution), equivalent to 6,6 % of the recommended maximum daily intake of 2 g sodium for an adult, per 300 ml bag.

4.5 Interactions

Unless there are facilities available for close observation and monitoring of blood pressure, LINOBACT IV should not be administered to patients taking serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), directly and indirectly acting sympathomimetic medicines (including the adrenergic bronchodilators, pseudoephedrine and phenylpropanolamine), vasopressive medicines (e.g. epinephrine, norepinephrine), dopaminergic medicines (e.g. dopamine, dobutamine), meperidine, pethidine or buspirone (see section 4.3 and 4.4).

Monoamine oxidase inhibitors and medicines producing elevation of blood pressure

LINOBACT IV is a reversible, non-selective inhibitor of monoamine oxidase (MAOI); it is contraindicated in patients treated with monoamine oxidase inhibitors or within two weeks of taking such a medicine (see section 4.3).

LINOBACT IV produces a mild, reversible enhancement of the pressor responses induced by pseudoephedrine and phenylpropanolamine hydrochloride. Thus, the potential for interaction with sympathomimetic or adrenergic medicines should be considered and doses of compounds, such as dopamine or epinephrine (adrenalin), should be titrated to achieve the desired response.

Serotonergic interactions

Serotonin syndrome, associated with the simultaneous administration of LINOBACT IV and serotonergic medicines, including antidepressants such as SSRIs has been reported (see section 4.3 and 4.4).

Although LINOBACT IV has the potential for interaction with serotonergic medicines, no serotonin effects were observed in patients receiving linezolid and dextromethorphan.

Where administration of LINOBACT IV and concomitant serotonergic medicines is clinically appropriate, patients should be closely observed for signs and symptoms of serotonin syndrome such as cognitive dysfunction, hyperpyrexia, hyperreflexia and incoordination. If signs or symptoms occur medical practitioners should consider discontinuation of either one or both medicines. If the concomitant serotonergic medicine is withdrawn, discontinuation symptoms can be observed.

Tyramine-rich foods

No significant pressor response was observed in patients receiving both linezolid and 100 mg tyramine. This suggests that is only necessary to avoid ingesting excessive amounts of food and beverages with high tyramine content (e.g. mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products such as soy sauce), to prevent a pressor response.

Cytochrome P450 interactions

LINOBACT IV is not detectably metabolised by the cytochrome P450 (CYP) enzyme system and it does not induce or inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Therefore, no CYP450-induced medicine interactions are expected with LINOBACT IV.
No interactions have been reported in pharmacokinetic studies with either aztreonam or gentamicin.

Warfarin

When warfarin was added to linezolid therapy at steady-state, there was a 10 % reduction in mean maximum international normalised ratio (INR) on co-administration with a 5 % reduction in AUC INR. There are insufficient data from patients who have received warfarin and linezolid (such as LINOBACT IV) to assess the clinical significance, if any, of these findings.

Rifampicin

Concomitant administration of rifampicin with LINOBACT IV may cause a decrease of about 20 % in linezolid C_{max} and a decrease of about 30 % in linezolid AUC. The mechanism of this interaction and the clinical significance thereof is unknown.

4.6 Fertility, pregnancy and lactation

The use of LINOBACT IV intravenous solution in pregnancy and lactation is contraindicated, as safety has not been demonstrated.

Pregnancy

Studies in animals have shown reproductive toxicity; a potential risk for humans exists.

Breastfeeding

LINOBACT IV may be secreted into breast milk. Breastfeeding should therefore be discontinued prior to and throughout administration.

Fertility

Linezolid, as in LINOBACT IV, caused a reduction in fertility in animals. The possible effect on the human male reproductive system has not been established.

4.7 Effects on ability to drive and use machines

Patients should be informed not to drive or handle machinery or tools if they experience dizziness or visual impairment (see section 4.8).

4.8 Undesirable effects

Summary of the safety profile

Frequently reported adverse reactions are headache, diarrhoea, nausea, vomiting, metallic taste, abnormal liver function tests and vaginal moniliasis.

The most frequently reported medicine-related adverse events which led to discontinuation of treatment were headache, diarrhoea, nausea and vomiting.

Tabulated summary of adverse reactions

Infections and infestations:	
Frequent:	Oral and vaginal candidiasis, fungal infections.
Less frequent:	Vaginitis, antibiotic-associated colitis, *Clostridium difficile* associated diarrhoea (CDAD), pseudomembranous colitis (may be fatal; see section 4.4).
Blood and the lymphatic system disorders:	
Less frequent:	Reversible anaemia, leukopenia, neutropenia, thrombocytopenia, eosinophilia, pancytopenia (see section 4.4).
Frequency unknown:	Myelosuppression, sideroblastic anaemia (see section 4.4).
Immune system disorders:	
Less frequent:	Anaphylaxis, angioedema.

Metabolism and nutrition disorders:

Less frequent: Hyponatraemia, increased serum creatine phosphokinase, hyperglycaemia, lactic acidosis (see section 4.4).

Psychiatric disorders:

Frequent: Insomnia.

Nervous system disorders:

Frequent: Headache, taste perversion (metallic taste), dizziness.

Less frequent: Convulsions (see section 4.4), hypoaesthesia, paraesthesia, serotonin syndrome (see sections 4.3 and 4.5), peripheral neuropathy (see section 4.4).

Eye disorders:

Less frequent: Blurred vision, changes in visual field defect (see section 4.4).

Frequency unknown: Optic neuropathy, optic neuritis, loss of vision, changes in visual acuity, changes in colour vision (see section 4.4).

Ear and labyrinth disorders:

Less frequent: Tinnitus.

Cardiac disorders:

Less frequent: Dysrhythmia (tachycardia).

Vascular disorders:

Less frequent: Transient ischaemic attacks, phlebitis, thrombophlebitis, hypertension, hypotension.

Gastrointestinal disorders:

Frequent: Diarrhoea, nausea, vomiting, localised or general abdominal pain.

Less frequent: Pancreatitis, gastritis, abdominal distention, dry mouth, glossitis, loose stools, stomatitis, tongue discolouration or disorder, constipation, dyspepsia, increased thirst, superficial tooth discolouration.

Hepatobiliary disorders:

Frequent: Abnormal liver function tests; increased AST, ALT or alkaline phosphatase.

Less frequent: Increased total bilirubin.

Skin and subcutaneous tissue disorders:

Less frequent: Pruritus, rash, urticaria, dermatitis, diaphoresis

Bullous skin disorders such as Stevens-Johnson syndrome and toxic epidermal necrolysis.

Frequency unknown: Alopecia.

Renal and urinary disorders:

Frequent: Increased BUN (blood urea)

Less frequent: Renal failure, increased creatinine, polyuria.

Reproductive system and breast disorders:

Less frequent: Vulvovaginal disorder.

General disorders and administration site conditions:	
Less frequent:	Fever, localised pain, chills, fatigue, injection site pain.
Investigations:	
Frequent:	**Chemistry:** Increased lactate dehydrogenase (LDH), creatine kinase, lipase, amylase or non-fasting glucose. Decreased total protein, albumin, sodium or calcium. Increased or decreased potassium or bicarbonate. **Haematology**: Increased neutrophils or eosinophils. Decreased haemoglobin, haematocrit or red blood cell count. Increased or decreased platelet or white blood cell counts.
Less frequent:	**Chemistry**: Increased sodium or calcium. Decreased non-fasting glucose. Increased or decreased chloride. **Haematology**: Increased reticulocyte count, decreased neutrophils.

Description of selected adverse reactions

The following adverse reactions to linezolid (as in LINOBACT IV) were considered to be serious in rare cases: localised abdominal pain, transient ischaemic attacks and hypertension.

Paediatric population

Safety data do not indicate that the safety profile of linezolid for paediatric patients differs from that for adult patients.

Reporting of suspected adverse reactions

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

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

4.9 Overdose

In overdose, side effects can be precipitated and/or be of increased severity, see section 4.8.

Supportive care is advised together with maintenance of glomerular filtration. Approximately 30 % of a LINOBACT IV dose is removed during 3 hours of haemodialysis, but no data are available for the removal of LINOBACT IV by peritoneal dialysis or haemoperfusion.

5. PHARMACOLOGICAL ACTION

5.1 Pharmacodynamic properties

A 20.1.1 Broad and medium spectrum antibiotics

Pharmacotherapeutic group: Other antibacterial, ATC code: J 01 X X 08

Mechanism of action

Linezolid is a synthetic antibiotic that belongs to the oxazolidinone class of antibiotics. It has *in vitro* activity against aerobic Gram-positive bacteria and anaerobic microorganisms. Linezolid selectively inhibits bacterial protein synthesis through binding to sites on the bacterial ribosome and prevents the formation of a functional 70S-initiation complex, which is a necessary component of the translation process.

Linezolid is not active against Gram-negative pathogens (see section 4.1).

Resistance:

Linezolid's mechanism of action differs from that of other antibiotics, e.g. the aminoglycosides, beta-lactams, folic acid antagonists, glycopeptides, lincosamides, quinolones, rifamycins, streptogramins, tetracyclines and chloramphenicol. Therefore, cross-resistance between linezolid and these classes of medicines is not expected.

In vitro studies showed that resistance to linezolid develops slowly via multiple step mutations in 23S ribosomal RNA and occurs at frequencies of less than 1×10^{-9} to 1×10^{-11}.

Resistant organisms:

Haemophilus influenzae

Enterobacteriaceae

Neisseria species

Pseudomonas species

5.2 Pharmacokinetic properties

Distribution:

The volume of distribution at steady-state is about 40 to 50 litres in healthy adults and approximates to total body water. Plasma protein binding is about 31 %.

Biotransformation:

Linezolid is metabolised by a non-enzymatic process. Metabolic oxidation of the morpholine ring results primarily in the formation of two inactive open-ring carboxylic acid derivatives. The hydroxyethyl glycine metabolite (B) is the predominant human metabolite and the amino ethoxy acetic acid metabolite (A) is less abundant. Linezolid is not detectably metabolised by cytochrome P450 (CYP) isoenzymes *in vitro* and it does not inhibit the activities of clinically significant human CYP isoforms (1A2, 2C9, 2C19, 2D6, 2E1, 3A4). Linezolid does not induce human CYP2C9.

Elimination:

Under steady-state conditions, linezolid is primarily excreted in the urine as metabolite B (40 %), parent compound (30 - 35 %) and metabolite A (10 %). The parent compound has a mean elimination half-life of 5-7 hours. Non-renal clearance accounts for approximately 65 % of the total clearance of linezolid.

Special populations

Elderly:

The pharmacokinetics of linezolid is not significantly altered in elderly patients aged 65 and over.

Renal insufficiency:

No dose adjustment is necessary in patients with either mild, moderate or severe renal insufficiency, as linezolid clearance is independent of creatinine clearance. There is evidence that the primary metabolites of linezolid accumulate in patients with severe renal insufficiency (i.e. CL_{CR} < 30 ml/min). The clinical significance of this has not been established. As approximately 30 % of a dose is removed during 3 hours of haemodialysis (beginning 3 hours after administration), LINOBACT IV should be given after dialysis in patients receiving such treatment.

Hepatic insufficiency:

The pharmacokinetics of linezolid are not altered in patients with mild to moderate hepatic insufficiency. Dose adjustment of LINOBACT IV in such patients is therefore not required. The pharmacokinetics of linezolid in patients with severe hepatic insufficiency have not been evaluated. However, as linezolid is metabolised by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism.

Children:

The pharmacokinetics of linezolid following a single IV dose were investigated in paediatric patients ranging in age from birth through 17 years (including premature and full-term neonates).

The C_{max} and the volume of distribution (V_{ss}) are similar, regardless of age in paediatric patients. However, clearance of linezolid varies as a function of age. With the exclusion of pre-term neonates less than one week of age, clearance is most rapid in the youngest age groups ranging from > 1 week old to 11 years, resulting in lower single-dose systemic exposure (AUC) and shorter half-life as compared with adults. As age of paediatric patients increases, the clearance of linezolid gradually decreases, and by adolescence mean clearance values

approach these observed for the adult population. There is wider inter-patient variability in linezolid clearance and systemic medicine exposure (AUC) across all paediatric age groups as compared with adults.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Glucose monohydrate

Sodium citrate (E331)

Citric acid anhydrous (E330)

Hydrochloric acid (E507)

Sodium hydroxide (E524)

Water for injection

6.2 Incompatibilities

Additives should not be introduced into this solution.

If LINOBACT IV solution for infusion is to be given concomitantly with another medicine, each medicine should be given separately, in accordance with the recommended dosage and route of administration for each product.

Similarly, if the same intravenous line is to be used for sequential infusion of several medicines, the line should be flushed prior to and following linezolid administration with a compatible infusion solution (see section 6.6).

LINOBACT IV solution for infusion is physically incompatible with the following medicines: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isethionate, phenytoin sodium, erythromycin lactobionate and trimethoprim-sulfamethoxazole. .

LINOBACT IV solution for infusion is chemically incompatible with ceftriaxone sodium.

6.3 Shelf life

Before opening: 24 months

After opening: From a microbiological point of view, unless the method of opening precludes the risk of microbial contamination, the product should be used immediately. If not used immediately, in-use storage times and conditions are the responsibility of the user.

6.4 Special precautions for storage

Store at room temperature, at or below 25 °C. Do not freeze.

Protect from light. The infusion bags must be kept in their foil overpouch, until ready to use.

For storage conditions after first opening of the LINOBACT IV, see section 6.3.

6.5 Nature and contents of the container

LINOBACT IV is packaged in a single-use plastic container-closure system (infusion bag) which consists of the following components and materials:

- One multi-layer co-extruded polyolefin plastic bag of 300 ml;
- One multi-layer co-extruded polyolefin plastic port tube;
- One gamma sterilised polyolefin twist-off connector.

Each single-dose infusion bag is imprinted with a hot stamp foil and sealed into a foil overpouch (secondary packaging).

Each bag contains 300 ml solution (600 mg linezolid) and is packaged in a carton box containing 1 or 10 bags.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The infusion bags are intended for single-use only. Discard any unused solution.

LINOBACT IV solution for infusion is supplied in single-use, ready-to-use infusion bags. Remove overpouch only when ready to use. Use LINOBACT IV solution for infusion immediately after breaking the seal.

Do not use the intravenous infusion bag in series connections and do not introduce additives into the intravenous solution.

Parenteral medicines should always be inspected visually for particulate matter prior to administration. Check for minute leaks by firmly squeezing the bag. If leaks are detected, discard the solution, as sterility may be impaired.

No special requirements for disposal. Any unused medicine or waste material should be disposed of in accordance with local requirements. Do not reconnect partially used bags.

Compatible solutions: sodium chloride 0,9 % *m/v* injection, dextrose 5 % *m/v* injection, Ringer's lactate injection.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Astral Pharma (Pty) Ltd

49 Riboville Road

Randjiesfontein

Midrand, 1683

South Africa

8. REGISTRATION NUMBER

Reg no: 56/20.1.1/0637

9. DATE OF FIRST AUTHORISATION/RENEWAL OF AUTHORISATION

21 November 2024

10. DATE OF REVISION OF THE TEXT

TBA