PROFESSIONAL INFORMATION FOR ZENILID IV

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ZENILID IV 600 mg/300 ml: (Solution for infusion)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZENILID IV 600 mg/300 ml: Each 1 mL contains 2 mg linezolid. The 300 mL infusion bag contains 600 mg linezolid.
Contains sugar: 50,24 mg/mL or 15 072 mg/300 mL glucose monohydrate.
Contains sodium: 1,64 mg/mL For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Solution for infusion.
Clear, colourless solution, practically free from particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZENILID IV 600 mg/300 ml is indicated for the treatment of the following infections caused by susceptible strains of the designated micro-organisms.
ZENILID IV 600 mg/300 ml 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 pneumoniae* (including multi-drug resistant *S. pneumoniae* (MDRSP) strains)
- **Complicated skin and skin structure infections** caused by *Staphylococcus aureus* (methicillin-susceptible and -resistant strains), *Streptococcus pyogenes*, or *Streptococcus agalactiae*. **ZENILID IV 600 mg/300 ml** has not been studied 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-drug 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 **ZENILID IV 600 mg/300 ml** 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:

Recommended Dosage:

ZENILID IV 600 mg/300 ml solution for infusion may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to oral presentation when clinically indicated. In such circumstances, no dose adjustment is required as the oral formulation has a bioavailability of approximately 100 %.
The recommended **ZENILID IV 600 mg/300 ml** dosage should be administered intravenously (IV) as described in the tables below.

Adult and adolescent (12 years and older):

Infections (including those associated with concurrent bacteraemia)	Dosage and route of administration	Duration of treatment
Community-acquired pneumonia, including concurrent bacteraemia	600 mg IV every 12 hours	10-14 consecutive days
Nosocomial pneumonia, including concurrent bacteraemia		
Skin and soft tissue infections, including concurrent bacteraemia	600 mg IV every 12 hours depending on clinical severity	
Enterococcal infections, including vancomycin-resistant infections, and those with concurrent bacteraemia	600 mg IV every 12 hours	14-28 consecutive days

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 younger than 7 days old (gestational age less than 34 weeks) have lower systemic **ZENILID IV 600 mg/300 ml** clearance values and larger systemic exposure/ area under the curve (AUC) values than many full-term neonates and older infants. By day 7 of age, **ZENILID IV 600 mg/300 ml** clearance and AUC values are similar to those of full-term neonates and older infants.

Special populations:

Elderly patients:
No dose adjustment is necessary.

Patients with renal insufficiency:
No dose adjustment is required.

Patients with severe renal insufficiency (i.e., CLCR < 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 **ZENILID IV 600 mg/300 ml** in patients with severe renal insufficiency, **ZENILID IV 600 mg/300 ml** should be used with special caution in these patients and only when the anticipated benefit is considered to outweigh the theoretical risk.
As approximately 30 % of a **ZENILID IV 600 mg/300 ml** dose is removed during 3 hours of haemodialysis, **ZENILID IV 600 mg/300 ml** should be given after dialysis in patients receiving such treatment. The primary metabolites of **ZENILID IV 600 mg/300 ml** 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, **ZENILID IV 600 mg/300 ml** 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.
To date, there is no experience of **ZENILID IV 600 mg/300 ml** 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 **ZENILID IV 600 mg/300 ml** should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk.

Method of administration:
ZENILID IV 600 mg/300 ml is given by intravenous infusion.
The solution for infusion should be administered over a period of 30-120 minutes.
For instructions on administration and other handling, see *section 6.6*.

4.3 Contraindications

- **ZENILID IV 600 mg/300 ml** is contraindicated for use in patients who have known hypersensitivity to linezolid or any of the excipients (see *section 6.1*).
- **Monoamine Oxidase Inhibitors (MAOI's)**
  ZENILID IV 600 mg/300 ml should not be used in patients taking any medicine which inhibits monoamine oxidase (e.g. phenelzine, isocarboxazid) or within two weeks of taking any such medicine.
- **Potential interactions producing elevation of blood pressure**
  Unless patients are monitored for potential increases in blood pressure, **ZENILID IV 600 mg/300 ml** should not be administered to patients with uncontrolled hypertension, pheochromocytoma, hyperthyroidism and/ or patients taking any of the following types of medications: 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, **ZENILID IV 600 mg/300 ml** should not be administered to patients with carcinoid syndrome and/ or patients taking any of the following medications: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT_1 receptor agonists (triptans), meperidine or buspirone (see *section 4.5*).

4.4 Special warnings and precautions for use
Prescribers must adhere to the principles of antibiotic stewardship

Antibiotic-associated diarrhoea and pseudomembranous colitis
Pseudomembranous colitis has been reported with **ZENILID IV 600 mg/300 ml** 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 this antibacterial agent.

Clostridium difficile associated diarrhoea (CDAD) has been reported with **ZENILID IV 600 mg/300 ml** and may range in severity from mild diarrhoea to fatal colitis. Treatment with **ZENILID IV 600 mg/300 ml** alters the normal flora of the colon leading to overgrowth of *C. 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. Medicines inhibiting peristalsis should not be used in this situation. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

Myelosuppression

Reversible myelosuppression (including anaemia, thrombocytopenia, leukopenia, and pancytopenia) that may be dependent on duration of therapy has been reported in some patients receiving **ZENILID IV 600 mg/300 ml**. Therefore, close monitoring of blood counts is recommended in patients who: have pre-existing anaemia, granulocytopenia or thrombocytopenia; are receiving concomitant medications that may decrease haemoglobin levels, depress blood counts or adversely affect platelet count or function; have severe renal insufficiency; receive more than 14 days of therapy. **ZENILID IV 600 mg/300 ml** should be administered to such patients only when close monitoring of haemoglobin levels, blood counts and platelet counts is possible. In addition, it is recommended that complete blood counts (including haemoglobin levels, platelet counts and total and differentiated leucocyte counts) should be monitored on a weekly basis regardless of baseline count.

In cases where the outcome is known, when **ZENILID IV 600 mg/300 ml** was discontinued, the affected haematologic parameters have risen toward pre-treatment levels. The risk of these effects appears to be related to the duration of treatment. Elderly patients treated with **ZENILID IV 600 mg/300 ml** may be at greater risk of experiencing blood dyscrasias than younger patients.

Thrombocytopenia may occur more commonly in patients with severe renal insufficiency, whether or not on dialysis.
If significant myelosuppression occurs during Z**ENILID IV 600 mg/300 ml** therapy, treatment should be stopped unless it is considered absolutely necessary to continue therapy, in which case intensive monitoring of blood counts and appropriate management strategies should be implemented.

Peripheral and optic neuropathy

Peripheral neuropathy, optic neuropathy and optic neuritis sometimes progressing to loss of vision, have been reported in patients treated with **ZENILID IV 600 mg/300 ml**. 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 **ZENILID IV 600 mg/300 ml** 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 taking **ZENILID IV 600 mg/300 ml** for extended periods (greater than or equal to 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with **ZENILID IV 600 mg/300 ml**. If peripheral or optic neuropathy occurs, the continued use of **ZENILID IV 600 mg/300 ml** in these patients should be weighed against the potential risks.

Lactic acidosis

Lactic acidosis has been reported with the use of **ZENILID IV 600 mg/300 ml**. Patients who develop signs and symptoms of metabolic acidosis including recurrent nausea or vomiting, abdominal pain, a low bicarbonate level or hyperventilation while receiving **ZENILID IV 600 mg/300 ml** should receive immediate medical attention. If lactic acidosis occurs, the benefits of continued use of **ZENILID IV 600 mg/300 ml** should be weighed against the potential risks.

Convulsions

Convulsions have been reported to occur in patients when treated with **ZENILID IV 600 mg/300 ml**. In some of these cases, a history of seizures or risk factors for seizures were reported.

Gram negative pathogens

ZENILID IV 600 mg/300 ml has no clinical activity against Gram-negative pathogens and is not indicated for the treatment of Gram-negative infections. Specific Gram-negative therapy is required if a concomitant Gram-negative pathogen is documented or suspected. **ZENILID IV 600 mg/300 ml** 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. **ZENILID IV 600 mg/300 ml** is not approved for the treatment of patients with catheter-related bloodstream infections.
In complicated skin and soft tissue infections **ZENILID IV 600 mg/300 ml** should only be used in patients with known or possible co-infection with Gram-negative organisms if there are no alternative treatment options available (see *section 4.1*). In these circumstances treatment against Gram-negative organisms must be initiated concomitantly.

Superinfections

The effects of **ZENILID IV 600 mg/300 ml** therapy on normal flora have not been evaluated in clinical trials.
The use of antibiotics may occasionally result in an overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

Duration of treatment

The safety and effectiveness of **ZENILID IV 600 mg/300 ml** when administered for periods longer than 28 days have not been established.

Renal insufficiency

ZENILID IV 600 mg/300 ml should be used with special caution in patients with severe renal insufficiency and only when the anticipated benefit is considered to outweigh the theoretical risk.

Hepatic insufficiency

It is recommended that **ZENILID IV 600 mg/300 ml** should not be used in patients with severe hepatic insufficiency.

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of **ZENILID IV 600 mg/300 ml** and serotonergic medicines including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported. Co-administration of **ZENILID IV 600 mg/300 ml** and serotonergic medicines is therefore contraindicated (see *section 4.3*) except where administration of **ZENILID IV 600 mg/300 ml** 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.

Use with tyramine-rich foods
Patients should be advised against consuming large amounts of tyramine-rich foods (see *section 4.5*).

Excipients

Glucose
ZENILID IV 600 mg/300 ml contains glucose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not be given **ZENILID IV 600 mg/300 ml**.

Sodium
ZENILID IV 600 mg/300 ml contains more than 17 mmol (391 mg) sodium in the dose. To be taken into consideration by patients on a controlled sodium diet.

4.5 Interaction with other medicines and other forms of interaction

Medicines metabolised by cytochrome P450
ZENILID IV 600 mg/300 ml 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 drug interactions are expected. Medicines such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with **ZENILID IV 600 mg/300 ml** without changes in dosage regimen.
No interactions have been observed in pharmacokinetic studies with either aztreonam or gentamicin.

Monoamine oxidase inhibitors
ZENILID IV 600 mg/300 ml is a reversible, non-selective MAOI. Clinical studies have shown that it produces a mild, reversible enhancement of the pressor responses induced by pseudoephedrine and phenylpropanolamine hydrochloride. Thus, the potential for interaction with sympathomimetic or adrenergic agents should be considered and doses of compounds, such as dopamine or adrenalin, should be titrated to achieve the desired response.

Use with tyramine-rich foods
No significant pressor response was observed in subjects receiving both **ZENILID IV 600 mg/300 ml** and less than 100 mg tyramine. This suggests that it is only necessary to avoid ingesting large amounts of food and beverages with a high tyramine content (e.g. mature cheese, yeast extracts, undistilled alcoholic beverages and fermented soya bean products such as soy sauce).

Potential serotonergic interactions
Although **ZENILID IV 600 mg/300 ml** has the potential for interaction with serotonergic agents, no serotonin effects (e.g. confusion, delirium, restlessness, tremors, blushing, diaphoresis and hyperpyrexia) were observed in subjects receiving linezolid and dextromethorphan.

Spontaneous reports of serotonin syndrome associated with the co-administration of **ZENILID IV 600 mg/300 ml** and serotonergic agents, including antidepressants such as SSRIs have been reported.

Where administration of **ZENILID IV 600 mg/300 ml** and concomitant serotonergic agents 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 physicians should consider discontinuation of either one or both agents. If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed.

Rifampicin
The mechanism of this interaction and its clinical significance are unknown.

Aztreonam and gentamycin
No interactions have been observed in pharmacokinetic studies with either aztreonam or gentamicin.

4.6 Fertility, pregnancy and lactation

Pregnancy:
The safety of **ZENILID IV 600 mg/300 ml** in pregnancy and lactation has not been demonstrated.
There are limited data from the use of **ZENILID IV 600 mg/300 ml** in pregnant women. Studies in animals have shown reproductive toxicity. A potential risk for humans exists.

Lactation:
Animal data suggest that linezolid and its metabolites may pass into breast milk and, accordingly, breastfeeding should be discontinued prior to and throughout administration of **ZENILID IV 600 mg/300 ml**.

Fertility:
In animal studies linezolid caused a reduction in fertility. The possible effects of **ZENILID IV 600 mg/300 ml** on the human male reproductive system are not known.

4.7 Effects on ability to drive and use machines
Patients should be warned about the potential for dizziness or symptoms of visual impairment while receiving **ZENILID IV 600 mg/300 ml** and should be advised not to drive or operate machinery if any of these symptoms occurs.

4.8 Undesirable effects
a. Summary of the safety profile
The adverse effects most frequently reported were headache, diarrhoea, nausea, vomiting, metallic taste, abnormal liver function tests and vaginal candidiasis.

b. Tabulated summary of adverse reactions

MedDRA SOC	Frequency	Adverse events
Infections and infestations	Frequent	candidiasis (including oral and vaginal), fungal infections
	Less frequent	vaginitis, antibiotic-associated colitis, including pseudomembranous colitis*
Blood and lymphatic system disorders	Frequent	anaemia*
	Less frequent	eosinophilia, leukopenia*, neutropenia, thrombocytopenia, pancytopenia
	Unknown	myelosuppression*, sideroblastic anaemia*
Immune system disorders	Unknown	anaphylaxis
Metabolism and nutrition disorders	Less frequent	increased serum creatine phosphokinase, hyperglycaemia, lactic acidosis*, hyponatraemia
Psychiatric disorders	Frequent	insomnia
Nervous system disorders	Frequent	headache, taste perversion (metallic taste), dizziness
	Less frequent	hypoaesthesia, paraesthesia, peripheral neuropathy*, convulsions*
	Unknown	serotonin syndrome**
Eye disorders	Less frequent	blurred vision* optic neuropathy*, changes in visual field defect*
	Unknown	optic neuritis*, loss of vision*, changes in visual acuity*, changes in colour vision*
Ear and labyrinth disorders	Less frequent	tinnitus
Cardiac disorders	Less frequent	hypotension, tachycardia, dysrhythmia
Vascular disorders	Frequent	hypertension
	Less frequent	transient ischaemic attacks, phlebitis, thrombophlebitis
Gastrointestinal disorders	Frequent	localised or general abdominal pain, cramps or distension, diarrhoea, nausea, vomiting, constipation, dyspepsia
	Less frequent	dry mouth, gastritis, increased thirst, pancreatitis, stomatitis, tongue discolouration or disorder, superficial tooth discolouration glossitis
Hepatobiliary disorders	Frequent	abnormal liver function test; increased AST, ALT or alkaline phosphatase
	Less frequent	increased total bilirubin
Skin and subcutaneous tissue disorders	Frequent	pruritus, rash
	Less frequent	dermatitis, diaphoresis, urticaria, angioedema, bullous skin disorders such as Stevens Johnson syndrome
	Unknown	toxic epidermal necrolysis, alopecia
Renal and urinary disorders	Frequent	increased BUN
	Less frequent	renal failure, polyuria
Reproductive system and breast disorders	Less frequent	vulvovaginal disorder
General disorders and administration site disorders	Frequent	fever, localised pain
	Less frequent	injection site pain, chills, fatigue, phlebitis
Investigations	Frequent	Chemistry: Increased LDH, creatine kinase, lipase, amylase. Decreased total protein, albumin or calcium. Increased or decreased potassium or bicarbonate Haematology: Increased neutrophils. Decreased haemoglobin or haematocrit. Increased or decreased platelet or white blood cell counts.
	Less frequent	Chemistry: Increased sodium, creatinine or calcium. Decreased non fasting glucose. Increased or decreased chloride Haematology: Increased reticulocyte count.

* See *section 4.4.* ** See *sections 4.3* and *4.5.*

Paediatric population
Safety data from clinical studies on paediatric patients (from birth to 17 years) do not indicate that the safety profile of **ZENILID IV 600 mg/300 ml** 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. 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
No specific antidote is known.
No cases of overdose with **ZENILID IV 600 mg/300 ml** have been reported. However, the following information may prove useful: Supportive care is advised together with maintenance of glomerular filtration. Approximately 30 % of a **ZENILID IV 600 mg/300 ml** dose is removed during 3 hours of haemodialysis, but no data are available for the removal of ZENILID IV 600 mg/300 ml by peritoneal dialysis or haemoperfusion. The two primary metabolites of linezolid are also removed to some extent by haemodialysis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
A 20.1.1 Broad and medium spectrum antibiotics
Linezolid is a synthetic antibacterial agent of the oxazolidinone class of antibiotics (antimicrobials). It has *in vitro* activity against aerobic Gram-positive bacteria and anaerobic microorganisms. It selectively inhibits bacterial protein synthesis. Specifically, it binds to a site on the bacterial ribosome (23S of the 50S subunit) and prevents the formation of a functional 70S initiation complex that is an essential component of the translation process.

The *in vitro* post-antibiotic effect (PAE) of linezolid for *Staphylococcus aureus* was approximately 2 hours. When measured in animal models, the *in vivo* PAEs were 3,6 and 3,9 hours for *Staphylococcus aureus* and *Streptococcus pneumoniae*, respectively. In animal studies, the key pharmacodynamic parameter for efficacy was the time that the linezolid plasma levels exceeded the minimum inhibitory concentration (MIC) of the infecting organism. Linezolid was efficacious when plasma levels exceeded the MIC of the infecting organism for a minimum of 40 % of the dosing interval.

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 local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.

Resistant organisms
Haemophilus influenzae
Enterobacteriaceae
Neisseria species
Pseudomonas species
Moraxella catarrhalis

Resistance

Cross 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, there is no cross-resistance between linezolid and these classes of medicines.

In vitro studies with clinical isolates (including methicillin-resistant staphylococci, vancomycin-resistant enterococci and penicillin- and erythromycin-resistant streptococci) indicate that linezolid is usually active against organisms which are resistant to one or more other classes of antimicrobial agents.

As documented with other antibiotics when used in patients with difficult to treat infections and/ or for prolonged periods, emergent decreases in susceptibility have been observed with linezolid. Resistance to linezolid has been reported in enterococci, *Staphylococcus aureus* and coagulase negative staphylococci. This generally has been associated with prolonged courses of therapy and the presence of prosthetic materials or undrained abscesses. When antibiotic-resistant organisms are encountered in the hospital, it is important to emphasise infection control policies.

5.2 Pharmacokinetic properties
ZENILID IV 600 mg/300 ml primarily contains linezolid that is biologically active and is metabolised to form inactive metabolites. The aqueous solubility of linezolid is approximately 3 mg/mL and is independent of pH between pH 3-9.

Absorption
Maximum plasma concentrations are reached within 2 hours of dosing.
Plasma linezolid C_{max} and C_{min} (mean and [SD]) at steady state following twice daily intravenous dosing of 600 mg have been determined to be 15,1 [2,5] mg/L and 3,68 [2,68] mg/L, respectively.

Distribution
The volume of distribution at steady state averages at about 40-50 litres in healthy adults and approximates to total body water. Plasma protein binding is about 31 % and is not concentration dependent.
Linezolid concentrations have been determined in various fluids from a limited number of subjects in volunteer studies following multiple dosing. The ratio of linezolid in saliva and sweat relative to plasma was 1,2:1,0 and 0,55:1,0 respectively. The ratio for epithelial lining fluid and alveolar cells of the lung was 4,5:1,0 and 0,15:1,0, when measured at steady-state C_{max} respectively.
In a small study of subjects with ventricular peritoneal shunts and essentially non-inflamed meninges, the ratio of linezolid in cerebrospinal fluid to plasma at C_{max} was 0,7:1,0 after linezolid dosing.

Biotransformation
Linezolid is metabolised by a non-enzymatic process. Metabolic oxidation of the morpholine ring results primarily in two inactive open-ring carboxylic acid derivatives. The hydroxyethyl glycine metabolite (PNU-142586) is the predominant human metabolite and is believed to be formed by a non-enzymatic process and the amino ethoxy acetic acid metabolite (PNU-142300) is less abundant. Other minor, inactive metabolites have been characterised.

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 significantly induce major cytochrome P450 isoenzymes in rats and does not induce human CYP2C9.

Elimination
In patients with normal renal function or mild to moderate renal insufficiency, linezolid is primarily excreted under steady-state conditions in the urine as PNU-142586 (40 %), parent drug (30 %) and PNU-142300 (10 %). Virtually no parent drug is found in the faeces whilst approximately 6 % and 3 % of each dose appears as PNU-142586 and PNU-142300, respectively.

The elimination half-life of the parent drug averages at about 5-7 hours.
Non-renal clearance accounts for approximately 65 % of the total clearance of linezolid. A small degree of non-linearity in clearance is observed with increasing doses of linezolid. This appears to be due to lower renal and non-renal clearance at higher linezolid concentrations. However, the difference in clearance is small and is not reflected in the apparent elimination half-life.

Special populations

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

Renal insufficiency
After single doses of 600 mg, there was a 7-8-fold increase in exposure to the two primary metabolites of linezolid in the plasma of patients with severe renal insufficiency (i.e. creatinine clearance < 30 mL/min). However, there was no increase in AUC of parent drug. Although there is some removal of the major metabolites of linezolid by haemodialysis, metabolite plasma levels after single 600 mg doses were still considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

Hepatic insufficiency
The pharmacokinetics of linezolid are not altered in patients with mild to moderate hepatic insufficiency. Dose adjustment in such patients is, therefore, not required.
Limited data indicate that the pharmacokinetics of linezolid, PNU-142300 and PNU-142586 are not altered in patients with mild to moderate hepatic insufficiency (i.e. Child-Pugh class A or B). The pharmacokinetics of linezolid in patients with severe hepatic insufficiency (i.e. Child-Pugh class C) 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 (see *section 4.2* and *4.4*).

Paediatric patients
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. Pharmacokinetic studies indicate that after single and multiple doses in children (1 week to 12 years), linezolid clearance (based on kg body weight) was greater in paediatric patients than in adults but decreased with increasing age.

In children 1 week to 12 years old, administration of 10 mg/kg every 8 hours daily gave exposure approximating to that achieved with 600 mg twice daily in adults.
In neonates up to 1 week of age, the systemic clearance of linezolid (based on kg body weight) increases rapidly in the first week of life. Therefore, neonates given 10 mg/kg every 8 hours daily will have the greatest systemic exposure on the first day after delivery. However, excessive accumulation is not expected with this dosage regimen during the first week of life as clearance increases rapidly over that period.
In adolescents (12-17 years old), linezolid pharmacokinetics were similar to that in adults following a 600 mg dose. Therefore, adolescents administered 600 mg every 12 hours daily will have similar exposure to that observed in adults receiving the same dosage.

In paediatric patients with ventriculoperitoneal shunts who were administered linezolid 10mg/kg either 12 hourly or 8 hourly, variable cerebrospinal fluid (CSF) linezolid concentrations were observed following either single or multiple dosing of linezolid. Therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empirical treatment of paediatric patients with central nervous system infections is not recommended.

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-subject variability in linezolid clearance and systemic drug exposure across all paediatric age groups as compared with adults.

Female patients
Females have a slightly lower volume of distribution than males and the mean clearance is reduced by approximately 20 % when corrected for body weight. Plasma concentrations are higher in females and this can partly be attributed to body weight differences. However, because the mean half-life of linezolid is not significantly different in males and females, plasma concentrations in females are not expected to substantially rise above those known to be well tolerated and, therefore, dose adjustments are not required.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Anhydrous citric acid, glucose monohydrate, hydrochloric acid, sodium citrate, dehydrate, sodium hydroxide, water for injection.

6.2 Incompatibilities
- DO NOT use the intravenous infusion bag in series connections.
- DO NOT introduce additives into the IV solution. If **ZENILID IV 600 mg/300 ml** solution for infusion is to be given concomitantly with another drug, each drug should be given separately, in accordance with the recommended dosage and route of administration for each product.

- If the same IV line is to be used for sequential infusion of several drugs, the line should be flushed prior to and following linezolid administration with a compatible infusion solution (see *section 6.6*).
- DO NOT administer with the following medicines: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isethionate, phenytoin sodium, erythromycin lactobionate and trimethoprim-sulfamethoxazole
- DO NOT combine with ceftriaxone sodium, as it is physically incompatible.

6.3 Shelf life
36 months

6.4 Special precautions for storage
Store at or below 25 °C. This medicinal product does not require any special temperature storage conditions; keep the polyethylene container in the outer carton in order to protect from light.

6.5 Nature and contents of container
The 300 mL **ZENILID IV 600 mg/300 m**l solution for infusion is filled into polyethylene bags and then packed into carboard boxes.

6.6 Special precautions for disposal and other handling
ZENILID IV 600 mg/300 ml solution for infusion must be used immediately after the seal is first broken. **ZENILID IV 600 mg/300 ml** parenteral drug products should 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.

Instructions for use/ handling:

Intravenous administration:
ZENILID IV 600 mg/300 ml solution for infusion must be used immediately after the seal is first broken. **ZENILID IV 600 mg/300 ml** solution for infusion is supplied in single-use, ready-to-use infusion bags. Parenteral medicinaldrug products should 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.

Administer **ZENILID IV 600 mg/300 ml** solution for infusion over a period of 30-120 minutes. Do not use the intravenous infusion bag in series connections. Do not introduce additives into the intravenous solution. If **ZENILID IV 600 mg/300 ml** 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.

Compatibilities:
Compatible infusion solutions: 0,9 % sodium chloride injection, 5 % dextrose injection, lactated ringer's injection.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Glenmark Pharmaceuticals South Africa (Pty) Ltd
34 Monte Carlo Crescent,
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8. REGISTRATION NUMBER(S)

50/20.1.1/0184

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

6 July 2021

10. DATE OF REVISION OF THE TEXT

11 December 2020