SCHEDULING STATUS: S4

1. NAME OF THE MEDICINE

ZYVOXID® 600 mg Tablets

ZYVOXID® 200 mg/100 mL Solution for infusion

ZYVOXID® 600 mg/300 mL Solution for infusion

ZYVOXID® 20 mg/mL Granules for suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ZYVOXID 600 mg Tablets: Each film-coated tablet contains 600 mg linezolid.

ZYVOXID 200 mg/100 mL Solution for infusion: Each 1 mL contains 2 mg linezolid. The 100 mL infusion bag contains 200 mg linezolid.

ZYVOXID 600 mg/300 mL Solution for infusion: Each 1 mL contains 2 mg linezolid. The 300 mL infusion bag contains 600 mg linezolid.

ZYVOXID 20 mg/mL Granules for suspension: Following reconstitution with 123 mL water, each 1 mL contains 20 mg linezolid. Preservative content: Sodium benzoate 0,2 % m/v.

ZYVOXID solution for injection infusion contains sugar (dextrose monohydrate).

ZYVOXID granules for suspension contains sugar (sucrose, fructose, and the sweetener aspartame).

Excipient(s) with known effect

ZYVOXID solution for infusion contains 50,24 mg per mL of sugar (dextrose monohydrate)

ZYVOXID granules for suspension contains sugar [sucrose (1052,9 mg per 5 mL), fructose (500 mg/5 mL) and 35 mg per 5 mL of the sweetener aspartame.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

- Tablets
- Solution for infusion
- Granules for suspension

ZYVOXID 600 mg Tablets

A white to off-white coated tablet with 'ZYV' debossed on one side and '600' debossed on the other side.

ZYVOXID Solution for infusion

A ready-to-use infusion bag containing a clear, colourless to yellow solution free of visible particles.

ZYVOXID Granules for suspension

A white to yellow-orange granule/powder, may contain white to yellow-orange lumps. The constituted suspension appears as a white to yellow-orange homogeneous suspension.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

ZYVOXID formulations are indicated for the treatment of patients with the following infections caused by susceptible strains of the designated Gram-positive microorganisms (see section 5). **ZYVOXID 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-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*. ZYVOXID 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 ZYVOXID in the outpatient setting.

Prescribers should adhere to the principles of antibiotic stewardship.

Appropriate specimens for bacteriological examination should be obtained in order to isolate and identify the causative organisms and to determine their susceptibility to ZYVOXID. 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

ZYVOXID tablets, oral suspension or solution for infusion may be used as initial therapy. Patients who commence treatment on the parenteral formulation may be switched to either oral presentation when clinically indicated. In such circumstances, no dose adjustment is required as ZYVOXID has an oral bioavailability of approximately 100 %.

The solution for infusion should be administered over a period of 30 to 120 minutes.

The film-coated tablets or oral suspension may be taken with or without food.

The recommended ZYVOXID dosage should be administered IV or orally as described in the tables below.

In the treatment of beta-haemolytic streptococcal infections, a therapeutic dose should be administered for at least 10 days.

Adult and adolescent (12 years and older) patients

Infections (including those associated with concurrent bacteraemia)	***Dosage and route of administration***	***Recommended duration of treatment***
Community-acquired pneumonia, including concurrent bacteraemia	600 mg IV or orally* every 12 hours	10 – 14 consecutive days
Nosocomial pneumonia, including concurrent bacteraemia		
Skin and soft tissue infections, including concurrent bacteraemia	400 mg to 600 mg orally* every 12 hours or 600 mg IV every 12 hours depending on clinical severity	

Enterococcus infections, including vancomycin-resistant infections, and those with concurrent bacteraemia	600 mg IV or orally* every 12 hours	14 – 28 consecutive days
* Oral dosing either ZYVOXID tablets or oral suspension		

Paediatric patients (birth* through to 11 years)

Infections (including those associated with concurrent bacteraemia)	***Dosage and route of administration***	***Recommended duration of treatment***
Community-acquired pneumonia, including concurrent bacteraemia	10 mg/kg IV or oral$^{\delta}$ every 8 hours	10 – 14 consecutive days
Nosocomial pneumonia, including concurrent bacteraemia		
Skin and soft tissue infections, including concurrent bacteraemia		
Enterococcus infections, including vancomycin-resistant infections, and those with concurrent bacteraemia	10 mg/kg IV or oral$^{\delta}$ 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 ZYVOXID clearance values and larger AUC values than many full-term neonates and older infants. By day 7 of age, ZYVOXID clearance and AUC values are similar to those of full-term neonates and older infants $^{\delta}$Oral dosing using either ZYVOXID tablets or oral suspension

Special populations

Elderly patients

No dose adjustment is required.

Patients with renal insufficiency

No dose adjustment is required (see section 5.2).

Patients with severe renal insufficiency (i.e. 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 ZYVOXID in patients with severe renal insufficiency, ZYVOXID 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 ZYVOXID dose is removed during 3 hours of haemodialysis, ZYVOXID should be given after dialysis in patients receiving such treatment. The primary metabolites of ZYVOXID are removed to some extent by haemodialysis, but the concentrations of these metabolites are still very considerably higher following dialysis than those observed in patients with normal renal function or mild to moderate renal insufficiency.

Therefore, ZYVOXID 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 ZYVOXID 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 ZYVOXID should be used in such patients only when the anticipated benefit is considered to outweigh the theoretical risk (see section 5.2).

Method of administration

Instructions for use/handling

Intravenous administration:

ZYVOXID solution for infusion must be used immediately after the seal is first broken. ZYVOXID solution for infusion is supplied in single-use, ready-to-use infusion bags. Parenteral medicines 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 ZYVOXID solution for infusion over a period of 30 to 120 minutes.

Do not use the intravenous infusion bag in series connections.

Do not introduce additives into the intravenous solution.

If ZYVOXID 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 medicine.

ZYVOXID solution for infusion was physically incompatible with the following medicines when combined in simulated Y-site administration: amphotericin B, chlorpromazine HCl, diazepam, pentamidine isethionate, phenytoin sodium, erythromycin lactobionate and trimethoprim-sulfamethoxazole.

ZYVOXID solution for infusion was chemically incompatible when combined with ceftriaxone sodium.

Compatible infusion solutions

0,9 % Sodium Chloride Injection

5 % Dextrose Injection

Lactated Ringer's Injection

For instructions on constitution of ZYVOXID granules for suspension before administration, see section 6.6.

4.3 Contraindications

ZYVOXID formulations are contraindicated for use in patients with known hypersensitivity to linezolid or any excipients listed in section 6.1.

Monoamine oxidase inhibitors

ZYVOXID 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.

Potential interactions producing elevation of blood pressure

Unless patients are monitored for potential increases in blood pressure, ZYVOXID 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, ZYVOXID should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medicines: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5 - HT1 receptor agonists (triptans), meperidine or buspirone (see section 4.5).

4.4 Special warnings and precautions for use

Reversible myelosuppression (anaemia, thrombocytopenia**,** leukopenia, and pancytopenia) that may be dependent on duration of therapy has been reported in some patients receiving ZYVOXID.

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 medications that may decrease haemoglobin levels or platelet count or function, or who receive ZYVOXID for more than 2 weeks.

Pseudomembranous colitis has been reported with ZYVOXID 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 medicine.

Clostridium difficile associated diarrhoea (CDAD) has been reported with ZYVOXID and may range in severity from mild diarrhoea to fatal colitis. Treatment with ZYVOXID 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. CDAD must be considered in all patients who present with diarrhoea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial medicines.

Peripheral neuropathy and optic neuropathy have been reported in patients treated with ZYVOXID, primarily those patients treated for longer than the maximum recommended duration of 28 days. 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 ZYVOXID 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 ZYVOXID for extended periods (greater than or equal to 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with ZYVOXID. If peripheral or optic neuropathy occurs treatment with ZYVOXID should be discontinued.

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

Convulsions have been reported to occur in patients when treated with ZYVOXID. In most of these cases, a history of seizures or risk factors for seizures were reported.

ZYVOXID 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. ZYVOXID 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. ZYVOXID is not approved for the treatment of patients with catheter-related bloodstream infections.

The use of antibiotics may result in an overgrowth of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken.

The safety and effectiveness of ZYVOXID when administered for periods longer than 28 days have not been established.

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

ZYVOXID 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.

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

Pharmacokinetic information generated in paediatric patients with ventriculoperitoneal shunts showed variable cerebrospinal fluid (CSF) linezolid concentrations following single and multiple dosing of linezolid; therapeutic concentrations were not consistently achieved or maintained in the CSF. Therefore, the use of linezolid for the empiric treatment of paediatric patients with central nervous system infections is not recommended.

Fructose/sucrose

ZYVOXID granules for suspension contain fructose. Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency, glucose-galactose malabsorption or fructose intolerance should not take ZYVOXID granules for suspension.

ZYVOXID granules for suspension contain sucrose. Patients with rare hereditary conditions such as fructose intolerance, glucose-galactose malabsorption or sucrase-isomaltase insufficiency should not take ZYVOXID granules for suspension.

Contains sucrose, dextrose and fructose which may have an effect on the glycaemic control of patients with diabetes mellitus.

ZYVOXID Infusion contains glucose which may have an effect on the control of your blood sugar if you have diabetes mellitus.

4.5 Interaction with other medicines and other forms of interaction

ZYVOXID 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 ZYVOXID without changes in dosage regimen.

ZYVOXID is a reversible, non-selective monoamine oxidase inhibitor (MAOI). Therefore, some patients receiving ZYVOXID may experience a reversible enhancement of the pressor response induced by pseudoephedrine HCl or phenylpropanolamine HCl. Thus, the potential for interaction with sympathomimetic or adrenergic medicines should be considered and initial doses of compounds, such as dopamine or adrenaline, should be reduced and titrated to achieve the desired response (see section 4.3).

No significant pressor response was observed in subjects receiving both ZYVOXID 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).

Although ZYVOXID has the potential for interaction with serotonergic medicines, 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 ZYVOXID and serotonergic medicines, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) have been reported.

Where administration of ZYVOXID 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.

In healthy volunteers, co-administration of rifampicin with ZYVOXID resulted in a 21 % decrease in linezolid C_{max} and a 32 % decrease in linezolid AUC. The mechanism of this interaction and its clinical significance are unknown.

Spontaneous reports of serotonin syndrome with co-administration of ZYVOXID and serotonergic medicines have been reported (see section 4.4).

Antibiotics

The pharmacokinetics of ZYVOXID were not altered when administered together with either aztreonam or gentamicin.

The effect of rifampicin on the pharmacokinetics of ZYVOXID was studied in sixteen healthy adult male volunteers administered ZYVOXID 600 mg twice daily for 2,5 days with and without rifampicin 600 mg once daily for 8 days. Rifampicin decreased the linezolid C_{max} and AUC by a mean 21 % (90 % CI, 15, 27) and a mean 32 % (90 % CI, 27, 37), respectively. The mechanism of this interaction and its clinical significance are unknown (see section 4.4).

4.6 Fertility, pregnancy and lactation

The use of ZYVOXID formulations in pregnancy and lactation is contraindicated, as safety has not been demonstrated.

Fertility

In animal studies, ZYVOXID caused a reduction in fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Undesirable effects

Approximately 22 % of patients experienced adverse reactions.

Frequency terminology: Very common (≥ 1/10); Common (≥1/100 to <1/10); Uncommon (≥ 1/1 000 to <1/100); Rare (≥ 1/10 000 to <1/1 000); Very rare (<1/10 000), including isolated reports.

Table 1: Side effects reported in clinical trials

System organ class	**Frequency**	**Side effect**
Infections and infestations	Common	Moniliasis[+] or fungal infections

Blood and lymphatic system disorders	Uncommon	Eosinophilia, neutropenia
Metabolism and nutrition disorders	Uncommon	Increased serum creatine phosphokinase, hyperglycaemia
Nervous system disorders	Common	Headache[+], taste alteration[+]
	Uncommon	Dizziness, hypoaesthesia, insomnia, paraesthesia
Special senses	Common	Metallic taste
	Uncommon	Blurred vision, tinnitus
Cardiac disorders	Uncommon	Hypertension, hypotension
Gastrointestinal disorders	Common	Abdominal pain[+], cramps[+] or distension[+], diarrhoea[+], nausea[+], vomiting[+]
	Uncommon	Constipation, dry mouth, dyspepsia, gastritis, increased thirst, pancreatitis, stomatitis
Skin and subcutaneous tissue disorders	Uncommon	Dermatitis, diaphoresis, pruritus, urticaria
Urogenital disorders	Common	Vaginal moniliasis
	Uncommon	Vulvovaginal disorder, polyuria, vaginitis

General disorders and administration site conditions	Uncommon	Chills, fatigue, fever, injection site pain, phlebitis/ thrombophlebitis, localised pain
Investigations	Common	Chemistry: Increased total bilirubin, AST, ALT, LDH, alkaline phosphatase, BUN, creatine kinase, lipase, amylase or non-fasting glucose, decreased total protein, albumin, sodium, 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.

	Uncommon	*Chemistry:* Increased creatinine, sodium, calcium, decreased non-fasting glucose, increased or decreased chloride. *Haematology:* Increased reticulocyte count, decreased neutrophils
[+] Events considered medicine-related in controlled clinical trials with an incidence of at least 1 %		

Table 2: Side effects reported during post-marketing use:

Blood and lymphatic system disorders	Pancytopenia^, leukopenia^, thrombocytopenia^, anaemia^, sideroblastic anaemia [‡]
Immune system disorders	Anaphylaxis
Metabolism and nutrition disorders	Lactic acidosis^
Nervous system disorders	Convulsions ^, peripheral neuropathy^
Eye disorders	*Optic neuropathy*^[a]
Gastrointestinal disorders	*Tongue discolouration or disorder, superficial tooth discolouration*[b]
Skin and subcutaneous tissue disorders	Bullous skin disorders including severe cutaneous adverse reactions (such as toxic epidermal necrolysis, Stevens-Johnson syndrome), angioedema, rash

‡ Primarily reported in patients receiving ZYVOXID for more than the maximum recommended duration of 28 days

^ See section 4.4

[a] Sometimes progressing to loss of vision, have been reported in patients treated with ZYVOXID. These reports have primarily been in patients treated for longer than the maximum recommended durations of 28 days

[b] The discoloration was removable with professional dental cleaning (manual descaling) in cases with known outcome

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 cases of overdose have been reported. However, the following information may prove useful: Supportive care is advised, together with maintenance of glomerular filtration. Approximately 30 % of a ZYVOXID dose is removed during 3 hours of haemodialysis, but no data are available for the removal of ZYVOXID by peritoneal dialysis or haemoperfusion.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Category and class: A 20.1.1 Broad and medium spectrum antibiotics

Mechanism of action

Linezolid is a synthetic antibacterial medicine of the oxazolidinone class of antibiotics. It has *in vitro* activity against aerobic Gram-positive bacteria and anaerobic microorganisms. It selectively

inhibits bacterial protein synthesis through binding to sites on the bacterial ribosome 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.

Resistant organisms: *Haemophilus influenzae* *Enterobacteriaceae* *Neisseria* species *Pseudomonas* species
Organisms with varied susceptibility: *Legionella* species *Mycoplasma* species *Moraxella catarrhalis*

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 have shown 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}.

5.2 Pharmacokinetic properties

Linezolid 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 to 9.

Absorption

Maximum plasma concentrations are reached within 2 hours of dosing. Absolute oral bioavailability of linezolid (oral and intravenous dosing in a crossover study) is complete (approximately 100 %). Absorption is not significantly affected by food and absorption from the oral suspension is similar to that achieved with the film-coated tablets**.**

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.

In another study following oral dosing of 600 mg twice daily to steady-state, C_{max} and C_{min} were determined to be 21,2 (5,8) mg/l and 6,15 (2,94) mg/l, respectively. Steady-state conditions are achieved by the second day of dosing.

Distribution

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.

Metabolism

Linezolid is primarily metabolised by oxidation of the morpholine ring resulting mainly in the formation of two inactive open-ring carboxylic acid derivatives, the aminoethoxyacetic acid metabolite (PNU-142300) and the hydroxyethyl glycine metabolite (PNU-142586). The hydroxyethyl glycine metabolite (B) is the predominant human metabolite and is believed to be formed by a non-enzymatic process.

The aminoethoxyacetic acid metabolite (A) 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 metabolite B (40 %), parent medicine (30 - 35 %) and metabolite A (10 %).

Virtually no parent medicine is found in the faeces while approximately 6 % and 3 % of each dose appears as metabolite B and metabolite A, 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.

There is non-linearity in clearance 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

Patients with 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.

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).

As approximately 30 % of a dose is removed during 3 hours of haemodialysis (beginning 3 hours after administration), linezolid should be given after dialysis in patients receiving such treatment.

However, there was no increase in AUC of parent medicine. 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.

In 24 patients with severe renal insufficiency, 21 of whom were on regular haemodialysis, peak plasma concentrations of the two major metabolites after several days dosing were about 10-fold those seen in patients with normal renal function. Peak plasma levels of linezolid were not affected.

The clinical significance of these observations has not been established as limited safety data are currently available (see section 4.2).

Patients with hepatic insufficiency

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). Dose adjustment in such patients is, therefore, not required. The pharmacokinetics of linezolid in patients with severe hepatic insufficiency (i.e. Child-Pugh class C) has 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).

Children and adolescents (< 18 years old)

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

In adolescents (12 - 17 years of age), linezolid pharmacokinetics were similar to that in adults following a 600 mg dose.

In children 1 week to 12 years of age, administration of 10 mg/kg every 8 hours daily gave exposure approximating to that achieved with 600 mg twice daily in adults.

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

Elderly patients

The pharmacokinetics of linezolid are not significantly altered in elderly patients 65 years of age and over.

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.

5.3 Preclinical safety data

Linezolid decreased fertility and reproductive performance of male rats at exposure levels approximately equal to those in humans. In sexually mature animals these effects were reversible. However, these effects did not reverse in juvenile animals treated with linezolid for nearly the entire period of sexual maturation. Abnormal sperm morphology in testis of adult male rats, and epithelial cell hypertrophy and hyperplasia in the epididymis were noted. Linezolid appeared to affect the maturation of rat spermatozoa. Supplementation of testosterone had no effect on linezolid-mediated fertility effects. Epididymal hypertrophy was not observed in dogs

treated for 1 month, although changes in the weights of prostate, testes and epididymis were apparent.

Reproductive toxicity studies in mice and rats showed no evidence of a teratogenic effect at exposure levels 4 times or equivalent, respectively, to those in humans. The same linezolid concentrations caused maternal toxicity in mice and were related to increased embryo death including total litter loss, decreased fetal body weight and an exacerbation of the normal genetic predisposition to sternal variations in the strain of mice. In rats, slight maternal toxicity was noted at exposures lower than clinical exposures. Mild fetal toxicity, manifested as decreased fetal body weights, reduced ossification of sternebrae, reduced pup survival and mild maturational delays were noted. When mated, these same pups showed evidence of a reversible dose-related increase in pre-implantation loss with a corresponding decrease in fertility. In rabbits, reduced fetal body weight occurred only in the presence of maternal toxicity (clinical signs, reduced body weight gain and food consumption) at low exposure levels 0.06 times compared to the expected human exposure based on AUCs. The species is known to be sensitive to the effects of antibiotics.

Linezolid and its metabolites are excreted into the milk of lactating rats and the concentrations observed were higher than those in maternal plasma. Linezolid produced reversible myelosuppression in rats and dogs.

In rats administered linezolid orally for 6 months, non-reversible, minimal to mild axonal degeneration of sciatic nerves was observed at 80 mg/kg/day; minimal degeneration of the sciatic nerve was also observed in 1 male at this dose level at a 3-month interim necropsy. Sensitive morphologic evaluation of perfusion-fixed tissues was conducted to investigate evidence of optic nerve degeneration. Minimal to moderate optic nerve degeneration was evident in 2 of 3 male rats after 6 months of dosing, but the direct relationship to drug was equivocal because of the acute nature of the finding and its asymmetrical distribution. The optic nerve degeneration observed was microscopically comparable to spontaneous unilateral optic nerve

degeneration reported in aging rats and may be an exacerbation of common background change.

Preclinical data, based on conventional studies of repeated-dose toxicity and genotoxicity, revealed no special hazard for humans beyond those addressed in other sections of this Summary of Product Characteristics. Carcinogenicity / oncogenicity studies have not been conducted in view of the short duration of dosing and lack of genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

ZYVOXID film-coated tablets contain the following inactive ingredients: hydroxypropylcellulose, maize starch, magnesium stearate, microcrystalline cellulose and sodium starch glycollate.
The film coating contains carnuba wax and opadry white. The printing ink contains red iron oxide.

ZYVOXID 200 mg/100 mL and ZYVOXID 600 mg/300 mL Solution for infusion contain the following inactive ingredients: citric acid anhydrous, dextrose monohydrate, hydrochloric acid or sodium hydroxide, sodium citrate dihydrate and water for injections.

ZYVOXID 20 mg/mL Granules for suspension contains the following inactive ingredients: aspartame, carboxymethylcellulose sodium, colloidal silicon dioxide anhydrous, citric acid anhydrous, flavourings (orange, orange cream, peppermint, vanilla), mannitol, microcrystalline cellulose, sodium benzoate, sodium chloride, sodium citrate hydrous, sucrose, sweeteners (fructose, maltodextrin, monoammonium glycyrrhizinate and sorbitol) and xanthan gum.

6.2 Incompatibilities

Not applicable

6.3 Shelf life

ZYVOXID 600 mg Tablets: 36 months when stored in PVC/Al blisters or HDPE containers

ZYVOXID 20 mg/mL Granules for suspension: 36 months

ZYVOXID 200 mg/100 mL Solution for infusion: 36 months

ZYVOXID 600 mg/300 mL Solution for infusion: 36 months

6.4 Special precautions for storage

Tablets

Store at room temperature at or below 25 °C.

Tablets packed in HDPE bottles must be stored in a dry place and protected from light.

Infusion

Store at room temperature at or below 25 °C.

Infusion bags must be kept in overwrap until ready to use.

Protect from light.

Single-use infusion bags. Do not freeze.

Discard any unused solution.

Granules for suspension

Store at or below room temperature of 25 °C.

Constituted suspension

Store at or below room temperature of 25 °C and use within 21 days.

6.5 Nature and contents of container

ZYVOXID 600 mg Tablets

White HDPE bottles of 10 or 30 tablets or PVC/foil blisters of 10 or 30 tablets.

ZYVOXID 200 mg/100 mL Solution for infusion

Single-use infusion bags packaged in a foil overwrap available in a pack size of 100 mL (200 mg linezolid).

ZYVOXID 600 mg/300 mL Solution for infusion

Single-use infusion bags packaged in a foil overwrap available in a pack size of 300 mL (600 mg linezolid).

ZYVOXID Granules for suspension

Granules for suspension in 240 mL amber glass bottles. Once constituted, the volume of suspension is 150 mL.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements

Constitution of oral suspension

ZYVOXID granules for suspension is supplied as a powder/granule for constitution. Gently tap bottle to loosen powder. Add a total of 123 mL distilled water in two portions. After adding the first half, shake vigorously to wet all of the powder. Then add the second half of the water and shake vigorously to obtain a uniform suspension. After constitution, each 5 mL of the suspension contains 100 mg of linezolid.

Before using the constituted suspension, gently mix by inverting the bottle several times.

Do not shake.

7. HOLDER OF CERTIFICATE OF REGISTRATION

Pfizer Laboratories (Pty) Ltd

85 Bute Lane

Sandton 2196

South Africa

Tel: +27 (0)11) 320 6000 / 0860 734 937 (Toll-free South Africa)

8. REGISTRATION NUMBERS

ZYVOXID 600 mg Tablets: 35/20.1.1/0310

ZYVOXID 20 mg/mL Granules for suspension: 35/20.1.1/0311

ZYVOXID 200 mg/100 mL Solution for infusion: 35/20.1.1/0312

ZYVOXID 600 mg/300 mL Solution for infusion: 35/20.1.1/0313

9. DATE OF FIRST AUTHORISATION

ZYVOXID 20 mg/mL Granules for suspension and ZYVOXID 600 mg Tablets: 02 August 2002

ZYVOXID 200 mg/100 mL Solution for infusion and ZYVOXID 600 mg/300 mL Solution for infusion: 20 May 2002

10. DATE OF REVISION OF THE TEXT

24 February 2023

BOTSWANA: Schedule 2

ZYVOXID 600 mg Tablets: Reg. No.: BOT1202199

ZYVOXID 20 mg/mL Granules for Suspension:

Reg. No.: BOT1302358

ZYVOXID 200 mg/100 mL Solution for Infusion:

Reg. No.: BOT1302287

ZYVOXID 600 mg/300 mL Solution for Infusion:

Reg. No.: BOT1302288

NAMIBIA: S2

ZYVOXID 600 mg Tablets: Reg. No.: 06/20.1.1/0188

ZYVOXID 20 mg/mL Granules for Suspension:

Reg. No.:06/20.1.1/0185

ZYVOXID 200 mg/100 mL Solution for Infusion:

Reg. No.: 06/20.1.1/0186

ZYVOXID 600 mg/300 mL Solution for Infusion:

Reg. No.: 06/20.1.1/0187