AUSTRALIAN PRODUCT INFORMATION – ZYVOX® (linezolid)

1. NAME OF THE MEDICINE

Linezolid.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets

Each Zyvox tablet contains 600 mg linezolid.

Granules for oral suspension

Following reconstitution with 123 mL of water, each mL contains 20 mg of linezolid.

Solution for injection

Each 1 mL of Zyvox solution for injection (Zyvox injection) contains 2 mg of linezolid.

Excipient(s) with known effect

Granules for oral suspension

Each mL contains 210.6 mg sucrose, 100 mg mannitol (E421) and 7 mg aspartame (E951), sodium as sodium citrate dihydrate (3 mg), sodium benzoate (2 mg) and sodium chloride (2.7 mg). Fructose and sorbitol (E420) are present in mafco magna sweet (12 mg) and sweet-am powder (6 mg).

Solution for injection

Each mL contains 50.24 mg glucose monohydrate and sodium as sodium citrate dihydrate (1.64 mg).

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Tablets

Zyvox 600 mg tablets are white to off-white coated tablet with “ZYV” debossed on one side and “600” debossed on the other.

Granules for oral suspension

Zyvox granules for oral suspension are white to yellow-orange and may contain white to yellow-orange-brown lumps. The reconstituted suspension is white to yellow-orange and orange flavoured.

Solution for injection

Zyvox injection is in an isotonic, clear, colourless to yellow solution with pH between 4.4-5.2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zyvox is indicated for the treatment of suspected or proven infections due to Gram-positive organisms resistant to multiple classes of antibiotics, including methicillin-resistant *Staphylococcus* species and vancomycin-resistant *Enterococcus* species.

Zyvox is active against Gram-positive bacteria only. Zyvox has no clinical activity against Gram-negative pathogens. Specific Gram-negative therapy is required if a concomitant Gram-negative pathogen is documented or suspected.

4.2 Dose and method of administration

Dosage

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 Zyvox has an oral bioavailability of approximately 100%.

The injection should be administered over a period of 30 to 120 minutes. The maximum recommended duration of treatment is 28 days. Serious adverse effects have been associated with treatment prolonged beyond 28 days. See Section 4.4 Special warnings and precautions for use, Myelosuppression and Peripheral neuropathy and optic neuropathy.

Adults and children 12 years or older

The recommended dosage should be administered intravenously or orally (twice daily) bid as shown in Table 1. Duration of treatment is variable. It is dependent on the pathogen, the site of infection and its severity, and on the patient's clinical response. The maximum recommended duration of treatment is 28 days. No increase in the recommended dosage or duration of treatment is required for infections associated with concurrent bacteraemia.

Table 1: Dosage guidelines for Zyvox for adults and children 12 years or older

Infections (including those associated with concurrent bacteraemia)	**Twice daily dosage and route of administration**	**Duration of treatment**
Community-acquired pneumonia	600 mg IV or orally	10 to 14 consecutive days
Nosocomial (hospital-acquired) pneumonia		
Skin and soft tissue infections	400 mg to 600 mg orally or 600 mg IV depending on clinical severity	
Enterococcal infections	600 mg IV or orally	14 to 28 consecutive days

Children less than 12 years old

The recommended dosage should be administered intravenously or orally as shown in Table 2. The maximum recommended duration of treatment is 28 days.

Table 2: Dosage guidelines for Zyvox for paediatric patients from birth through 11 years of age

Infections (including those associated with concurrent bacteraemia)	Dosage for paediatric patients from birth through 11 years of age§	Duration of treatment
Nosocomial (hospital-acquired) pneumonia	10 mg/kg IV or orally* once every 8 hours	10 to14 consecutive days
Skin and soft tissue infections		
Enterococcal infections	10 mg/kg IV or orally* every 8 hours	14 to 28 consecutive days

* Oral dosing using either Zyvox tablets or Zyvox oral suspension.
§ Neonates <7 days: most pre-term neonates <7 days of age (gestational age <34 weeks) have lower systemic linezolid clearance values and larger AUC values than many full-term neonates and older infants. These neonates should be initiated with dosing regimes of 10 mg/kg every 12 hours. Consideration may be given to the use of 10 mg/kg every 8 hours regime in neonates with sub-optimal clinical response. All neonatal patients should receive 10 mg/kg every 8 hours by 7 days of life (see Section 5.2 Pharmacokinetic properties, Special populations, Children and adolescents).

Method of administration

Tablets and Granules for oral suspension

Administered orally with or without food.

Granules for oral suspension

Instructions for use and handling

Keep the bottle tightly closed before reconstitution.

The granules should be reconstituted using 123 mL of water in two approximately equal aliquots to produce 150 mL oral suspension. Shake well to obtain a uniform suspension. Keep the bottle in the outer carton after reconstitution.

Before use, gently mix by inverting the bottle several times. DO NOT SHAKE. Discard if not used within 3 weeks after reconstitution.

Solution for injection

Instructions for use and handling

Keep bags in foil overwrap and carton until ready to use. Remove overwrap then check for minute leaks by squeezing the bag firmly. Do not use if the bag leaks as sterility may be impaired.

Zyvox injection contains no preservative. The product is for single use in one patient only. Discard any residue. Do not use the bags in series connections. Do not reconnect partially used bags.

Any solutions which are discoloured, hazy or contain visible particulate matter should not be used.

Dosage adjustment

No dose adjustment is required in the elderly, in patients with impaired hepatic function or impaired renal function. However, Zyvox should be administered after haemodialysis in patients receiving such treatment (see Section 5.2 Pharmacokinetic properties).

4.3 Contraindications

Hypersensitivity to linezolid or to any of the excipients in the relevant pharmaceutical form (see Sections 2 Qualitative and quantitative composition and 6.1 List of excipients).

Monoamine oxidase inhibitors

Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B (e.g., phenelzine) or within two weeks of taking any such medicinal product.

Potential interactions producing elevation of blood pressure

Unless patients are monitored for potential increases in blood pressure, linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma, thyrotoxicosis and/or patients taking any of the following types of medications: directly and indirectly acting sympathomimetic agents (e.g., pseudoephedrine), vasopressive agents (e.g., adrenaline (epinephrine), noradrenaline (norepinephrine)), dopaminergic agents (e.g., dopamine, dobutamine) (see Sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions).

Potential serotonergic interactions

Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, linezolid should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin reuptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), pethidine or buspirone (see Sections 4.4 Special warnings and precautions for use and 4.5 Interactions with other medicines and other forms of interactions).

4.4 Special warnings and precautions for use

It is recommended that therapy with Zyvox should be initiated in a hospital environment following guidance from appropriate specialists.

Myelosuppression

Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) has been reported in patients receiving linezolid. In cases where the outcome is known, the affected

haematological parameters have risen towards pre-treatment levels when linezolid was discontinued.

Thrombocytopenia may occur more often in patients with severe renal insufficiency, whether or not on dialysis, and in patients with moderate to severe hepatic impairment. Complete blood counts should be monitored weekly in patients who receive linezolid for longer than two weeks, particularly those with pre-existing myelosuppression, who have severe renal insufficiency or moderate to severe hepatic impairment, those receiving concomitant drugs that produce bone marrow suppression or may decrease haemoglobin levels or platelet count or function, or those with a chronic infection who have received previous antibiotic therapy. Discontinuation of therapy should be considered in patients who develop or who have a worsening of myelosuppression.

Peripheral neuropathy and optic neuropathy

Peripheral neuropathy and optic neuropathy have been reported in patients treated with linezolid, primarily those patients treated for longer than the maximum recommended duration of 28 days. When outcome was known, recovery was reported in some cases following Zyvox withdrawal. In cases of optic neuropathy that progressed to loss of vision, patients were treated for extended periods beyond the maximum recommended duration.

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 linezolid for extended periods (greater than or equal to 3 months) and in all patients reporting new visual symptoms regardless of length of therapy with linezolid. If peripheral or optic neuropathy occurs, the continued use of linezolid in these patients should be weighed against the potential risks.

The safety and effectiveness of Zyvox when administered for periods longer than 28 days have not been established. Treatment prolonged beyond 28 days has been associated with serious adverse effects, including myelosuppression, peripheral neuropathy and optic neuropathy.

Lactic acidosis

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

Convulsions

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

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the coadministration of Zyvox and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and opioids have been reported (see Sections 4.3 Contraindications and 4.5 Interactions with medicines and other forms of interactions).

Rhabdomyolysis

Rhabdomyolysis has been reported with the use of linezolid. If signs or symptoms of rhabdomyolysis are observed, linezolid should be discontinued and appropriate therapy initiated.

Hyponatraemia and/or Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH)

Hyponatraemia and/or Syndrome of Inappropriate Antidiuretic Hormone Secretion (SIADH) have been observed in some patients treated with linezolid. It is recommended that serum sodium levels be monitored regularly in the elderly, in patients taking diuretics, and in other patients at risk of hyponatraemia.

Antibiotic-associated pseudomembranous colitis

Antibiotic-associated pseudomembranous colitis has been reported with nearly all antibacterial agents including linezolid. A toxin produced with *Clostridium difficile* appears to be the primary cause. The severity of the colitis may range from mild to life threatening. It is important to consider this diagnosis in patients who develop diarrhoea or colitis in association with antibiotic use (this may occur up to several weeks after cessation of antibiotic therapy). Mild cases usually respond to drug discontinuation alone. However, in moderate to severe cases appropriate therapy with a suitable oral antibacterial agent effective against *Clostridium difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Drugs which delay peristalsis, e.g., opiates and diphenoxylate with atropine may prolong and/or worsen the condition and should not be used. Hypertoxin producing strains of *C. difficile* cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy.

Superinfection

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

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

Mortality in subjects with catheter-related infections

An open-label, randomised clinical trial was conducted in adult patients with catheter-related Gram-positive bloodstream infections comparing linezolid (600 mg q12h IV/PO) to vancomycin 1 g IV q12h or oxacillin 2 g IV q6h/dicloxacillin 500 mg PO q6h with a treatment duration of 7 to 28 days. The mortality rates in this study were 78/363 (21.5%) and 58/363 (16.0%) on linezolid and the comparator, respectively. Based on results from a logistic regression, the estimated odds ratio is 1.426 [95% CI 0.970, 2.098]. While causality has not been established, this observed imbalance occurred primarily in linezolid-treated patients in whom either Gram-negative pathogens, mixed Gram-negative and Gram-positive pathogens, or no pathogens were identified at baseline. Patients randomised to linezolid who had only a Gram-positive infection at baseline, including the subgroup of patients with Gram-positive bacteraemia experienced a survival rate similar to the comparator.

Use in the elderly

The pharmacokinetics of linezolid are not significantly altered in elderly patients aged 65 years and over. No dose adjustment is required.

Paediatric use

The clearance of linezolid is most rapid in the youngest age groups (excluding neonates less than 1 week old), resulting in a shorter half-life. As children mature, the clearance of linezolid gradually decreases and by adolescence the clearance values approach those observed for the adult population. While drug clearance in adolescents (ages 12 through 17 years) is usually similar to the clearance in adults, there is wider intersubject variation in this age group compared with adults (see Sections 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties). Results of clinical studies showed similar efficacy in adult and adolescent patients. Given the wider inter subject variation in adolescents, the slight possibility that high clearance may result in decreased efficacy in some adolescent patients should be considered. The dosage for paediatric patients younger than 12 years of age should be 10 mg/kg every 8 hours, while children 12 years and older should receive the same dose as adult patients, 600 mg every 12 hours (see Section 4.2 Dose and method of administration).

In limited clinical experience, 5 out 6 (83%) paediatric patients with infections due to Gram-positive pathogens with MICs of 4 μg/mL treated with Zyvox had clinical cures. However, paediatric patients with a sub-optimal clinical response, particularly those with pathogens with MIC of 4 μg/mL, lower systemic exposure, site and severity of infection and the underlying medical condition should be considered when assessing clinical response (see Sections 5.2 Pharmacokinetic properties, Special populations, Children and adolescents and 4.2 Dose and method of administration).

Use in renal impairment

Linezolid 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.

Use in hepatic impairment

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

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Linezolid 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 with Zyvox. Drugs such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with Zyvox without changes in dosage regimen.

Zyvox is a reversible, non-selective inhibitor of monoamine oxidase (MAOI). Limited clinical studies have shown that coadministration of Zyvox with either pseudoephedrine or phenylpropanolamine resulted in mild, reversible enhancement of the pressor responses in

normotensive patients. Similar studies in hypertensive subjects have not been conducted. The potential for interaction with sympathomimetic and adrenergic agents should be considered (see Section 4.3 Contraindications). Initial doses of potent vasopressors, such as dopamine and adrenaline (epinephrine), should be reduced and carefully titrated to achieve the desired response when coadministered with Zyvox (see Section 4.3 Contraindications).

No significant pressor response was observed in subjects receiving both Zyvox and less than 100 mg tyramine. This suggests that it is only necessary to avoid ingesting excessive 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).

Zyvox has the potential for interaction with serotonergic agents. Limited clinical studies have shown that coadministration of Zyvox with dextromethorphan was not associated with serotonin syndrome effects (e.g., confusion, delirium, restlessness, tremors, blushing, diaphoresis and hyperpyrexia). The effects of other serotonin uptake inhibitors have not been studied.

Spontaneous reports of serotonin syndrome associated with coadministration of Zyvox and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and opioids, have been reported (see Sections 4.3 Contraindications and 4.4 Special warnings and precautions for use). Patients who are treated with Zyvox and concomitant serotonergic agents should be closely observed for signs and symptoms of serotonin syndrome (e.g., cognitive dysfunction, hyperpyrexia, hyperreflexia, incoordination). If any signs or symptoms occur physicians should consider discontinuation of either one or both agents (Zyvox or concomitant serotonergic agents). If the concomitant serotonergic agent is withdrawn, discontinuation symptoms can be observed.

Antibiotics

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

The effect of rifampicin on the pharmacokinetics of linezolid was studied in sixteen healthy adult male volunteers administered linezolid 600 mg bid 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.

4.6 Fertility, pregnancy and lactation

Effects on fertility

Whilst linezolid did not affect female rat fertility or reproductive performance, it reversibly decreased the fertility of adult male rats at oral doses of 50 mg/kg/day with exposure levels (based on AUCs) approximately equal to those expected in humans. The reversible effects on fertility were mediated by altered spermatogenesis. Affected spermatids contained abnormally formed and oriented mitochondria and were non-viable. The presence of abnormal sperm in the epididymis was accompanied by epithelial cell hypertrophy and hyperplasia.

Dogs administered linezolid at PO doses up to 40 mg/kg/day (0.7 times clinical exposure) for 3 months or IV doses up to 40 mg/kg/day (1.3 times clinical exposure) for 1 month showed no effects on the testes or epididymides.

Sexually mature male rats showed slightly decreased fertility following oral treatment as juveniles throughout most of their period of sexual development (50 mg/kg/day from postnatal days 7 to 36, and 100 mg/kg/day from days 37 to 55), at exposures up to 1.7 times the mean AUC in paediatric patients aged 3 months to 11 years. Decreased fertility was not observed following a shorter treatment period of about 2-weeks, *in utero* through the early neonatal period (gestation day 6 through postnatal day 5), neonatal exposure (postnatal days 5 to 21), or juvenile exposure (postnatal days 22 to 35). Reversible reductions in sperm motility and altered sperm morphology were observed in rats following treatment on postnatal days 22 to 35.

Juvenile dogs administered linezolid for 1 month at doses up to 100 mg/kg/day PO (2.2 times clinical paediatric exposure) showed no direct effects on the testes or epididymides.

Use in pregnancy – Pregnancy Category B3

There are no adequate data from the use of Zyvox in pregnant women. Studies in animals have shown reproductive effects (see below). The potential risk for humans is unknown.

Zyvox should not be used during pregnancy unless clearly necessary, i.e., only if the potential benefit outweighs the potential risk.

Linezolid and/or its metabolites crossed the placenta in rats. Linezolid was not teratogenic in mice or rats at exposure levels 4 times (mice) or equivalent to (rats) the expected human exposure level, based on AUCs.

Embryo fetal effects were observed in mice at 450 mg/kg/day (4 times the clinical exposure based on AUC) and in rats at 15 mg/kg/day (0.14 times the clinical exposure based on AUC). Decreased fetal weights and delayed ossification occurred in rats without maternal toxicity. In mice, increased embryo death including total litter loss, decreased fetal body weights and an exacerbation of the normal genetic predisposition to sternal variations in the strain of mice used were seen at doses causing maternal toxicity (clinical signs and decreased body weight gain).

Linezolid was also not teratogenic in rabbits, when administered bid at total oral doses up to 15 mg/kg/day (0.06 times the clinical exposure, based on AUC), although maternal toxicity (clinical signs, reduced body weight gain and food consumption) occurred at 5 and 15 mg/kg/day, and reduced fetal body weight occurred at 15 mg/kg/day. Linezolid exposures were low due to the characteristic sensitivity of rabbits to antibiotics.

Use in lactation

Animal data suggest that linezolid is likely to pass into breast milk. Breastfeeding should be discontinued prior to administration.

Linezolid and its metabolites were excreted into the milk of rats. The concentration of total drug-related materials in milk was similar to or greater than that in maternal plasma. The development of pups from rats treated orally with 50 mg/kg/day linezolid during gestation and lactation (0.6 times the clinical exposure based on AUC) was slightly delayed, manifest as decreased body weight gain, delayed pinna detachment and balanopreputial separation and decreased negative geotaxis response. These pups when allowed to mature showed slightly decreased fertility, increased implantation loss and decreased epididymides and testes weights.

4.7 Effects on ability to drive and use machines

Patients should be warned about the potential for dizziness or symptoms of visual impairment (as described in Sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects (undesirable effects)) whilst receiving linezolid and should be advised not to drive or operate machinery if any of these symptoms occurs.

4.8 Adverse effects (undesirable effects)

The information provided is based on data generated from clinical studies in adult and paediatric patients.

Adult patients

More than 2,000 patients received the recommended Zyvox doses for up to 28 days. In these studies, the majority of adverse reactions to Zyvox were of mild to moderate intensity, of limited duration and did not require discontinuation of treatment. The adverse reactions were not dose dependent.

Approximately 22% of patients experienced adverse reactions; those most commonly reported were headache, diarrhoea, nausea, vomiting, taste perversion, abnormal liver function tests and candidiasis (particularly oral and vaginal). The most commonly reported drug-related adverse events which lead to discontinuation of treatment were headache, diarrhoea, nausea and vomiting. Table 3 shows the incidence of adverse reactions reported in at least 1% of patients in these trials.

Table 3: Incidence (%) of adverse reactions reported in ≥1% of patients in comparator-controlled clinical trials with Zyvox and 600 mg bid patients in the VRE dose-response study

Event	Zyvox (n=2125)	All comparators* (n=2001)
Gastrointestinal disorders		
Diarrhoea	4.2	3.2
Nausea	3.3	2.3
Vomiting	1.2	0.4
Hepato-biliary disorders		
Abnormal liver function tests	1.0	0.3
Nervous system disorders		
Headache	2.1	1.3
Taste perversion	1.1	0.7
Infections and infestations		
Vaginal candidiasis	1.1	0.6

* Comparators included cefpodoxime, proxetil, ceftriaxone, clarithromycin, dicloxacillin, oxacillin and vancomycin.

Changes observed in laboratory parameters (without regard to drug relationship) generally reflected resolution of the infection, were not clinically significant, did not lead to

discontinuation of therapy and were reversible. The incidence of patients with at least one substantially abnormal haematologic or serum chemistry value is presented in Table 4.

Table 4: Percent of patients who experienced at least one substantially abnormal* haematology or chemistry laboratory value in comparator-controlled clinical trials with Zyvox

Laboratory assay	Zyvox	All comparators[a]
Haemoglobin	5.4	4.8
Platelet count	2.4	1.5
Leucocytes	1.6	1.1
Neutrophils	0.8	0.9
AST	4.1	5.3
ALT	7.4	7.2
LDH	1.4	1.1
Alkaline phosphatase	2.6	2.3
Lipase	3.9	3.7
Amylase	1.8	1.5
Total bilirubin	0.7	0.8
BUN	1.6	1.1
Creatinine	0.2	0.5

* Haematology:
<75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline.
<75% (<50% for neutrophils) of LLN and of baseline for values abnormal at baseline.
Chemistry:
>2 Upper Limit of Normal (ULN) for values normal at baseline.
>2 ULN and >2 x baseline for values abnormal at baseline.
[a] Comparators included clarithromycin, cefpodoxime proxetil, ceftriaxone, dicloxacillin, oxacillin and vancomycin.

Paediatric patients

The safety of Zyvox formulations was evaluated in 215 paediatric patients ranging in age from birth through 11 years and in 248 paediatric patients aged 5 through 17 years (146 of these, 248 were aged 5 through 11 years and 102 were aged 12 to 17 years). These patients were enrolled in two Phase 3 comparator-controlled clinical trials and were treated for up to 28 days. In these studies 83% and 99% respectively, of the adverse events reported with Zyvox were described as mild to moderate in intensity. In the study of hospitalised paediatric patients (birth through 11 years) with Gram-positive infections, who were randomised 2 to 1 (linezolid:vancomycin), mortality was 6.0% (13/215) in the linezolid arm and 3.0% (3/101) in the vancomycin arm. However, given the severe underlying illness in the patient population, no causality could be established. Table 5 shows the incidence of drug-related adverse events reported in more than 1% of paediatric patients (and more than 1 patient) in either treatment group in the comparator-controlled Phase 3 trials.

Table 5: Incidence (%) of drug related adverse events occurring in >1% of paediatric patients (and >1 patient) in either treatment group in comparator-controlled clinical trials

Event	Other comparator-controlled clinical trial†		Study 082‡	
	Zyvox (n= 248)	Cefadroxil (n= 251)	Zyvox (n= 215)	Vancomycin (n=101)
% of patients with 1 drug-related adverse event	19.2	14.1	18.8	34.3
% of patients discontinuing due to a drug-related adverse event	1.6	2.4	0.9	6.1
Diarrhoea	5.7	5.2	3.8	6.1
Nausea	3.3	2.0	1.4	0
Headache	2.4	0.8	0	0
Loose stools	1.2	0.8	1.9	0
Thrombocytopenia	0	0	1.9	0
Vomiting	1.2	2.4	1.9	1.0
Generalised abdominal pain	1.6	1.2	0	0
Localised abdominal pain	1.6	1.2	0	0
Anaemia	0	0	1.4	1.0
Eosinophilia	0.4	0.4	1.4	0
Rash	0.4	1.2	1.4	7.1
Vertigo	1.2	0.4	0	0
Oral moniliasis	0	0	0.9	4.0
Fever	0	0	0.5	3.0
Pruritus non application site	0.4	0	0	2.0
Anaphylaxis	0	0	0	10.1*

† Patients 5 through 11 years of age received Zyvox 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h.
† Patients 12 years or older received Zyvox 600 mg PO q12h or cefadroxil 500 mg PO q12h.
‡ Patients from birth through 11 years received Zyvox 10 mg/kg IV/PO or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.
* These reports were of "red-man syndrome", which were coded as anaphylaxis.

In a study of severely ill, hospitalised paediatric patients ranging in age from birth through 11 years, the percentage of patients who developed a substantially low platelet count was 12.9% with Zyvox and 13.4% with vancomycin. In an outpatient study of paediatric patients aged from 5 through 17 years, the percentage of patients who developed a substantially low platelet count was 0% with Zyvox and 0.4% with cefadroxil. Other changes observed in laboratory parameters, were not clinically significant, did not lead to discontinuation of therapy

and were reversible. The incidence of paediatric patients with at least one substantially abnormal haematologic or serum chemistry value is presented in Table 6.

Table 6: Percent of paediatric patients who experienced at least one substantially abnormal* haematology or serum chemistry laboratory value in comparator-controlled clinical trials with Zyvox

Laboratory Assay	**Other comparator-controlled clinical trial†**		**Study 082‡**	
	Zyvox	Cefadroxil	Zyvox	Vancomycin
Haemoglobin (g/dL)	0.0	0.0	15.7	12.4
Platelet count (x $10^3/mm^3$)	0.0	0.4	12.9	13.4
WBC (x $10^3/mm^3$)	0.8	0.8	12.4	10.3
Neutrophils (x $10^3/mm^3$)	1.2	0.8	5.9	4.3
ALT (U/L)	0.0	0.0	10.1	12.5
Lipase (U/L)	0.4	1.2	---	---
Amylase (U/L)	---	---	0.6	1.3
Total bilirubin (mg/dL)	---	---	6.3	5.2
Creatinine (mg/dL)	0.4	0.0	2.4	1.0

*Haematology:
<75% (<50% for neutrophils) of Lower Limit of Normal (LLN) for values normal at baseline.
<75% (<50% for neutrophils, <90% for haemoglobin) of LLN and of baseline for values abnormal at baseline.
Serum chemistry:
>2 Upper Limit of Normal (ULN) for values normal at baseline.
>2 ULN and >2 x baseline for values abnormal at baseline.
Dosage:
†Patients 5 through 11 years of age receive Zyvox 10 mg/kg PO q12h or cefadroxil 15 mg/kg PO q12h.
†Patients 12 years or older received Zyvox 600 mg PO q12h or cefadroxil 500 mg PO q12h.
‡Patients from birth through 11 years received Zyvox 10 mg/kg IV/PO or vancomycin 10 to 15 mg/kg IV q6-24h, depending on age and renal clearance.

Post-marketing experience

Table 7: Adverse drug reactions (ADRs) by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC

System Organ Class	**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**	**Frequency not known (cannot be estimated from the available data)**
Blood and lymphatic system disorders	Thrombocytopenia^ Anaemia^	Pancytopenia^ Leucopenia^	Sideroblastic anaemia‡^		Myelosuppression
Immune system disorders			Anaphylaxis		

System Organ Class	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	Frequency not known (cannot be estimated from the available data)
Metabolism and nutrition disorders			Lactic acidosis^		
Nervous system disorders		Convulsions^ Peripheral neuropathy^			Serotonin syndrome^[c]
Eye disorders		Optic neuropathy^[a]			
Gastrointestinal disorders	Abdominal pain#	Abdominal distension# Abdominal cramps# Tongue discolouration	Trichoglossia Superficial tooth discolouration[b]		
Skin and subcutaneous tissue disorders	Rash	Bullous skin disorders Severe cutaneous adverse reactions Angioedema	Toxic epidermal necrolysis Stevens-Johnson syndrome Hypersensitivity vasculitis		
Musculoskeletal and connective tissue disorders			Rhabdomyolysis^		

^ See Section 4.4 Special warnings and precautions for use.
# Considered drug-related in controlled clinical trials.
[a] Sometimes progressing to loss of vision, have been reported in patients treated with linezolid. These reports have primarily been in patients treated for longer than the maximum recommended duration of 28 days.
[b] The discolouration was removable with professional dental cleaning (manual descaling) in cases with known outcome.
[c] Reported in patients receiving concomitant serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and Zyvox.

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions at www.tga.gov.au/reporting-problems.

4.9 Overdose

No specific antidote is known.

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 linezolid dose is removed during 3 hours of haemodialysis, but no data are available for the removal of linezolid by peritoneal dialysis or haemoperfusion. The two primary metabolites of linezolid are also removed to some extent by haemodialysis.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

Linezolid is a synthetic, antibacterial agent belonging to a class of antibiotics, the oxazolidinones, with *in vitro* activity against Gram-positive aerobic bacteria, some Gram-positive anaerobic bacteria and certain Gram-negative bacteria. It selectively inhibits bacterial protein synthesis via a mechanism of action different from that of other antibacterial agents. Linezolid binds to the 23S ribosomal RNA of the 50S subunit of the bacterial ribosome and prevents the formation of a functional 70S initiation complex which is an essential component of the bacterial translation process. The results of time-kill studies have shown linezolid to be bacteriostatic against enterococci and staphylococci. For streptococci, linezolid was found to be bactericidal for the majority of strains.

Breakpoints

The Minimum Inhibitory Concentration (MIC) breakpoints in Table 8 separate susceptible from non-susceptible isolates.

Table 8: MIC breakpoints for linezolid

Pathogen	**Susceptibility interpretive criteria**					
	MIC in micrograms/mL			**Disk diffusion (zone diameters in mm)**		
	S	**I**	**R**	**S**	**I**	**R**
Enterococcus species	< 2	4	> 8	> 23	21-22	< 20
Staphylococcus species	< 4	---*	---	> 21	---	---*
Streptococcus pneumoniae	< 2	---	---	> 21	---	---*
Streptococcus species other than *S. pneumoniae*	< 2	---	---	> 21	---	---*

* The current absence of data on resistant strains precludes defining categories other than "susceptible". Strains yielding results suggestive of a "non-susceptible" category should be re-tested and, if confirmed, the isolate should be submitted to a reference laboratory for further testing.
S = susceptible, I = intermediate susceptible, R = resistant

The studies used to define the above breakpoints employed standard NCCLS (National Committee for Clinical Laboratory Standards) microdilution and agar diffusion methods.

Susceptibility

Prevalence of resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. Therefore, the following information gives only an approximate guidance on the probabilities as to whether or not microorganisms will be susceptible to linezolid. Only microorganisms relevant

to the given clinical indications are presented here. An asterisk indicates that clinical efficacy has been demonstrated for susceptible isolates in approved clinical indications.

Susceptible organisms

Gram-positive aerobes

- *Corynebacterium jeikeium*
- *Enterococcus faecalis* (including glycopeptide resistant strains)
- *Enterococcus faecium* (including glycopeptide resistant strains)
- *Enterococcus casseliflavus*
- *Enterococcus gallinarum*
- *Listeria monocytogenes*
- *Staphylococcus aureus* (including methicillin-resistant strains)
- *Staphylococcus aureus* (including glycopeptide intermediate resistant strains)
- *Staphylococcus epidermidis* (including methicillin-resistant strains)
- *Staphylococcus haemolyticus*
- *Staphylococcus lugdunensis*
- *Streptococcus agalactiae*
- *Streptococcus intermedius*
- S*treptococcus pneumoniae* (including penicillin intermediate and resistant strains)
- *Streptococcus pyogenes*
- *Viridans group streptococci*
- Group C streptococci
- Group G streptococci.

Gram-negative aerobes

- *Pasteurella canis*
- *Pasteurella multocida*.

Gram-positive anaerobes

- *Clostridium perfringens*
- *Peptostreptococcus anaerobius*
- *Peptostreptococcus* species.

Gram-negative anaerobes

- *Bacteroides fragilis*
- *Prevotella* species.

Other

- *Chlamydia pneumoniae*

Intermediately susceptible organisms

- *Legionella* species
- *Moraxella catarrhalis*.

Resistant organisms

- *Haemophilus influenzae*
- *Neisseria* species

- *Enterobacteriaceae*
- *Pseudomonas aeruginosa*.

Resistance

The mechanism of action of linezolid differs from other classes of antibiotics. Cross-resistance between linezolid and other classes of antibiotics is thus less likely to occur.

Resistance to linezolid developed under selective pressure. The presence of multiple 23S ribosomal RNA genes in most species suggest that the level of resistance is associated with the number of copies with mutations. Spontaneous resistance occurs at frequencies of less than 10^{-9} *in vitro*. These same mutations and/or other genetic changes have been reported in clinical isolates of *Staphylococcus aureus, Streptococcus pneumoniae* and Enterococci resistant or non-susceptible to linezolid. In clinical trials, resistance to linezolid developed in 6 patients infected with *E. faecium* (4 patients received 200 mg twice daily (bid), lower than the recommended dose, and 2 patients received 600 mg bid). In a compassionate use program, resistance to linezolid developed in 8 patients with *E. faecium* and in 1 patient with *E. faecalis*. All patients had either unremoved prosthetic devices or undrained abscesses. In cases where linezolid non-susceptible enterococci are identified, strict infection control measures and adherence to antibiotic guidelines should be maintained.

Clinical trials

There are no data from comparator-controlled clinical trials on the use of Zyvox in the treatment of endocarditis, central nervous system infections and osteomyelitis.

Nosocomial pneumonia

Adult patients with clinically and radiologically documented nosocomial pneumonia participated in a randomised, multi-centre, double-blind clinical trial. Patients were treated for 7 to 21 days. One group (No. enrolled = 205) received Zyvox injection 600 mg bid, and another group (No. enrolled = 197) received vancomycin 1 g bid intravenously. Both groups received concomitant aztreonam (1 to 2 g every 8 hours IV). Zyvox demonstrated efficacy equivalent to vancomycin in the treatment of patients with nosocomial pneumonia in all outcome measurements. The overall clinical cure rates in the ITT population was 53% in the Zyvox group and 52% in the vancomycin group. These cure rates do not include patients with missing or indeterminate outcomes. The clinical cure rate for microbiologically evaluable patients is presented in Table 9.

Table 9: Clinical cure rates at the test-of-cure visit for microbiologically evaluable patients with nosocomial pneumonia (subjects with indeterminate or missing outcomes excluded)

Pathogen	**Cured**	
	Zyvox **n/N (%)**	**Vancomycin** **n/N (%)**
Staphylococcus aureus	25/41 (61)	14/23 (61)
Streptococcus pneumoniae	9/9 (100)	9/9 (100)

Community-acquired pneumonia

Adult patients with clinically and radiologically documented community-acquired pneumonia participated in two randomised, comparator-controlled, multi-centre trials.

One of these trials was an open-label study in which hospitalised patients received study medications administered IV followed by medications administered orally for a total of 7 to 14 days of treatment. One group of patients (No. enrolled = 389) received Zyvox injection (600 mg bid) followed by Zyvox tablets (600 mg bid), and another group (No. enrolled = 370) received ceftriaxone (1 g bid IV) followed by cefpodoxime proxetil tablets (200 mg bid orally).

The second study was an investigator-blinded trial in outpatients with community-acquired pneumonia who were treated for 10 – 14 days. One group of patients received Zyvox tablets 600 mg bid (No. enrolled = 278) and another group received cefpodoxime proxetil tablets 200 mg bid (No. enrolled = 270).

In these trials, Zyvox demonstrated efficacy equivalent to ceftriaxone or cefpodoxime proxetil by all outcome measurements. The overall clinical cure rates in the ITT population in Zyvox and comparator groups were 83% vs 76% and 82% vs 86% in respective studies. These cure rates do not include patients with missing or indeterminate outcomes. Table 10 shows the clinical cure rates for microbiologically evaluable patients in these studies.

Table 10: Clinical cure rates at the test-of-cure visit for microbiologically evaluable patients with community-acquired pneumonia (subjects with indeterminate or missing outcomes excluded)

Pathogen	**Cured**	
	Zyvox **n/N (%)**	**Ceftriaxone and cefpodoxime proxetil** **n/N (%)**
Streptococcus pneumoniae	88/98 (90)	81/90 (90)
Staphylococcus aureus	29/32 (91)	22/29 (76)
Haemophilus influenzae	13/14 (93)*	23/26 (88)

* Excluding patients who received concomitant treatment with aztreonam.

Complicated skin and skin structure infections

Adult patients with clinically documented complicated skin and skin structure infections participated in a randomised, multi-centre, double-blind trial comparing study medications administered IV followed by medications given orally for a total of 10 to 21 days of treatment. One group of patients (No. enrolled = 403) received Zyvox injection (600 mg bid) followed by Zyvox tablets (600 mg bid); another group (No. enrolled = 423) received oxacillin 2 g every 6 hours (q6h) IV followed by dicloxacillin 500 mg q6h orally. Zyvox demonstrated equivalent efficacy to oxacillin and dicloxacillin against a variety of common pathogens by all outcome measurements. The overall clinical cure rates in the ITT population was 85% in the Zyvox group and 77% in the oxacillin group, respectively. These cure rates do not include patients with missing or indeterminate outcomes. The clinical cure rates for microbiologically evaluable patients are presented in Table 11.

Table 11: Clinical cure rates at the test-of-cure visit for microbiologically evaluable patients with complicated skin and skin structure infections (subjects with indeterminate or missing outcomes excluded)

Pathogen	Cured	
	Zyvox n/N (%)	**Oxacillin and dicloxacillin n/N (%)**
Staphylococcus aureus	83/93 (89)	88/103 (85)
Staphylococcus epidermidis	19/19 (100)	10/12 (83)
Streptococcus pyogenes	23/29 (79)	27/32 (84)
Streptococcus agalactiae	7/7 (100)	4/6 (67)

Methicillin-resistant staphylococcus aureus (MRSA) infections

Adult patients with documented MRSA infections participated in a randomised, multi-centre, open-label trial. One group of patients (No. enrolled = 243) received Zyvox injection 600 mg bid followed by Zyvox tablets 600 mg bid. Another group of patients (No. enrolled = 225) received vancomycin 1 g bid IV. Both groups were treated for 7 to 28 days. Zyvox was comparable to vancomycin in the treatment of patients with MRSA pneumonia and skin and soft tissue infections. The overall clinical cure rates in the ITT population was 57% in the Zyvox group and 55% in the comparator groups respectively. These cure rates do not include patients with missing or indeterminate outcomes. The clinical cure rates for microbiologically evaluable patients with MRSA are presented in Table 12.

Table 12: Clinical cure rates at the test-of-cure visit for microbiologically evaluable patients with MRSA infections (subjects with indeterminate or missing outcomes excluded)

Infection	Cured	
	Zyvox n/N (%)	**Vancomycin n/N (%)**
MRSA pneumonia	9/12 (75)	12/16 (75)
MRSA skin and soft tissue infection	27/34 (79)	22/30 (73)

Vancomycin-resistant enterococcus (VRE) infections

Adult patients with documented or suspected VRE infections participated in a randomised, multi-centre, double-blind trial comparing a high dose (600 mg bid IV or orally) with a low dose of linezolid (200 mg bid IV or orally) for 7 to 28 days. 79 patients were enrolled in the high dose group and 66 enrolled in the low dose group.

Patients with VRE infections were also treated with Zyvox 600 mg bid IV or orally in an open-label, non-comparative, compassionate-use trial. These patients were treated for up to 21 days. 144 patients with VRE infections were enrolled in this trial.

The overall clinical cure rates in the ITT populations were 67% and 54% in the high dose compared to low dose group in the controlled study and 90% (evaluable population) in the compassionate use trial. These cure rates do not include patients with missing or indeterminate

outcomes. The clinical cure rates for clinically evaluable patients are presented in Table 13 by source of infection.

Table 13: Clinical cure rates at the test-of-cure visit for clinically evaluable patients with suspected or proven VRE infections (subjects with indeterminate or missing outcomes excluded)

Source of Infection	**Cured**		
	Linezolid 600 mg bid n/N (%)		**Linezolid 200 mg bid n/N (%)**
	VRE Patients in Compassionate Use Study	**Dose-Comparator Study**	**Dose-Comparator Study**
Bacteraemia of unknown origin	10/12 (83)	6/9 (67)	2/2 (100)
Other	33/35 (94)	11/11 (100)	7/11 (64)
Peritonitis*	11/12 (92)	1/1 (100)	3/6 (50)
Intra-abdominal*	11/12 (92)	4/4 (100)	2/2 (100)
Catheter-related*	9/9 (100)	3/3 (100)	1/1 (100)
Not classified*†	2/2 (100)	3/3 (100)	1/2 (50)
Pneumonia	1/1 (100)	2/2 (100)	---
Skin and soft tissue	7/9 (78)	8/9 (89)	6/6 (100)
Urinary tract	1/1 (100)	12/13 (92)	13/19 (68)

* Data for these sources of infections are subset of 'Other'.
† Includes sources of infection such as hepatic abscess, biliary sepsis, necrotic gall bladder, pericolonic abscess, and pancreatitis.

Paediatric patients

Infections due to resistant gram-positive organisms

A safety and efficacy study (Study 082) provided experience on the use of Zyvox in paediatric patients for the treatment of hospital-acquired pneumonia, complicated skin and skin structure infections, catheter-related bacteraemia, of unidentified source, and other infections due to resistant gram-positive bacterial pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), methicillin-resistant *Staphylococcus epidermidis* (MRSE), penicillin-resistant *Streptococcus pneumoniae* (PRSP) and vancomycin-resistant *Enterococcus faecium* (VRE). Paediatric patients ranging in age from birth through 11 years with infections caused by the documented or suspected above organisms were enrolled in a randomised, open-label, comparator-controlled trial. One group of patients received Zyvox injection 10 mg/kg every 8 hours followed by Zyvox oral suspension 10 mg/kg every 8 hours. A second group received vancomycin 10 to 15 mg/kg IV every 6 to 24 hours, depending on age and renal clearance. Patients who had confirmed VRE infections were placed in a third arm of the study and received Zyvox 10 mg/kg every 8 hours IV and/or orally. All patients were treated for a total of 10 to 28 days and could receive concomitant gram-negative antibiotics if clinically indicated. There were 215 linezolid-treated and 101 vancomycin-treated patients enrolled in

the study. One hundred and fifty-one (70.2%) linezolid-treated patients and 73 (72.3%) vancomycin-treated patients were clinically evaluable. The cure rates in clinically evaluable patients were 89% in linezolid-treated patients and 85% in vancomycin-treated patients. The cure rates for clinically and microbiologically evaluable patients are presented in Table 14.

Table 14: Cure rates at the test-of-cure visit for microbiologically evaluable paediatric patients with infections due to Gram-positive pathogens

Pathogen	**Cured**	
	Zyvox n/N (%)	**Vancomycin n/N (%)**
Enterococcus faecalis	7/10 (70)	3/4 (75)
Enterococcus faecium	5/5 (100)	0/0
Staphylococcus aureus	37/39 (95)	24/26 (92)
Staphylococcus epidermidis	23/29 (79)	11/13 (85)
All coagulase-negative Staphylococci*	32/38 (84)	12/15 (80)
Streptococcus pneumoniae	3/3 (100)	1/1 (100)
Streptococcus pyogenes	2/2 (100)	1/2 (50)

* Coagulase-negative *staphylococci* were considered pathogens in catheter-related bacteraemia and in neonates.

5.2 Pharmacokinetic properties

The mean pharmacokinetic parameters (standard deviation) of linezolid following single and multiple (i.e., twice daily administration to steady-state) intravenous (IV) and oral dosing are given in Table 15.

Table 15: Mean (standard deviation) pharmacokinetic parameters of linezolid in adults derived from plasma concentrations

Healthy adult volunteers						
Linezolid dosage regimen	**C_{max} µg/mL (SD)**	**C_{min} µg/mL (SD)**	**T_{max} hrs (SD)**	**AUC* µgh/mL (SD)**	**$t_{½}$ hrs (SD)**	**CL mL/min (SD)**
600 mg Injection ‡						
single dose	12.90 (1.60)	-----	0.50 (0.10)	80.20 (33.30)	4.40 (2.40)	138 (39)
bid dose	15.10 (2.52)	3.68 (2.36)	0.51 (0.03)	89.70 (31.00)	4.80 (1.70)	123 (40)

Healthy adult volunteers						
Linezolid dosage regimen	**C_{max} µg/mL (SD)**	**C_{min} µg/mL (SD)**	**T_{max} hrs (SD)**	**AUC* µgh/mL (SD)**	**$t_{½}$ hrs (SD)**	**CL mL/min (SD)**
600 mg tablet						
single dose	12.70	-----	1.28	91.40	4.26	127
	(3.96)		(0.66)	(39.30)	(1.65)	(48)
bid dose	21.20	6.15	1.03	138.00	5.40	80
	(5.78)	(2.94)	(0.62)	(42.10)	(2.06)	(29)
600 mg granules for oral suspension						
single dose	11.00	-----	0.97	80.80	4.60	141
	(2.76)		(0.88)	(35.10)	(1.71)	(45)

*AUC for single dose = $AUC_{0-\infty}$
*AUC for multiple doses = $AUC_{0-\tau}$
‡ Data normalised from 625 mg dose
C_{max} = Maximum plasma concentration
C_{min} = Minimum plasma concentration
T_{max} = Time to C_{max}
AUC = Area under concentration-time curve
$t_{½}$ = Elimination half-life
CL = Systemic clearance

As can be seen from the above table, average C_{min} values achieved in plasma using the 600 mg bid dosage regimen approximate to the highest MIC_{90} (4 µg/mL) for the least susceptible microorganisms.

Absorption

Linezolid is rapidly and extensively absorbed following oral dosing. Maximum plasma concentrations are reached within 2 hours of dosing and the absolute bioavailability is approximately 100%. Absorption from the oral suspension is similar to that achieved with the film-coated tablets. Steady-state conditions are achieved by the second or third day of dosing.

Zyvox may be administered without regard to the timing of meals. The time to reach the maximum concentration is delayed from 1.5 hours to 2.2 hours and C_{max} is decreased by about 17% when high fat food is given with linezolid. However, the total exposure measured as $AUC_{0-\infty}$ values is similar under both conditions.

Distribution

Linezolid is readily distributed to well perfused tissues. Its volume of distribution at steady-state averages 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 multiple linezolid dosing.

Metabolism

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

Excretion

In patients with normal renal function or mild to moderate renal insufficiency, linezolid is primarily excreted as metabolite A (40%), parent drug (30-35%) and metabolite B (10%) in the urine. Virtually no parent drug is found in the faeces whilst approximately 6% and 3% of each dose appears as metabolites A and B, respectively. The elimination half-life 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 (≥65 years)

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

Children and adolescents

The pharmacokinetics of linezolid following a single IV dose were investigated in healthy adolescent subjects, ranging in age from 12 through 17 years, and in paediatric patients, ranging in age from 1 week through 12 years. The pharmacokinetic parameters of linezolid are summarised in Table 16 for the paediatric populations studied and healthy adult subjects after administration of single IV dose.

The C_{max} and the volume of distribution (V_{ss}) of linezolid 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 those observed for the adult population. There is a wider inter-subject variability in linezolid clearance and systemic drug exposure (AUC) across all paediatric age groups as compared with adults.

Similar mean daily AUC values were observed in paediatric patients from birth to 11 years of age dosed every 8 hours relative to adolescents or adults dosed every 12 hours. Therefore, the dosage for paediatric patients up to 11 years of age should be 10 mg/kg every 8 hours.

Paediatric patients 12 years and older should receive 600 mg every 12 hours (see Section 4.2 Dose and method of administration).

Recommendations for the dosage regimen for pre-term neonates less than 7 days of age (gestational age less than 34 weeks) are based on pharmacokinetic data from 9 pre-term neonates. Most of these pre-term neonates have lower systemic linezolid clearance values and larger AUC values than many full term neonates and older infants. Therefore, these pre-term neonates should be initiated with a dosing regimen of 10 mg/kg every 12 hours. Consideration may be given to the use of a 10 mg/kg every 8 hours regimen in neonates with a sub-optimal clinical response. All neonatal patients should receive 10 mg/kg every 8 hours by 7 days of life (see Section 4.2 Dose and method of administration).

Table 16: Pharmacokinetic parameters of linezolid in paediatric and adult patients following a single intravenous infusion of 10 mg/kg or 600 mg linezolid (Mean (%CV): (Min., Max. values))

Age group	C_{max} µg/mL (SD)	V_{ss} L/kg (SD)	AUC* µg h/mL (SD)	$t_{½}$ hrs (SD)	CL mL/min/kg (SD)
Neonatal patients	12.7 (30%)	0.81 (24%)	108 (47%)	5.6 (46%)	2.0 (52%)
Pre-Term**	(9.6, 22.2)	(0.43, 1.05)	(41, 191)	(2.4, 9.8)	(0.9, 4.0)
<1 week (N = 9)					
Full-Term***	11.5 (24%)	0.78 (20%)	55 (47%)	3.0 (55%)	3.8 (55%)
<1 week (N = 10)†	(8.0, 18.3)	(0.45, 0.96)	(19, 103)	(1.3, 6.1)	(1.5, 8.8)
Full-Term***	12.9 (28%)	0.66 (29%)	34 (21%)	1.5 (17%)	5.1 (22%)
≥1 week to ≤28 days (N = 10)	(7.7, 21.6)	(0.35, 1.06)	(23, 50)	(1.2, 1.9)	(3.3, 7.2)
Infant patients	11.0 (27%)	0.79 (26%)	33 (26%)	1.8 (28%)	5.3 (34%)
>28 days to <3 months (N = 12)†	(7.2, 18.0)	(0.42, 1.08)	(17, 48)	(1.2, 2.8)	(3.5, 9.9)
Paediatric patients	15.1 (30%)	0.69 (28%)	58 (54%)	2.9 (53%)	3.8 (53%)
3 months through 11 years† (N = 59)	(6.8, 36.7)	(0.31, 1.50)	(19, 153)	(0.9, 8.0)	(1.0, 8.5)
Adolescents	16.7 (24%)	0.61 (15%)	95.0 (44%)	4.1 (46%)	2.1 (53%)
12 through 17 years‡	(9.9, 28.9)	(0.44, 0.79)	(32, 178)	(1.3, 8.1)	(0.9, 5.2)
(N = 18)					
Adults§	12.5 (21%)	0.65 (16%)	91 (33%)	4.9 (35%)	1.7 (34%)
(N = 29)	(8.2, 19.3)	(0.45, 0.84)	(53, 155)	(1.8, 8.3)	(0.9, 3.3%)

AUC = Area under the curve.
* AUC = single dose AUC t-∞
** In this data set "pre-term" is defined as <34 weeks gestational age (Note: only 1 patient enrolled was pre-term with a postnatal age between 1 week and 28 days).
*** In this data set 'full-term" is defined as ≥34 weeks of gestational age.
† Dose of 10 mg/kg.
‡ Dose of 10 mg/kg up to a maximum of 600 mg.

§ Dose normalised to 600 mg.
C_{max} = maximum plasma concentration.
V_{ss} = volume of distribution.
$t_{1/2}$ = apparent elimination half-life.
CL = systemic clearance normalised for body weight.

Renal impairment

No dose adjustment is necessary in patients with either mild, moderate or severe renal insufficiency as total clearance is independent of creatinine clearance. There is evidence that the two primary metabolites of linezolid accumulate in patients with severe renal insufficiency (CL_{CR} <30 mL/min). The clinical significance of this has not been established as limited safety data are currently available. As approximately 30% of a linezolid dose is removed during 3 hours of haemodialysis (beginning 3 hours after administration), Zyvox should be given after dialysis in patients receiving such treatment. The primary metabolites of linezolid are also removed 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. No information is available on the effect of peritoneal dialysis on the pharmacokinetics of linezolid.

Hepatic impairment

The pharmacokinetics of linezolid are not altered in patients with mild to moderate hepatic insufficiency. Dose adjustment in such patients is 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.

Gender

Some pharmacokinetic parameters of linezolid differ in female subjects. 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 somewhat 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

Genotoxicity

There was no evidence of genotoxicity in tests for gene mutations (bacteria and Chinese hamster ovary cells), chromosomal changes (human lymphocytes *in vitro* and mouse micronucleus assay *in vivo*) and DNA damage (unscheduled DNA synthesis *in vitro*).

Carcinogenicity

Lifetime studies in animals have not been conducted to evaluate the carcinogenic potential of linezolid.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets

Microcrystalline cellulose, maize starch, sodium starch glycollate, hyprolose, magnesium stearate and in the film coating, Opadry YS-1-18202-A White and carnauba wax.

Granules for oral suspension

Sucrose, mannitol, microcrystalline cellulose, carmellose sodium, aspartame, colloidal anhydrous silica, sodium citrate dihydrate, xanthan gum, sodium benzoate, citric acid and sodium chloride. The granules are flavoured with Mafco magnasweet, orange flavour, orange cream flavour, sweet-am powder, vanilla flavour and peppermint flavour.

Solution for injection

Glucose monohydrate, sodium citrate dihydrate, citric acid, hydrochloric acid/sodium hydroxide and water for injections.

6.2 Incompatibilities

Additives should not be introduced into Zyvox solution for injection. If Zyvox is to be given concomitantly with other drugs, each drug should be given separately in accordance with its own directions for use. Similarly, if the same intravenous line is to be used for sequential infusion of several drugs, the line should be flushed prior to and following Zyvox administration with a compatible infusion solution (5% glucose solution for injection, 0.9% sodium chloride solution for injection or compound sodium lactate solution for injection [Hartmann's solution for injection]).

Zyvox injection is known to be physically incompatible with the following compounds: amphotericin B, chlorpromazine hydrochloride, diazepam, pentamidine isethionate, erythromycin lactobionate, phenytoin sodium and sulphamethoxazole/ trimethoprim. Additionally, it is chemically incompatible with ceftriaxone sodium.

6.3 Shelf life

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

Granules for oral suspension

Before reconstitution: Keep the bottle tightly closed.

After reconstitution: Keep the bottle in the outer carton in order to protect from light. Keep the bottle in the outer carton after reconstitution. Discard if not used within 3 weeks after reconstitution.

Solution for injection

Store in the original package (overwrap and carton) until ready to use in order to protect from light.

After opening, from a microbiological point of view, the product should be used immediately. The product is for single use in one patient only. Discard any residue.

6.4 Special precautions for storage

Store below 25°C. Store in original container in order to protect from light.

6.5 Nature and contents of container

Tablets

PVC/AL blister packs of 10's and 30's.

Granules for oral suspension

Amber glass bottle with screw cap packaged in a box with a 2.5 mL/5 mL measuring spoon; 150 mL pack of 1.

Solution for injection

Single use, ready-to-use, film infusion bags. Bags are sealed inside a foil laminate overwrap and packed in boxes of 1 or 10 100 mL, 200 mL and 300 mL infusion bags.

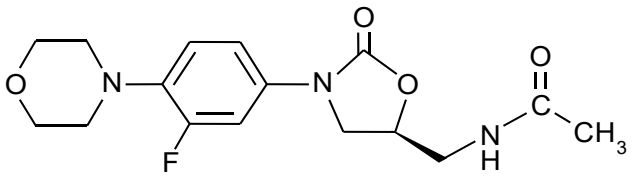
Not all pack sizes and presentations are supplied.

6.6 Special precautions for disposal

In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7 Physicochemical properties

Chemical structure



The chemical name is (S)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl] methyl]-acetamide. The empirical formula of linezolid is $C_{16}H_{20}FN_3O_4$ and the molecular weight of 337.35.

The aqueous solubility of linezolid is approximately 3 mg/mL, independent of pH between pH 3 to 9.

CAS number

165800-03-3.

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4, Prescription only medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
Level 17, 151 Clarence Street
Sydney NSW 2000
Toll Free Number: 1800 675 229
www.pfizermedical.com.au

9. DATE OF FIRST APPROVAL

24 September 2001

10. DATE OF REVISION

24 July 2026

® Registered trademark.

Summary Table of Changes

Section changed	Summary of new information
All	Minor editorial changes
4.8	Update presentation and format of post-marketing experience ADRs including addition of trichoglossia.
4.9	Update to standard statement in alignment with PI template.
8	Update to Sponsor website address.