NEW ZEALAND DATA SHEET

1. PRODUCT NAME

Zyvox® 600 mg Film coated tablets (Tablets)

Zyvox® 20 mg/mL Granules for oral suspension (Granules)

Zyvox® 2 mg/mL Solution for infusion (Injection)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Tablets

Each Zyvox 600 mg tablet contains 600 mg linezolid.

Granules

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

Injection

Each 1 mL of Zyvox injection contains 2 mg of linezolid. The 300 mL infusion bag contains 600 mg of linezolid. The 200 mL infusion bag contains 400 mg linezolid. The 100 mL infusion bag contains 200 mg of linezolid.

Excipients with known effect

Granules

Each mL also contains 7 mg aspartame, 100 mg mannitol, 210.6 mg sucrose, 1.7 mg sodium as well as 2.4 mg fructose, 7.2 mg sorbitol (E420), ethanol (alcohol) and less than 20 mg ethanol (alcohol) available in sweeteners and flavouring.

Injection

Each mL injection contains 45.6 mg glucose and less than 0.5 mg sodium.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Tablets

Off-white coated tablet with “ZYV” debossed on one side and “600” debossed on the other.

Granules

White to yellow-orange granules and may contain white to yellow-orange-brown lumps. The constituted suspension is white to yellow-orange and orange flavoured.

Injection

Isotonic, clear, colourless to yellow solution with pH range of 4.4-5.2.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Zyvox is indicated for the treatment of infections when known or suspected to be caused by susceptible organisms including those associated with concurrent bacteraemia such as:

- Pneumonia - community acquired and nosocomial pneumonia
- Skin and soft tissue infections
- Enterococcal infections.

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

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Dose and Method of Administration

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%.

Adults and Children 12 Years or Older

The recommended dosage should be administered intravenously (IV) or orally twice daily 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. To date, the maximum treatment duration in controlled clinical trials has been 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

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	10-14 consecutive days
Nosocomial 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	14-28 consecutive days

Children Less than 12 Years Old

The recommended dosage should be administered intravenously (IV) or orally as shown in Table 2. As for adults and adolescents, the 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.

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

Infections (including those associated with concurrent bacteraemia)	Dosage for paediatric patients from birth to 11 years of age[§]	Duration of treatment
Community acquired pneumonia	10 mg/kg IV or orally* once every 8 hours	10 to 14 consecutive days
Nosocomial pneumonia		
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 for 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, Paediatric patients)**.**

Elderly

No dose adjustment is required.

Renal impairment

No dose adjustment is required. However, Zyvox should be administered after haemodialysis in patients receiving such treatment (see Sections 4.4 and 5.2).

Hepatic impairment

No dose adjustment is required.

Method of administration

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

A 600 mg dose is provided by 30 mL of reconstituted suspension (i.e., six 5 mL spoonfuls). For instructions on reconstitution of the medicinal product before administration, see section 6.6.

The injection should be administered over a period of 30 to 120 minutes.

4.3 Contraindications

Hypersensitivity to linezolid or to any of the excipients in the relevant pharmaceutical form (see excipients listed in Section 6.1).

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, noradrenaline), dopaminergic agents (e.g., dopamine, dobutamine) (see Section 4.5).

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 re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT1 receptor agonists (triptans), pethidine or buspirone (see Section 4.5).

4.4 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, those receiving concomitant drugs that produce bone marrow suppression or may decrease haemoglobin levels or platelet count or function, who have severe renal insufficiency or moderate to severe hepatic impairment, 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.

Clinical trials

Controlled clinical trials did not include patients with diabetic foot lesions, decubitus, or ischaemic lesions, severe burns or gangrene. Therefore, experience in the use of linezolid in the treatment of these conditions is limited.

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.

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 co-administration of Zyvox and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs) and opioids have been reported (see Sections 4.3 and 4.5).

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.

Rifampicin

In healthy volunteers, coadministration of rifampin with linezolid resulted in a 21% decrease in linezolid Cmax and a 32% decrease in linezolid AUC (see Section 4.5). The clinical significance of this interaction is unknown.

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, randomized 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 randomized 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 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. 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 Sections 4.2, 5.1 and 5.2.).

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 5.1 and 4.2).

Use in renal impairment

Linezolid should be used with special caution in patients with severe renal impairment 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 impairment 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.

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

The effect of rifampin on the pharmacokinetics of linezolid was studied in sixteen healthy adult male volunteers administered linezolid 600 mg twice daily for 2.5 days with and without rifampin 600 mg once daily for 8 days. Rifampin decreased the linezolid Cmax 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).

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). Initial doses of potent vasopressors, such as dopamine and adrenaline, should be reduced and carefully titrated to achieve the desired response when coadministered with Zyvox (see Section 4.3).

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.

Very rare spontaneous reports of serotonin syndrome with co-administration of linezolid and serotonergic agents have been reported. 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. See Section 4.3 Contraindications and Section 4.4 Special warnings and precautions for use.

4.6 Fertility, Pregnancy and Lactation

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 approximately equal to those expected in humans.

Epithelial hypertrophy of the epididymis may have contributed to the decreased fertility by affecting sperm maturation. However, an effect on spermatogenesis cannot be excluded as delayed spermiation in the testes occurred at 100 mg/kg/day (twice the clinical exposure). Sperm counts in the testes were unaffected but sperm counts in the cauda epididymis were decreased and sperm from the vas deferens had decreased motility. Most sperm from the epididymis in rats treated with 100 mg/kg/day had detached head/neck from the tail.

Epithelial hypertrophy was not observed in beagle dogs which suggests that the above effects are species specific to rats.

Slightly decreased fertility occurred in juvenile male rats treated orally with linezolid at 50 mg/kg/day from 7 days to 42 days old and at 100 mg/kg/day from 43 days to 55 days old. Delayed spermatid development was observed in juvenile rats treated with linezolid at 63 mg/kg/day and single-cell spermatocyte/spermatid degeneration or necrosis (apoptosis) was observed in juvenile rats treated with linezolid at 100 mg/kg/day (all reversible).

Pregnancy

Australian 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.

Embryofetal 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).

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 Machinery

The effect of linezolid on the ability to drive or operate machinery has not been systematically evaluated.

4.8 Undesirable Effects

Clinical Trials

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

Adults

More than 2,000 adult patients received the recommended linezolid 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 and candidiasis (particularly oral and vaginal candidiasis; see table below). Abdominal pain, abdominal cramps and abdominal distension were considered drug-related adverse events in controlled clinical trials with an incidence of at least 1%. The most commonly reported drug-related adverse events which led 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
Abnormal liver function tests	1.0	0.3
General body		
Headache	2.1	1.3
Special senses		
Taste perversion	1.1	0.7
Urogenital		
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 to 11 years and in 248 paediatric patients aged 5 to 17 years (146 of these, 248 were age 5 to 11 and 102 were age 12 to 17). 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 to 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	Uncomplicated skin and skin structure infections[†]		All other indications[‡]	
	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

Event	Uncomplicated skin and skin structure infections†		All other indications‡	
	ZYVOX (n= 248)	Cefadroxil (n= 251)	ZYVOX (n= 215)	Vancomycin (n=101)
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 to 11 years of age received ZYVOX 10mg/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 to 11 years received ZYVOX 10 mg/kg IV/PO or vancomycin 10 to 15 mg/kg IV q6-24, 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 to 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 to 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	Uncomplicated skin and skin structure infections†		All other indications‡	
	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 to 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 to 11 years received ZYVOX 10 mg/kg IV/PO or vancomycin 10 to 15 mg/kg IV q6-24, depending on age and renal clearance.

Post-marketing experience

Reversible myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) and sideroblastic anaemia have been reported.

Peripheral neuropathy, and optic neuropathy 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 (see Section 4.4).

Lactic acidosis (see Section 4.4), rash, convulsions, angioedema, anaphylaxis and hypersensitivity vasculitis have been reported.

Very rare reports of bullous skin disorders including severe cutaneous adverse reactions such as those described as toxic epidermal necrolysis and Stevens Johnson syndrome have been received.

Gastrointestinal Disorders: Tongue discoloration. Superficial tooth discoloration has been reported very rarely with the use of linezolid. The discoloration was removable with professional dental cleaning (manual descaling) in cases with known outcome.

Reporting suspected adverse effects

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/.

4.9 Overdosage

No cases of overdose have been reported. Symptomatic and supportive care is advised together with maintenance of glomerular filtration. Approximately 30% of a linezolid dose is removed during 3 hours of haemodialysis. No data are available for the removal of linezolid by peritoneal dialysis or haemoperfusion.

Contact the Poisons Information Centre 0800 764 766 for advice on the management of an overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

General Properties

Linezolid is a synthetic, antibacterial agent belonging to the 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 MIC breakpoints in Table 7 separate susceptible from non-susceptible isolates.

Table 7: 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 = intermediately 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
Streptococcus 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 that of other classes of antibiotics and cross-resistance between linezolid and other classes of antibiotics is unlikely.

Resistance to linezolid developed under selective pressure *in vitro* and was associated with point mutations in the 23S ribosomal RNA. Spontaneous resistance occurs at frequencies of less than 10^{-9} *in vitro*. In clinical trials, resistance to linezolid developed in 6 patients infected with *E. faecium* (4 patients received 200 mg twice daily, lower than the recommended dose, and 2 patients received 600 mg twice daily). 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.

Clinical efficacy and safety

Adult

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 twice daily (bid), and another group (no. enrolled = 197) received vancomycin 1 g bid intravenously (IV). 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 8.

Table 8: 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 9 shows the clinical cure rates for microbiologically evaluable patients in these studies.

Table 9: 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 10.

Table 10: 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 11.

Table 11: 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 12 by source of infection.

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)

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

Uncomplicated Skin and Skin Structure Infections

Paediatric patients (5 to 17 years of age) with clinically documented uncomplicated skin and skin structure infections were enrolled in a randomised, multi-centre, double-blind trial comparing ZYVOX versus cefadroxil for a total of 10 to 21 days of treatment. Patients aged 5 to 11 years received ZYVOX for Oral Suspension 10 mg/kg every 12 hours or cefadroxil oral suspension 15 mg/kg every 12 hours. Patients aged 12 years or older received ZYVOX Tablets 600 mg every 12 hours or cefadroxil capsules 500 mg every 12 hours. There were 248 linezolid-treated and 251 cefadroxil-treated patients enrolled in the study. Two hundred twenty-four (90.3%) linezolid-treated patients and 216 (86.1%) cefadroxil-treated patients were clinically evaluable. The cure rates in clinically evaluable patients were 91% in linezolid-treated patients and 90% in cefadroxil-treated patients. The cure rates by pathogen for microbiologically evaluable patients are presented in Table 13.

Table 13: Cure rates at the test-of-cure visit for microbiologically evaluable paediatric patients with uncomplicated skin and skin structure infections

Pathogen	Cured	
	Zyvox n/N (%)	Cefadroxil n/N (%)
Staphylococcus aureus	120/133(90)	111/125 (89)
Methicillin-resistant *S. aureus*	12/13 (92)	6/7 (86)
Streptococcus agalactiae	1/1 (100)	2/2 (100)
Streptococcus pyogenes	32/33 (97)	26/27 (96)

Infections Due to Resistant Gram-Positive Organisms

A safety and efficacy study 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, 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 to 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 IV Injection 10 mg/kg every 8 hours followed by ZYVOX for 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

Linezolid is biologically active and is metabolised to form inactive derivatives. The aqueous solubility of linezolid is approximately 3 mg/mL, independent of pH between pH 3 to 9.

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} mcg/mL (SD)**	**C_{min} mcg/mL (SD)**	**T_{max} hrs (SD)**	**AUC* mcg.h/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)
600 mg film coated tablet						
single dose	12.70 (3.96)	-----	1.28 (0.66)	91.40 (39.30)	4.26 (1.65)	127 (48)
bid dose	21.20 (5.78)	6.15 (2.94)	1.03 (0.62)	138.00 (42.10)	5.40 (2.06)	80 (29)
600 mg granules for oral suspension						
single dose	11.00 (2.76)	-----	0.97 (0.88)	80.80 (35.10)	4.60 (1.71)	141 (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 twice daily dosage regimen approximate to the highest MIC_{90} (4 micrograms/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 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 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.

Elimination

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

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 (*i.e.,* Child-Pugh class A or B). Dose adjustment in such patients is not required. The pharmacokinetics of linezolid in patients with severe hepatic insufficiency (*i.e.,* Child-Pugh class C) have not been evaluated. However, as linezolid is metabolised by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism.

Paediatric Patients

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

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).

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					
Pre - Term ** < 1 week (N = 9)	12.7 (30%) (9.6, 22.2)	0.81 (24%) (0.43, 1.05)	108 (47%) (41, 191)	5.6 (46%) (2.4, 9.8)	2.0 (52%) (0.9, 4.0)
Full – Term*** < 1 week (N = 10) †	11.5 (24%) (8.0, 18.3)	0.78 (20%) (0.45, 0.96)	55 (47%) (19, 103)	3.0 (55%) (1.3, 6.1)	3.8 (55%) (1.5, 8.8)
Full – Term *** ≥1 week to ≤ 28 days (N = 10)	12.9 (28%) (7.7, 21.6)	0.66 (29%) (0.35, 1.06)	34 (21%) (23, 50)	1.5 (17%) (1.2, 1.9)	5.1 (22%) (3.3, 7.2)
Infant Patients > 28 days to < 3 months (N = 12) †	11.0 (27%) (7.2, 18.0)	0.79 (26%) (0.42, 1.08)	33 (26%) (17, 48)	1.8 (28%) (1.2, 2.8)	5.3 (34%) (3.5, 9.9)

Paediatric Patients 3 months to 11 years † (N = 59)	15.1 (30%) (6.8, 36.7)	0.69 (28%) (0.31, 1.50)	58 (54%) (19, 153)	2.9 (53%) (0.9, 8.0)	3.8 (53%) (1.0, 8.5)
Adolescents 12 to 17 years ‡ (N = 18)	16.7 (24%) (9.9, 28.9)	0.61 (15%) (0.44, 0.79)	95.0 (44%) (32, 178)	4.1 (46%) (1.3, 8.1)	2.1 (53%) (0.9, 5.2)
Adults§ (N = 29)	12.5 (21%) (8.2, 19.3)	0.65 (16%) (0.45, 0.84)	91 (33%) (53, 155)	4.9 (35%) (1.8, 8.3)	1.7 (34%) (0.9, 3.3%)

AUC = Area Under the Curve

* AUC = single dose AUC $_{t-\infty}$

** 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 normalized to 600 mg

C_{max} = maximum plasma concentration

V_{ss} = volume of distribution

$t_{1/2}$ = apparent elimination half-life

CL = systemic clearance normalized for body weight

Elderly

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

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

Carcinogenicity

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

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*).

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

Zyvox tablets contain, in the core, microcrystalline cellulose, maize starch, sodium starch glycollate type A, hyprolose, magnesium stearate and, in the film coating, Opadry YS-1-18202-A White and carnauba wax.

Zyvox granules contain 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.

Zyvox injection contains 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 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 linezolid administration with a compatible infusion solution (5% glucose injection, 0.9% sodium chloride injection or compound sodium lactate 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 sulfamethoxazole/trimethoprim. Additionally, it is chemically incompatible with ceftriaxone sodium.

6.3 Shelf Life

Tablets: 36 months. Store at or below 25ºC.

Granules: Unreconstituted: 36 months. Stored at or below 25°C. Reconsitituted: 3 weeks. Stored at or below 25°C.

6.4 Special Precautions for Storage

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

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and Contents of Container

Tablets

PVC/Al Blister packs of 10 and 30 tablets.

Granules

Amber glass bottle with a nominal volume of 150 mL containing 20 mg/mL granules for oral suspension. Each bottle has a screw cap packaged in a box with a 2.5 mL/5 mL measuring spoon.

Injection

200 mg/100 mL, 400 mg/200 mL and 600 mg/300 mL solution in single use, ready-to-use, film infusion bags (which do not contain latex). Bags are sealed inside a foil laminate overwrap and packed in boxes of 1 or 10* infusion bags.

* Not all pack sizes and presentations may be commercially available.

6.6 Special Precautions for Disposal and Other Handling

Granules

Keep the bottle tightly closed before reconstitution. The granules should be reconstituted using 123 mL 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.

Injection

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 these 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.

7. MEDICINE SCHEDULE

S4, Prescription Medicine.

8. SPONSOR

Pfizer New Zealand Limited

P O Box 3998

Auckland, New Zealand, 1140.

Toll Free Number: 0800 736 363.

9. DATE OF FIRST APPROVAL

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Summary table of changes

Section changed	Summary of new information
4.4	Update to warning text to include risk factors of moderate to severe hepatic impairment and severe renal insufficiency associated with thrombocytopenia, and blood monitoring for patients who receive concomitant medications that may decrease haemoglobin levels or platelet count or function.