AUSTRALIAN PRODUCT INFORMATION –LINEZOLID KABI (LINEZOLID) SOLUTION FOR INTRAVENOUS INFUSION

1 NAME OF THE MEDICINE

Linezolid

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Linezolid Kabi 2 mg/mL solution for intravenous infusion.

The solution also contains glucose monohydrate, sodium citrate, citric acid, hydrochloric acid/sodium hydroxide and water for injections.

3 PHARMACEUTICAL FORM

Each 300 mL infusion bag or bottle contains 600 mg linezolid (i.e. 2 mg/mL) in an isotonic, clear, colourless to yellow solution.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Linezolid 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.

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.

4.2 DOSE AND METHOD OF ADMINISTRATION

Patients who commence treatment on the parenteral formulation may be switched to an oral preparation when clinically indicated. In such circumstances, no dose adjustment is required as linezolid has an oral bioavailability of approximately 100%.

The injection should be administered over a period of 30–120 minutes. An oral preparation may be taken with or without food.

The maximum recommended duration of treatment is 28 days.

An oral preparation of Linezolid Kabi is not available; where clinically indicated, another brand of an oral linezolid dosage form is to be administered.

Adults and Children 12 years or older

The recommended dosage should be administered intravenously 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. 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 linezolid for adults and children 12 years and 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	10–14 consecutive days
Nosocomial (hospital acquired) pneumonia		
Skin and soft tissue infections	600 mg IV or 400–600 mg orally 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 or orally as shown in Table 2. The maximum recommended duration of treatment is 28 days.

Table 2. Dosage guidelines for linezolid 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	10–14 consecutive days
Skin and soft tissue infections		
Enterococcal infections		14–28 consecutive days

§ Neonates < 7 days: most pre-term neonates < 7 days of age (gestational age < 34 weeks) have low systemic linezolid clearance values and large 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 5.1 Pharmacodynamic Properties, Paediatric).

Dosage Adjustments in Special Populations

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

Incompatibilities

Additives should not be introduced into linezolid injection. If linezolid is to be given concomitantly with other medicines, each medicine 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, 0.9% sodium chloride or compound sodium lactate (Hartmann's solution for injection)].

Linezolid 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.

Instructions for Use and Handling

Injection

If using **free***flex*® bags, keep in foil overwrap and carton until ready to use. Remove overwrap and check for minute leaks by squeezing the bag firmly. Do not use if the bag leaks as sterility may be impaired. If using Kabi**Pac**® bottles, keep in carton until ready to use.

Any solutions which are discoloured, hazy or contain visible particulate matter should not be used. Do not use **free***flex*® bags or Kabi**Pac**® bottles in series connections. Do not reconnect partially used bags or bottles.

Linezolid Kabi contains no preservative. It is for single use in one patient only. Discard any residue.

4.3 CONTRAINDICATIONS

Hypersensitivity to linezolid or to any of the excipients (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 medicine which inhibits monoamine oxidases A or B (*e.g.* phenelzine) or within two weeks of taking any such medicine.

Potential Interactions Producing Elevation of Blood Pressure

Unless patients are monitored for potential increases in blood pressure, linezolid should not be administered to patients with uncontrolled hypertension, pheochromocytoma,

thyrotoxicosis and/or patients taking any of the following types of medicines: directly- and indirectly-acting sympathomimetic agents (*e.g.* pseudoephedrine), vasopressive agents (*e.g.* adrenaline, noradrenaline), 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 medicines: serotonin re-uptake inhibitors, tricyclic antidepressants, serotonin 5-HT_1 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 linezolid 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. 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 medicines that produce bone marrow suppression 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 linezolid 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.

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 was reported.

Serotonin syndrome

Spontaneous reports of serotonin syndrome associated with the co-administration of linezolid and serotonergic agents, including antidepressants such as selective serotonin reuptake inhibitors (SSRIs), have been reported (see Sections 4.4 Special warnings and precautions for use and 4.5 Interactions with medicines and other forms of interactions).

Antibiotic associated pseudomembranous colitis

Antibiotic-associated pseudomembranous colitis has been reported with nearly all antibacterial agents including linezolid. A toxin produced by *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 *C. difficile* should be considered. Fluids, electrolytes and protein replacement should be provided when indicated. Medicines 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.

The safety and effectiveness of linezolid 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.

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 for 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 every 12 hours IV/PO) to vancomycin 1 g IV every 12 hours or oxacillin 2 g IV every 6 hours/dicloxacillin 500 mg orally every 6 hours with a treatment duration of 7–28 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 pathogen 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.

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.

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.

Use in 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 metabolized by a non-enzymatic process, impairment of hepatic function would not be expected to significantly alter its metabolism.

Use in 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), linezolid 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.

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 12–17 years) is usually similar to the clearance in adults, there is wider inter-subject variation in this age group compared with adults (see 5.1 Pharmacodynamic Properties, Paediatrics). 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 linezolid 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 Pharmacodynamic Properties).

Effects on laboratory tests

No data available

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Linezolid is not detectably metabolized 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 linezolid. Medicines such as warfarin and phenytoin, which are CYP2C9 substrates, may be given with linezolid without changes in dosage regimen.

Linezolid is a reversible, non-selective inhibitor of monoamine oxidase. Limited clinical studies have shown that co-administration of linezolid 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, should be reduced and carefully titrated to achieve the desired response when co-administered with linezolid (see Section 4.3 Contraindications).

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

Linezolid has the potential for interaction with serotonergic agents. Limited clinical studies have shown that co-administration of linezolid 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 co-administration of linezolid and serotonergic agents, including antidepressants such as SSRIs, have been reported (see Section 4.3 Contraindications). Patients who are treated with linezolid 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 (linezolid 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 twice daily for 2½ 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 oral doses up to 40 mg/kg/day (0.7× clinical exposure) for 3 months or IV doses up to 40 mg/kg/day (1.3× 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 7–36, and 100 mg/kg/day from days 37–55), at exposures up to 1.7× 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 5–21) or juvenile

exposure (postnatal days 22–35). Reversible reductions in sperm motility and altered sperm morphology were observed in rats following treatment on postnatal days 22–35.

Juvenile dogs administered linezolid for 1 month at doses up to 100 mg/kg/day *orally* (2.2× 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 linezolid in pregnant women. Studies in animals have shown reproductive effects (see below). The potential risk for humans is unknown.

Linezolid 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× (mice) or equivalent to (rats) the expected human exposure level, based on AUCs.

Embryofoetal effects were observed in mice at 450 mg/kg/day (4× the clinical exposure based on AUC) and in rats at 15 mg/kg/day (0.14× the clinical exposure based on AUC). Decreased foetal weights and delayed ossification occurred in rats without maternal toxicity. In mice, increased embryo death including total litter loss, decreased foetal 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 twice daily at total oral doses up to 15 mg/kg/day (0.06× the clinical exposure, based on AUC), although maternal toxicity (clinical signs, reduced bodyweight gain and food consumption) occurred at 5 and 15 mg/kg/day and reduced foetal bodyweight 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× the clinical exposure based on AUC) was slightly delayed, manifested 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 Section 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 occur

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Clinical Trials

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 linezolid doses for up to 28 days. In these studies, the majority of adverse reactions to linezolid 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 linezolid 600 mg bid in the VRE dose-response study

Event	Linezolid (%) (n = 2,125)	All comparators* (%) (n = 2,001)
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 haematological or serum chemistry value is presented in Table 4.

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

Laboratory assay	Linezolid (%)	All comparators** (%)
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× baseline for values abnormal at baseline

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

Paediatric Patients

The safety of linezolid formulations was evaluated in 215 paediatric patients ranging in age from birth through 11 years and in 248 paediatric patients aged 5–17 years (146 were aged 5–11 and 102 were aged 12–17). These patients were enrolled in two phase III 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 linezolid were described as mild to moderate in intensity. In the study of hospitalized paediatric patients (birth through 11 years) with Gram-positive infections, who were randomized 2:1 (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 III 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‡	
	Linezolid (%) (n = 248)	Cefadroxil (%) (n = 251)	Linezolid (%) (n = 215)	Vancomycin (%) (n = 101)
Patients with one drug-related adverse event	19.2	14.1	18.8	34.3
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
Generalized abdominal pain	1.6	1.2	0	0
Localized 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 linezolid 10 mg/kg orally every 12 hours or cefadroxil 15 mg/kg orally every 12 hours

† Patients 12 years or older received linezolid 600 mg orally every 12 hours or cefadroxil 500 mg orally every 12 hours

‡ Patients from birth through 11 years received linezolid 10 mg/kg IV/orally or vancomycin 10–15 mg/kg IV every 6-24 hours, depending on age and renal clearance

* These reports were of “red-man syndrome”, which were coded as anaphylaxis

In a study of severely ill, hospitalized 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 linezolid and 13.4% with vancomycin. In an outpatient study of paediatric patients aged 5–17 years, the percentage of patients who developed a substantially low platelet count was 0% with linezolid 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 haematological or serum chemistry value is presented in Table 6.

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

Event	Other comparator-controlled clinical trial†		Study 082‡	
	Linezolid (%)	Cefadroxil (%)	Linezolid (%)	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 received linezolid 10mg/kg orally every 12 hours or cefadroxil 15 mg/kg orally every 12 hours
† Patients 12 years or older received linezolid 600 mg orally every 12 hours or cefadroxil 500 mg orally every 12 hours
‡ Patients from birth through 11 years received linezolid 10 mg/kg IV/orally or vancomycin 10–15 mg/kg IV every 6-24 hours, depending on age and renal clearance

Post-Marketing Surveillance

Myelosuppression (including anaemia, leucopenia, pancytopenia and thrombocytopenia) and sideroblastic anaemia has 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 Special warnings and precautions for use). Lactic acidosis (see Section 4.4 Special warnings and precautions for use), 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.

Serotonin syndrome has been reported in patients receiving concomitant serotonergic agents, including antidepressants such as serotonin reuptake inhibitors (SSRIs) and linezolid (see Section 4.4 Special warnings and precautions for use).

Gastrointestinal Disorders: Tongue discolorationSuperficial tooth discoloration has been reported very rarely with the use of linezolid. The discoloration was removable with professional dental cleaning (manual scaling) in cases with known outcome. Abdominal pain, abdominal cramps and abdominal distension have been reported and considered drug related in controlled clinical trials.

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 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.

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 new 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 (µg/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*
- *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 pneumonia

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 *S. aureus*, *S. pneumoniae* and Enterococci resistant or non-susceptible to linezolid. In clinical trials, resistance to linezolid developed in six patients infected with *E. faecium* (four patients received 200 mg twice daily, lower than the recommended dose, and two patients received 600 mg twice daily). In a compassionate use program, resistance to linezolid developed in eight patients with *E. faecium* and in one 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

Adult

There are no data from comparator controlled clinical trials on the use of linezolid 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 randomized, multi-centre, double-blind clinical trial. Patients were treated for 7–21 days. One group (No. enrolled = 205) received linezolid injection 600 mg twice daily (bid), and another group (No. enrolled = 197) received vancomycin 1 g bid IV. Both groups

received concomitant aztreonam (1–2 g every 8 hours IV). Linezolid demonstrated efficacy equivalent to vancomycin in the treatment of patients with nosocomial pneumonia in all outcome measurements. The overall clinical cure rates in the Intention-To-Treat (ITT) population was 53% in the linezolid 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	
	Linezolid n/N (%)	Vancomycin n/N (%)
S. aureus	25/41 (61)	14/23 (61)
S. pneumoniae	9/9 (100)	9/9 (100)

Community-acquired pneumonia

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

One of these trials was an open-label study in which hospitalized patients received study medications administered IV followed by medications administered orally for a total of 7–14 days of treatment. One group of patients (No. enrolled = 389) received linezolid injection (600 mg bid) followed by linezolid 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 linezolid tablets 600 mg bid (No. enrolled = 278) and another group received cefpodoxime proxetil tablets 200 mg bid (No. enrolled = 270).

In these trials, linezolid demonstrated efficacy equivalent to ceftriaxone or cefpodoxime proxetil by all outcome measurements. The overall clinical cure rates in the ITT population in linezolid and comparator groups were 83% *versus* 76% and 82% *versus* 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	
	Linezolid n/N (%)	Ceftriaxone and Cefpodoxime proxetil n/N (%)
S. aureus	29/32 (91)	22/29 (76)
S. pneumoniae	88/98 (90)	81/90 (90)
H. 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 randomized, multi-centre, double-blind trial comparing study medications administered IV followed by medications given orally for a total of 10–21 days of treatment. One group of patients (No. enrolled = 403) received linezolid injection (600 mg bid) followed by linezolid tablets (600 mg bid); another group (No. enrolled = 423) received oxacillin 2 g every 6 hours IV followed by dicloxacillin 500 mg every 6 hours orally. Linezolid 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 linezolid group and 77% in the oxacillin group. 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	
	Linezolid n/N (%)	Oxacillin and Dicloxacillin n/N (%)
S. aureus	83/93 (89)	88/103 (85)
S. epidermidis	19/19 (100)	10/12 (83)
S. pyogenes	23/29 (79)	27/32 (84)
S. agalactiae	7/7 (100)	4/6 (67)

Methicillin-Resistant *S. aureus* (MRSA) infections

Adult patients with documented MRSA infections participated in a randomized, multi-centre, open-label trial. One group of patients (No. enrolled = 243) received linezolid injection 600 mg bid followed by linezolid tablets 600 mg bid. Another group of patients (No. enrolled = 225) received vancomycin 1 g bid IV. Both groups were treated for 7–28 days. Linezolid 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 linezolid group and 55% in the comparator group. 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	
	Linezolid 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 randomized, 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 7–28 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 linezolid 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% in the high-dose compared to 54% in the 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 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 linezolid 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 MRSA, methicillin-resistant *S. epidermidis*, penicillin-resistant *S. pneumoniae* 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 randomized, open-label, comparator-controlled trial. One group of patients received linezolid IV injection 10 mg/kg every 8 hours followed by linezolid oral suspension 10 mg/kg every 8 hours. A second group received vancomycin 10–15 mg/kg IV every 6–24 hours, depending on age and renal clearance. Patients who had confirmed VRE infections were placed in a third arm of the study and received linezolid 10 mg/kg every 8 hours IV and/or orally. All patients were treated for a total of 10–28 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 13.

Table 13. Cure rates at the test-of-cure visit for microbiologically evaluable paediatric patients with infections due to Gram-positive pathogens

Pathogen	Cured	
	Linezolid n/N (%)	Vancomycin n/N (%)
E. faecalis	7/10 (70)	3/4 (75)
E. faecium	5/5 (100)	0/0
S. aureus	37/39 (95)	24/26 (92)
S. epidermidis	23/29 (79)	11/13 (85)
*All coagulase-negative Staphylococci**	32/38 (84)	12/15 (80)
S. pneumoniae	3/3 (100)	1/1 (100)
S. 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 14.

Table 14. 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}** h (SD)	**AUC*** µg.h/mL (SD)	**$t_{1/2}$** h (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 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 Oral Suspension						
single dose	11.00 (2.76)	–	0.97 (0.88)	80.80 (35.10)	4.60 (1.71)	141 (45)

‡ Data normalized from 625 mg dose
* AUC for single dose = $AUC_{0-\infty}$
* AUC for multiple doses = $AUC_{0-\tau}$
AUC = Area under concentration-time curve
C_{max} = Maximum plasma concentration
C_{min} = Minimum plasma concentration
T_{max} = Time to C_{max}
$t_{1/2}$ = 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 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.

Linezolid may be administered without regard to the timing of meals. The time to reach the maximum concentration is delayed 1.5–2.2 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 metabolized 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 characterized.

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

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

Paediatric

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 summarized in Table 3 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 15. Pharmacokinetic parameters of linezolid in paediatric and adult patients following a single IV infusion of 10 mg/kg or 600 mg linezolid

Age Group	C_{max} µg/mL	V_{ss} L/kg	AUC* µg.h/mL	$t_{1/2}$ h	CL mL/min/kg
	Mean (% CV) (Min., Max. Values)				
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 years 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%)

* 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
AUC = Area Under the Curve
C_{max} = maximum plasma concentration

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), linezolid 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.

Use in 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 metabolized 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

Refer to Section 2 - Qualitative and quantitative composition.

6.2 INCOMPATIBILITIES

Refer to Section 4.2 Dose and Method of Administration .

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.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C in original packaging (including carton) until ready to use.

Protect from light.

6.5 NATURE AND CONTENTS OF CONTAINER

Single use, ready-to-use, latex-free, multi-layered polyolefin film **free***flex*® infusion bag sealed inside a foil laminate overwrap or a polyethylene bottle (as the primary packaging) with a polyethylene or polypropylene cap and polyisoprene stopper (Kabi**Pac**®).

free*flex*® and Kabi**Pac**® contain 300 mL solution (600 mg linezolid) and are packaged within a carton.

free*flex*® is supplied in cartons of 10, 30 or 50 infusion bags.*

Kabi**Pac**® is supplied in cartons of 1, 10, 20, 30 or 50 bottles.*

* Not all pack sizes may be marketed.

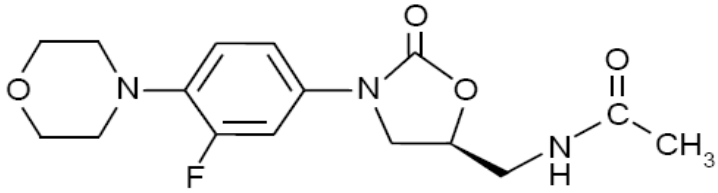
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Linezolid is a synthetic antibacterial agent of the oxazolidinone class. It is biologically active and is metabolized to form inactive derivatives. The aqueous solubility of linezolid is approximately 3 mg/mL, independent of pH between pH 3–9

Chemical structure



Chemical Name: (*S*)-N-[[3-[3-Fluoro-4-(4-morpholinyl)phenyl]-2-oxo-5-oxazolidinyl]methyl]acetamide

CAS registry number

165800-03-3

Molecular Formula: $C_{16}H_{20}FN_3O_4$

Molecular Weight: 337.35

7 MEDICINE SCHEDULE (POISONS STANDARD)

Australia: S4 - Prescription Only Medicine

New Zealand: Prescription

8 SPONSOR

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9 DATE OF FIRST APPROVAL

19 May 2017

10 DATE OF REVISION

6 August 2021

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
All	Change in format to SPC
4.4, 4.7, 4.8	Minor editorial & safety related changes as per innovator