Linezolid
Newborn use only

2020

Alert	Linezolid is not the standard first-line therapy for treatment of methicillin-resistant *Staphylococcus aureus* (MRSA) or coagulase-negative staphylococci (CoNS).[1] Antimicrobial stewardship team recommends this drug as restricted.
Indication	Treatment of Gram-positive infections either refractory to vancomycin or where vancomycin is contraindicated.
Action	Oxazolidinone class of antibiotic that act as a protein synthesis inhibitors on the ribosomal 50S subunit of the bacteria. This prevents the formation of the 70S initiation complex which is a prerequisite for bacterial reproduction. Linezolid possesses antimicrobial activity against a wide variety of Gram-positive pathogens, with bactericidal effects against most strains of *Streptococcus spp.* and bacteriostatic action against *Enterococcus spp.* and *Staphylococcus spp.*, including VRE, MRSA and methicillin-resistant CoNS. Linezolid is also active against anaerobes, atypical microbes such as *Chlamydia* and *Mycoplasma spp.*, some rapidly growing mycobacteria and selected Gram-negative bacilli.[2]
Drug type	Oxazolidinone antibiotic.
Trade name	Zyvox, Pharmacor Linezolid, Linezolid Kabi, Linezolid APO, Linezolid Amneal, Linevox
Presentation	IV: 600 mg in 300 mL infusion preparation (2 mg/mL) Oral suspension (after reconstitution): 100 mg/5 mL (20 mg/mL)
Dose	**Standard dosing** IV or Oral Intermittent regimen[2-4] Gestation: ≤34^{+6} weeks; Postnatal age: ≤7 days; Dose: 10 mg/kg/dose every 12 hours Gestation: ≤34^{+6} weeks; Postnatal age: >7 days; Dose: 10 mg/kg/dose every 8 hours Gestation: ≥35^{+0} weeks; Postnatal age: ; Dose: 10 mg/kg/dose every 8 hours IV continuous infusion[5] 30 mg/kg/day Higher dosing (for pathogens with MIC ≥2 mg/L) 12 mg/kg/dose 8-hourly. Watch for thrombocytopenia and lactic acidosis.[3]
Dose adjustment	Therapeutic hypothermia: Not enough evidence for dose adjustment ECMO: Adult data suggest standard dosing may not be sufficient.[6,7] Renal impairment: Consider therapeutic drug monitoring and adjust accordingly[8] (refer to monitoring section) Hepatic impairment: No dose adjustment is required[8]
Maximum dose	600 mg daily
Total cumulative dose	
Route	IV or Oral
Preparation	IV infusion: Use undiluted, supplied as ready-to-use infusion Oral suspension: Add 123 mL of water for irrigation to the powder in 2 parts and shake well to make a uniform suspension. Final reconstituted volume is 150 mL to make a final concentration of 20 mg/mL.
Administration	IV: Infuse over 30 to 120 minutes or administer as a continuous infusion. Oral: Shake well before use. May be given at any time with regards to feeds.
Monitoring	Periodic full blood count, lactate and liver function test for any development of thrombocytopenia, lactic acidosis and elevated transaminases, particularly if linezolid is used for >2 weeks[3,9] For use >4 weeks, monitor for cataracts and neuropathy[10,11] Therapeutic Drug Monitoring (TDM): TDM is not routine for linezolid in Australia. To balance linezolid efficacy and toxicity, suggested target trough concentrations in clinical studies were 2–8 mg/L, 3.6–8.2 mg/L or 2–7 mg/L.[8] In Australia, linezolid TDM is available at the following laboratories: St. Vincent's Hospital (NSW) – Ph: (02) 8382 9184 and Pathology Queensland – Ph: (07) 3646 0028.
Contraindications	Hypersensitivity to linezolid or any component of the formulation (MIMS online) Monoamine oxidase inhibitors: Linezolid should not be used in patients taking any medicinal product which inhibits monoamine oxidases A or B or within two weeks of taking any such medicinal product.[12] 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), vasopressor agents (e.g. adrenaline [epinephrine], noradrenaline [norepinephrine]), dopaminergic agents (e.g. dopamine, dobutamine)[12] Potential serotonergic interactions: Unless patients are carefully observed for signs and/or symptoms of serotonin syndrome, linezolid should not be administered to patients with carcinoid syndrome and/or patients taking any of the following medications: serotonin reuptake inhibitors, tricyclic antidepressants, pethidine or buspirone.[12]
Precautions	Infants with central nervous system infections due to variable linezolid CSF concentrations.[13] Myelosuppression (including anaemia, leukopenia, pancytopenia and thrombocytopenia) and lactic acidosis have been reported commonly. Serotonin syndrome: May occur with concomitant pro-serotonergic drugs, agents which reduce linezolid's metabolism or in patients with carcinoid syndrome. Avoid use in such patients unless clinically appropriate and under close monitoring for signs/symptoms of serotonin syndrome.[8] Peripheral and optic neuropathy has been reported in adults and children and may occur primarily with extended courses of therapy >28 days.[14-16]
Drug interactions	Sympathomimetic and adrenergic agents: As a non-selective monoamine oxidase (MAO) inhibitor, linezolid can raise noradrenaline (norepinephrine) concentrations and amplify adrenergic effects. Co-administration of linezolid with sympathomimetic agents or adrenergic agonists, such as pseudoephedrine and bronchodilators, increases the risk of adverse effects, including elevated blood pressure.[17] Serotonergic drugs: Co-administering linezolid with selective serotonin reuptake inhibitors (SSRI) or other serotonergic drugs can increase the risk of serotonin toxicity due to the additive serotonergic effects of MAO inhibitors.[18] If breastfeeding mother is on any antidepressants or antipsychotics, please contact clinical pharmacist to check if it is detected in breastmilk and risk of drug interactions. Rifampin and levothyroxine can increase clearance and decrease linezolid plasma concentrations.[8] Co-administration of linezolid with amiodarone or calcium channel blockers may also result in higher linezolid exposures.[8] Linezolid may interact with warfarin to increase the international normalised ratio (INR)[8]
Adverse reactions	Thrombocytopenia and anaemia occur in 2–5%. Lactic acidosis – rare. Elevated transaminases and diarrhoea occur in 5% Cataracts are reported in preterm infants Peripheral and optic neuropathy and convulsions have been reported, mainly in patients treated for longer than 28 days
Compatibility	Sodium chloride 0.9%, gucose 5%, Ringer's lactate (Hartmann's) Y-Site: Aciclovir, adrenaline (epinephrine), alfentanil, allopurinol, amikacin, aminophylline, amiodarone, amphotericin B lipid complex/liposome, ampicillin, anidulafungin, atenolol, atracurium, azithromycin, aztreonam, calcium chloride, calcium gluconate, cefazolin, cefotaxime, ceftriaxone, chloramphenicol, ciprofloxacin, clindamycin, dexamethasone sodium phosphate, dexmedetomidine, digoxin, diltiazem, dobutamine, fentanyl citrate, fluconazole, furosemide (frusemide), gentamicin, haloperidol, heparin sodium, hydralazine, hydrocortisone, insulin, labetalol, lidocaine (lignocaine), lorazepam, magnesium sulfate, meropenem, metronidazole, midazolam, morphine sulfate, naloxone, noradrenaline (norepinephrine), phenobarbital, piperacillin/tazobactam, potassium chloride, remifentanil. rocuronium, sodium bicarbonate, sufentanil, tobramycin, vancomycin, vecuronium, verapamil , zidovudine
Incompatibility	Amphotericin B conventional, ceftriaxone, chlorpromazine, diazepam, erythromycin, pantoprazole, pentamidine, phenytoin, thiopentone sodium, trimethoprim/sulfamethoxazole
Stability	IV injection may exhibit yellow colour that can intensify over time without affecting potency. Store at 25°C. Protect from light. Suspension is stable for 21 days after reconstitution. Store at 25°C (before and after reconstitution). Protect from light.
Storage	Store at room temperature, do not freeze. Protect from light.
Excipients	IV injection: Glucose, sodium citrate, citric acid, hydrochloric acid and/or sodium hydroxide and water for injection Oral suspension: Sucrose, mannitol, microcrystalline cellulose, carmellose sodium, aspartame, anhydrous colloidal silica, sodium citrate dihydrate, xanthan gum, sodium benzoate, citric acid and sodium chloride.

	The granules are flavoured with mafco magna sweet, orange flavour, orange cream flavour, sweet-am powder, vanilla flavour and peppermint flavour.
Special comments	
Evidence	**Efficacy** A systematic review by Kocher et al found that a dosage regimen of 10 mg/kg body weight given either orally or intravenously every 8 h in infants aged ≥1 week and the same dose given every 12 h in infants <1 week was shown to be safe and effective with a mean treatment duration of 10–28 days[2] (LOE I GOR B). Thibault et al[3] performed a retrospective pharmacokinetic study in 26 preterm infants with a median postnatal age of 24 days and weight of 1423 g using the dosing regimen recommended in this formulary. Considering Minimum Inhibitory Concentration (MIC_{90}) of 1 mg/L, all infants reached an area under the concentration-time curve/MIC >80. Li et al[19] demonstrated that the dosage of 10 mg/kg 8-hourly in 112 children aged 0.03–12 years would lead to a high risk of under-dosing in the presence of bacteria with MICs of >2 mg/L. To reach the pharmacokinetic target, an elevated dosage of 15 or 20 mg/kg q8h was suggested. However, Thibault et al, with a 12 mg/kg every 8 hours dose, 90% achieved linezolid concentrations at MICs ≥2 mg/L.[3] Sicard et al[5] performed a retrospective observational study in 16 preterm infants with linezolid dosing by continuous intravenous infusion (30 mg/kg/day) or the oral route (10 mg/kg every 8 h) when neonates were stabilised in the late phase of infection. Linezolid plasma concentrations were monitored during continuous intravenous administration or 7 ± 1.5 h after last oral administration. Except for one case, linezolid plasma concentrations were above the minimal inhibition concentration (MIC) for linezolid of 1–2 mg/L for both parenteral and oral administrations. Kaplan et al[20] conducted a multicentre, randomised, controlled trial to assess the efficacy and safety of linezolid versus vancomycin in antibiotic-resistant Gram-positive infections in 316 neonates and children up to 12 years of age. Linezolid IV 10 mg/kg every 8 h or vancomycin IV 10 to 15 mg/kg every 6 to 24 h was administered. After 3 days of IV therapy, patients ≥91 days old randomised to the linezolid group could be switched to oral linezolid 10 mg/kg every 8 h. Clinical cure rates were 79% vs. 74% (P = 0.36) and 89% vs. 85% (P = 0.31) for linezolid and vancomycin respectively. Cure rates were similar by age and infection diagnosis. Pathogen eradication rates were high for linezolid and vancomycin, respectively, for methicillin-susceptible *S. aureus* (95% vs. 94%; P = 0.82), methicillin-resistant *S. aureus* (88% vs.90%; P = 0.89) and methicillin-resistant coagulase-negative staphylococci (85% vs. 83%, P = 0.87). Linezolid-treated patients required significantly fewer days of intravenous therapy compared with vancomycin-treated patients (8.0 ± 4.8; 10.9 ± 5.8 days, respectively; P <0.001). Significantly fewer linezolid-treated patients had drug-related adverse events than did vancomycin-treated patients (19% vs. 34%, respectively; P = 0.003). Details of the 34 preterm infants in the abovementioned study were reported by Deville et al.[27] The clinical cure rate was 84% vs. 77% (P = 0.553) for linezolid and vancomycin, respectively. Pathogen eradication rates comparing both groups were 67% vs. 60% (P = 0.850) for *S. aureus* and 88% vs. 100% (P = 0.397) for CoNS. <u>Treatment of vancomycin-intermediate coagulase-negative staphylococci (hVICoNS CLABSI):</u> Although some CoNS strains display vancomycin heteroresistance, linezolid has not proven superior to vancomycin for the treatment of preterm infants with central-line associated bloodstream infections (CLABSI) with heteroresistant vancomycin-intermediate coagulase-negative staphylococci (hVICoNS)(LOE II GOR B). Blanchard et al[21] performed a retrospective cohort study in 89 NICU patients with heterogeneously resistant vancomycin-intermediate coagulase-negative staphylococci central line associated blood stream infections (hVICoNS CLABSI). Primary outcome was CLABSI duration. Intravenous (IV) or oral linezolid was administered at 10 mg/kg/dose q12h for infants ≤34weeks of gestational age (GA) between 0 and 7 days of life; q8h after 7 days of life in patients ≤34weeks of GA and in all patients ≥35weeks of GA. Mean duration of CLABSI was 4.6 days in the linezolid group compared with 3.6 days in the vancomycin group (P = 0.11). There was no statistically significant difference between linezolid and vancomycin in terms of CLABSI duration, recurrence or all-cause mortality. <u>CNS infections:</u> Ventricular fluid (VF) concentrations are variable and inflammation of the meninges does not seem to influence the penetration of linezolid to the VF. (LOE IV GOR D)

	Watanabe et al[28] reported a linezolid treatment of a neonate with bacterial meningitis with methicillin-resistant *Staphylococcus epidermidis* (MRSE). Vancomycin was administered for 3 days with no improvement and worsening CSF findings. Linezolid was administered 10 mg/kg/dose 8 hourly with clinical and CSF improvement by 8th day of linezolid. Intravenous administration of linezolid was continued for an additional 30 days resulting in negative CSF culture for *S. epidermidis*. Yogev et al 2010 studied hydrocephalic children and adolescents to assess the penetration of linezolid into cerebrospinal fluid and its relation to meningeal inflammation.[13] **Safety**: Linezolid was suggested to be associated with neurotoxicity through linezolid-induced inhibition of mitochondrial protein synthesis.[22] However, Sicard et al[1], in a multicentre, retrospective cohort study comparing the long-term outcomes of preterm infants ≤28 weeks gestation found no difference in the composite outcome of death or sNDI exposed to linezolid versus other anti-staphylococcal antimicrobials. But they found significantly more death by 18–21 months in the linezolid group (29.9% vs. 17.6%; P = 0.01). Increased death was thought to be due to the presence of unmeasured confounding variables including the possibility of higher severity of illness or disease burden in linezolid-exposed neonates. Thrombocytopenia and a slight increased risk for anaemia were evident at >2 weeks of linezolid treatment and these haematological abnormalities were consistent with mild, reversible, duration-dependent myelosuppression[23] Lactic acidosis is a toxic effect of linezolid but effects are reversible.[3,24] Structural homology between the bacterial and the mammalian mitochondrial rRNA may lead to inhibition of mammalian mitochondrial protein synthesis and thereby mitochondrial dysfunction. A case was reported of a preterm newborn who developed thrombocytopenia and bilateral cataracts during linezolid therapy and relieved one week after the discontinuation of the therapy.[10] However, it's mechanism of action in causing spontaneously regressed cataract in this case report remains unclear. **Pharmacokinetics**: Kearns et al studied the pharmacokinetic data and their findings support the currently approved dosing regimens for neonates, particularly for postnatal age greater than 7 days.[4] Total body clearance (CL) increased rapidly during the first week of life and as a function of postnatal age. Age stratification revealed lower values for CL in those infants aged less than 8 days, as compared with those aged 8 days to 12 weeks. Gestational age served to be the most useful predictor of volume of distribution (VD).[4] Thibault et al[3] found the current recommended dosing regimens reached the pharmacodynamic target and were well tolerated in critically ill premature infants. They also found that postnatal age (PNA) was the main determinant of clearance. In premature infants receiving either continuous linezolid intravenous infusion at 30 mg/kg/day or oral doses of 10 mg/kg every 8 h, an adequate linezolid plasma concentration (>MIC to linezolid of 2 mg/L) was reported in both oral and parenteral routes 7 ± 1.5 h after last administration.[5] **Bioavailability** Linezolid is rapidly absorbed after oral dosing with a bioavailability of nearly 100%. Therefore, the administration route of this agent can be switched from intravenous to oral in clinically stable patients without dose adjustment. Maximum plasma concentrations are reached within 1–2 hours of administration.[8] Clearance occurs by renal and non-renal mechanisms. Approximately 65% of the dose is cleared non-renally, and approximately 30% of the dose appears unchanged in the urine of subjects with normal renal function.[8]
Practice points	The established European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoint for Streptococci, Staphylococci, and Enterococci susceptibility is ≤2 mg/L.[25] The resistance breakpoint for these organisms is defined as ≥4 mg/L. However, strains with an MIC >2 mg/L have a probability of not attaining an efficacious target with a traditional dosage regimen.[8] It is prudent to limit linezolid treatment to infections with an MIC <2 mg/L.
References	1. Sicard M, Moussa A, Barrington K, et al. Neonatal and Neurodevelopmental Outcomes Following Linezolid for Coagulase-negative Staphylococcal Infection: Real World Evidence. Pediatr Infect Dis J. 2020;39(7):598-603. 2. Kocher S, Müller W, Resch B. Linezolid treatment of nosocomial bacterial infection with multiresistant Gram-positive pathogens in preterm infants: a systematic review. International journal of antimicrobial agents. 2010 Aug 1;36(2):106-10.

3. Thibault C, Kassir N, Goyer I, et al. Population Pharmacokinetics of Intravenous Linezolid in Premature Infants. Pediatr Infect Dis J. 2019;38(1):82-88. doi:10.1097/INF.0000000000002067
4. Kearns GL, Jungbluth GL, Abdel-Rahman SMet al. Impact of ontogeny on linezolid disposition in neonates and infants. Clin Pharmacol Ther 2003; 74:413–22.
5. Sicard M, Launay E, Caillon J, et al. Pharmacokinetics of linezolid treatment using intravenous and oral administrations in extremely premature infants. Eur J Clin Pharmacol. 2015;71(5):611-615. doi:10.1007/s00228-015-1813-3.
6. Nikolos P, Osorio J, Mohrien K, Rose C. Pharmacokinetics of linezolid for methicillin-resistant Staphylococcus aureus pneumonia in an adult receiving extracorporeal membrane oxygenation. American Journal of Health-System Pharmacy. 2020 Jun 1;77(11):877-81;
7. De Rosa FG, Corcione S, Baietto L, Ariaudo A, Di Perri G, Ranieri VM, D'Avolio A. Pharmacokinetics of linezolid during extracorporeal membrane oxygenation. Int J Antimicrob Ag 2013;590-591.
8. Rao GG, Konicki R, Cattaneo D, Alffenaar JW, Marriott DJ, Neely M. Therapeutic drug monitoring can improve linezolid dosing regimens in current clinical practice: a review of linezolid pharmacokinetics and pharmacodynamics. Therapeutic Drug Monitoring. 2020 Feb 1;42(1):83-92.
9. Gerson SL, Kaplan SL, Bruss JB, et al. Hematologic effects of linezolid: summary of clinical experience. Antimicrobial Agents and Chemotherapy. 2002;46(8):2723-2726. DOI: 10.1128/aac.46.8.2723-2726.
10. Ilarslan E, AydÊn B, Kabatas EU, et al. Cataract in a preterm newborn: a possible side effect of linezolid therapy. J Coll Physicians Surg Pak. 2014;24 Suppl 3:S281-S283
11. Nambiar S, Rellosa N, Wassel RT, Borders-Hemphill V, Bradley JS. Linezolid-associated peripheral and optic neuropathy in children. Pediatrics. 2011;127(6):e1528-e1532. doi:10.1542/peds.2010-2125
12. MIMS online. Linezolid. Accessed on 1 September 2020.
13. Yogev R, Damle B, Levy G, Nachman S. Pharmacokinetics and distribution of linezolid in cerebrospinal fluid in children and adolescents. Pediatr Infect Dis J. 2010;29(9):827-830.
14. Javaheri M, Khurana RN, O'hearn TM, et al. Linezolid-induced optic neuropathy: a mitochondrial disorder? Br J Ophthalmol. 2007;91:111–115.
15. Vishnu VY, Modi M, Goyal MK, et al. Linezolid induced reversible peripheral neuropathy. Am J Ther. 2016;23:e1839–e1841.
16. Vazquez JA, Arnold AC, Swanson RN, et al. Safety of long-term use of linezolid: results of an open-label study. Ther Clin Risk Manag. 2016;12:1347–1354.
17. Douros A, Grabowski K, Stahlmann R. Drug-drug interactions and safety of linezolid, tedizolid, and other oxazolidinones. Expert Opin Drug Metab Toxicol. 2015;11:1849–1859.
18. Quinn DK, Stern TA. Linezolid and serotonin syndrome. Prim Care Companion J Clin Psychiatry. 2009;11:353–356
19. Li SC, Ye Q, Xu H, Zhang L, Wang Y. Population Pharmacokinetics and Dosing Optimization of Linezolid in Pediatric Patients. Antimicrob Agents Chemother. 2019;63(4):e02387-18. Published 2019 Mar 27. doi:10.1128/AAC.02387-18
20. Kaplan SL, Deville JG, Yogev R, Morfin MR, Wu E, Adler S, Edge-Padbury B, Naberhuis-Stehouwer S, Bruss JB, Linezolid Pediatric Study Group. Linezolid versus vancomycin for treatment of resistant Gram-positive infections in children. The Pediatric infectious disease journal. 2003 Aug 1;22(8):677-86.
21. Blanchard AC, Fortin E, Laferrière C, et al. Comparative effectiveness of linezolid versus vancomycin as definitive antibiotic therapy for heterogeneously resistant vancomycin-intermediate coagulase-negative staphylococcal central-line-associated bloodstream infections in a neonatal intensive care unit. J Antimicrob Chemother. 2017;72:1812–1817.
22. De Vriese AS, Van Coster R, Smet J, Seneca S, Lovering A, Van Haute LL, Vanopdenbosch LJ, Martin JJ, Ceuterick-de Groote C, Vandecasteele S, Boelaert JR. Linezolid-induced inhibition of mitochondrial protein synthesis. Clinical infectious diseases. 2006 Apr 15;42(8):1111-7.
23. Gerson SL, Kaplan SL, Bruss JB, Le V, Arellano FM, Hafkin B, Kuter DJ. Hematologic effects of linezolid: summary of clinical experience. Antimicrobial agents and chemotherapy. 2002;46(8):2723-6.
24. Apodaca AA, Rakita RM. Linezolid-induced lactic acidosis. N Engl J Med. 2003;348:86–87
25. EUCAST. 2018. Breakpoint tables for interpretation of MICs and zone diameters. EUCAST, Växjö, Sweden
26. Duan, P., Fisher, J.W., Yoshida, K. et al. Physiologically Based Pharmacokinetic Prediction of Linezolid and Emtricitabine in Neonates and Infants. Clin Pharmacokinet 56, 383–394 (2017). https://doi.org/10.1007/s40262-016-0445-9

27. Deville JG, Adler S, Azimi PH, Jantausch BA, Morfin MR, Beltran S, et al. Linezolid versus vancomycin in the treatment of known or suspected resistant gram positive infections in neonates. Pediatr Infect Dis J 2003;22(9 Suppl.):S158–63.
28. Watanabe S, Tanaka A, Ono T, Ohta M, Miyamoto H, Tauchi H, Tanaka M, Suemaru K, Araki H. Treatment with linezolid in a neonate with meningitis caused by methicillin-resistant Staphylococcus epidermidis. European journal of pediatrics. 2013 Oct 1;172(10):1419-21.

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