Ganciclovir
Newborn use only

2021

Alert	**High risk medicine. Cytotoxic agent.**
Indication	Treatment of severe or moderately severe, symptomatic congenital CMV Treatment of acute severe CMV disease.
Action	Synthetic nucleoside analogue of 2-deoxyguanosine that inhibits replication of herpes viruses such as cytomegalovirus, herpes simplex virus 1 and 2, herpes virus type 6, 7 and 8, Epstein-Barr virus, varicella zoster virus and hepatitis B virus.
Drug type	Antiviral
Trade name	Cymevene, Ganciclovir SXP
Presentation	500 mg ganciclovir sodium vial for reconstitution
Dose	6 mg/kg/dose 12 hourly. Infants may be switched to oral valganciclovir if clinically stable and able to take oral medications. IV ganciclovir should generally not be used for more than 6 weeks. Please note, oral valganciclovir is the oral prodrug of ganciclovir and prescribed at a different dose.
Dose adjustment	
Maximum dose	
Total cumulative dose	
Route	IV
Preparation	**IV Provided by pharmacy** of the reconstituted/pre-diluted product. Final concentration should not be higher than 10 mg/mL. Cytotoxic agent so infusion should not be manipulated on the ward.
Administration	**IV** **Follow full cytotoxic precautions as per local policy.** IV infusion over 60 minutes preferably via central venous access.(15)
Monitoring	Full blood count, particularly neutrophils, should be followed weekly for 6 weeks, then at week 8, then monthly for the duration of therapy. IV site for phlebitis Liver function tests monthly throughout therapy. Renal function tests.
Contraindications	Hypersensitivity to ganciclovir, valganciclovir, aciclovir or valacyclovir. Patients with: • absolute neutrophil count below 0.5 x 10^9/L or • platelet count below 25 x 10^9/L unless thrombocytopenia is related to CMV disease, or • haemoglobin less than 80 g/L (8 g/dL).
Precautions	Ganciclovir has both gonadal toxicity and carcinogenicity in animal models and its long-term safety after administration to young children is not established.[1]
Drug interactions	Convulsions have been reported in patients receiving ganciclovir and imipenem-cilastatin concurrently. Concurrent use of tacrolimus and ganciclovir increases nephrotoxicity.
Adverse reactions	Commonly causes neutropenia. If absolute neutrophil count (ANC) falls below 0.5 x 10^9/L and if it is thought not to be due to CMV disease, withhold medication until ANC is above 0.75 x 10^9/L then restart medication at half dose. If ANC falls below 0.5 x 10^9/L again, consider discontinuing the medication. Can also cause anaemia and thrombocytopenia. Discontinue medication if platelet count below 25 x 10^9/L or haemoglobin less than 80 g/L occurs and is thought not to be due to CMV disease.
Compatibility	Fluids: Glucose 5%, sodium chloride 0.9%. Must not be administered in conjunction with any other drugs.
Incompatibility	
Stability	Compounding centres that are licensed by the Australian Therapeutic Goods Administration to reconstitute and/or further dilute cytotoxic medicines and have validated aseptic procedures and regular monitoring of aseptic technique may apply a shelf life of 15 days at 2 to 8°C (refrigerate, do not freeze) to ganciclovir IV infusions reconstituted with water and further diluted with sodium chloride

	0.9% or glucose 5%. Please contact your Pharmacy Department for more information or refer to expiry date on the product.
Storage	Store vial below 30°C. Pre-diluted solution: Store at 2 to 8°C or as instructed on product label by compounding facility.
Excipients	None.
Special comments	
Evidence	**Efficacy and safety:** **Symptomatic congenital cytomegalovirus disease:** A randomised, controlled trial in infants ≥ 32 weeks GA of 6 weeks IV ganciclovir 6 mg/kg every 12 hours demonstrated more infants had improved hearing or maintained normal hearing between baseline and 6 months in the IV ganciclovir group versus placebo (84% vs 59%, p = 0.06) and fewer infants had worsening hearing (0% vs 41%, p < 0.01).[1] This effect was sustained at 1 year of age, when 21% of infants in the treatment group had worsening hearing versus 68% in the placebo group (p < 0.01)[1]. Two-thirds of the treatment group developed significant neutropenia[1]. At 12 months, infants treated with 6 weeks IV ganciclovir had fewer developmental delays.[2] [LOE II, GOR B – see below for recommendation]. There are reports of the use of 10–12 mg/kg/day in 2 divided doses in extreme preterm infants.[10-14] **International Congenital Cytomegalovirus Recommendations Group:** Ganciclovir is now available as an oral prodrug, valganciclovir. A recent RCT now recommends valganciclovir treatment for congenitally-infected neonates ≥ 32 weeks of life, with moderate to severe symptomatic disease, to be commenced within the first month of life and for 6 months. Antiviral therapy should not be administered to neonates with asymptomatic congenital cytomegalovirus infections. Antiviral therapy is not routinely recommended for asymptomatic congenital cytomegalovirus infection with isolated sensorineural hearing loss or for neonates with mildly symptomatic congenital cytomegalovirus infection.[3] **Pharmacokinetics:** In symptomatic newborns with CMV, the mean elimination half-life of ganciclovir was 2.4 hours.[4] A target AUC_{12} (area under the concentration-time curve over a 12-h period) of 27 mg x h/L has been defined.[5] The clearance of intravenous ganciclovir nearly doubled and the AUC_{12} was reduced by almost one-half during the first 6 weeks of life.[5] Based on these data, it appears ganciclovir 6 mg/kg every 12 hours may be insufficient to achieve the pharmacokinetic target despite evidence for clinical and virological efficacy.[5] A pharmacokinetic study showed that oral valganciclovir 16 mg/kg every 12 hours achieved similar concentrations to IV ganciclovir 6 mg/kg every 12 hours. [5] [LOE III, GOR B]
Practice points	Central line is preferred as medication has high pH and can cause tissue irritation. Peripheral cannula may be used for short-term treatment but the IV site should be monitored carefully.
References	1. Kimberlin DW, Lin CY, Sanchez PJ, Demmler GJ, Dankner W, Shelton M, Jacobs RF, Vaudry W, Pass RF, Kiell JM, Soong SJ, Whitley RJ. Effect of ganciclovir therapy on hearing in symptomatic congenital cytomegalovirus disease involving the central nervous system: A randomized, controlled trial. Journal of Pediatrics. 2003;143:16-25. 2. Oliver SE, Cloud GA, Sanchez PJ, Demmler GJ, Dankner W, Shelton M, Jacobs RF, Vaudry W, Pass RF, Soong Sj, Whitley RJ, Kimberlin DW. Neurodevelopmental outcomes following ganciclovir therapy in symptomatic congenital cytomegalovirus infections involving the central nervous system. Journal of Clinical Virology. 2009;46:S22-S6. 3. Rawlinson WD, Boppana SB, Fowler KB, Kimberlin DW, Lazzarotto T, Alain S, Daly K, Doutre S, Gibson L, Giles ML, Greenlee J, Hamilton ST, Harrison GJ, Hui L, Jones CA, Palasanthiran P, Schleiss MR, Shand AW, van Zuylen WJ. Congenital cytomegalovirus infection in pregnancy and the neonate: consensus recommendations for prevention, diagnosis, and therapy. The Lancet Infectious Diseases. 2017;17:e177-e88. 4. Trang JM, Kidd L, Gruber W, Storch G, Demmler G, Jacobs R, Dankner W, Starr S, Pass R, Stagno S, Alford C, Soong SJ, Whitley RJ, Sommadossi JP. Linear single-dose pharmacokinetics of ganciclovir in newborns with congenital cytomegalovirus infections. Clinical Pharmacology and Therapeutics. 1993;53:15-21. 5. Kimberlin DW, Acosta EP, Sanchez PJ, Sood S, Agrawal V, Homans J, Jacobs RF, Lang D, Romero JR, Griffin J, Cloud GA, Lakeman FD, Whitley RJ, National Institute of A, Infectious Diseases

Collaborative Antiviral Study G. Pharmacokinetic and pharmacodynamic assessment of oral valganciclovir in the treatment of symptomatic congenital cytomegalovirus disease. J Infect Dis. 2008;197:836-45.
6. SHPA, Ganciclovir monograph, Australian Injectable Handbook 7th Ed, 2017
7. Roche, Valcyte monograph, MIMs, 2017
8. Roche, Cymevene monograph, MIMs, 2017
9. Trissel's 2 Clinical Pharmaceutics Database (Parenteral Compatibility), Ganciclovir monograph, accessed via Micromedex, 26/07/2017.
10. El-Sayed MF, Goldfarb DM, Fulford M, Pernica JM. Severe late-onset multisystem cytomegalovirus infection in a premature neonate previously treated for congenital infection. BMC Pediatr. 2013;13:142.
11. Fischer C, Meylan P, Bickle Graz M, Gudinchet F, Vaudaux B, Berger C, Roth-Kleiner M. Severe postnatally acquired cytomegalovirus infection presenting with colitis, pneumonitis and sepsis-like syndrome in an extremely low birthweight infant. Neonatology. 2010;97:339-45.
12. Mehler K, Oberthuer A, Lang-Roth R, Kribs A. High rate of symptomatic cytomegalovirus infection in extremely low gestational age preterm infants of 22-24 weeks' gestation after transmission via breast milk. Neonatology. 2014;105:27-32.
13. Muller A, Eis-Hubinger AM, Brandhorst G, Heep A, Bartmann P, Franz AR. Oral valganciclovir for symptomatic congenital cytomegalovirus infection in an extremely low birth weight infant. J Perinatol. 2008;28:74-6.
14. Okulu E, Akin IM, Atasay B, Ciftci E, Arsan S, Turmen T. Severe postnatal cytomegalovirus infection with multisystem involvement in an extremely low birth weight infant. J Perinatol. 2012;32:72-4.
15. Australian Injectable Drugs Handbook, 8th edition. Accessed on 25 November 2021.

VERSION/NUMBER	DATE
Original 1.0	**18/09/2017**
Revised 2.0	10/12/2020
Current 3.0	25/11/2021
REVIEW	25/11/2026

Authors Contribution

Original author/s	Jing Xiao
Evidence Review	Timothy Schindler, David Osborn
Expert review	Pam Palasanthiran, Brendan McMullan, Alison Kesson, Tony Lai on behalf of Infectious Diseases Group
Nursing Review	Eszter Jozsa, Kirsty Minter
Pharmacy Review	Michelle Jenkins
ANMF Group contributors	Nilkant Phad, Bhavesh Mehta, John Sinn, Carmen Burman, Jessica Mehegan, Thao Tran, Helen Huynh, Wendy Huynh
Final editing and review of the original	Ian Whyte
Electronic version	Cindy Chen, Ian Callander
Facilitator	Srinivas Bolisetty