Aciclovir
Newborn use only

2021

<table>
<tr><td>Alert</td><td>High risk medicine.
Increased risk of renal impairment if there is concomitant use of other nephrotoxic drugs, pre-existing renal disease or dehydration.
Turbidity or crystallisation may occur even when mixed with compatible fluids. Discard preparation if this occurs before or during the infusion.
Highly alkaline and IV extravasation can cause severe tissue damage.</td></tr>
<tr><td>Indication</td><td>Treatment of neonatal herpes simplex virus (HSV) infection.
Treatment of varicella zoster virus (VZV) infection
HSV suppression following treatment to prevent CNS sequelae.</td></tr>
<tr><td>Action</td><td>Inhibits viral DNA synthesis when activated in infected cells.</td></tr>
<tr><td>Drug type</td><td>Antiviral</td></tr>
<tr><td>Trade name</td><td>IV: Aciclovir Sandoz, DBL, Pfizer
Oral: Aciclovir GH, Aciclovir Sandoz, Acihexal, Acyclo-V, Chemmart Aciclovir, GenRx Aciclovir, Lovir, Ozvir, Pharmacor Aciclovir, Terry White Chemists Aciclovir, Zovirax</td></tr>
<tr><td>Presentation</td><td>IV: Aciclovir DBL, Pfizer: 250 mg/10 mL ampoule, 500 mg/20 mL ampoule
Aciclovir Sandoz: 250 mg, 500 mg vial (powder for reconstitution)
Oral: 200mg, 400mg, 800mg tablets (Acyclo-V, Lovir, Ozvir, Zovirax brands are dispersible)</td></tr>
<tr><td>Dose</td><td>Treatment of HSV and VZV
IV 20 mg/kg/dose 8 hourly
Consider 12 hourly dosing in infants <30 weeks corrected age where HSV or VSV is not confirmed.

Duration of therapy (expert recommendation)
<table>
<tr><td>Laboratory or clinically confirmed HSV confined to skin, eye, and mouth</td><td>10–14 days</td></tr>
<tr><td>HSV encephalitis or disseminated disease</td><td>21 days</td></tr>
<tr><td>Pre-emptive therapy (high-risk asymptomatic infant without laboratory confirmed infection)</td><td>10 days
(expert recommendation)</td></tr>
</table>
Suppression of HSV following treatment[5]
Oral 300 mg/m^2/dose three times per day for 6 months.

Body Surface Area (BSA) calculation:
$$BSA\ (m^2) = \sqrt{\frac{height\ (cm) \times weight\ (kg)}{3600}}$$</td></tr>
<tr><td>Dose adjustment</td><td>Renal impairment (IV Treatment of HSV and VZV)

<table>
<tr><th>Creatinine concentration</th><th>Dosage and Interval adjustment</th></tr>
<tr><td>70–100 micromol/L</td><td>20 mg/kg 12 hourly</td></tr>
<tr><td>101–130 micromol/L</td><td>20 mg/kg 24 hourly</td></tr>
<tr><td>> 130 micromol/L and/or urine output < 1 mL/kg/hour</td><td>10 mg/kg 24 hourly</td></tr>
</table></td></tr>
<tr><td>Maximum dose</td><td></td></tr>
<tr><td>Total cumulative dose</td><td></td></tr>
<tr><td>Route</td><td>IV or Oral</td></tr>
<tr><td>Preparation</td><td>IV: If using Sandoz brand, reconstitute 250 mg vial with 10 mL or 500 mg with 20 mL of water for injection to obtain 25 mg/mL solution. If using DBL or Pfizer brand, vials contain 25 mg/mL solution. Draw up 4 mL (100 mg) of aciclovir and add 16 mL sodium chloride 0.9% to make final volume 20 mL with a final concentration of 5 mg/mL.

Risk of phlebitis and extravasation increases at > 10 mg/mL. If a higher concentration is required, a solution of up to 25 mg/mL may be administered via a CENTRAL LINE ONLY.</td></tr>
</table>

	Oral: Acyclo-V, Lovir, Ozvir and Zovirax brands come as dispersible tablets. Consider rounding if dose is close to half or quarter of a tablet. Disperse fraction of tablet in small quantity of water (e.g. 2 mL) and give dose immediately. If this is not possible, disperse an entire tablet in a set quantity of water, ensure mixture is a uniform suspension, and draw up a fraction of this mixture and give immediately. If uniform suspension cannot be produced, contact pharmacy. Example: If dose is 30 mg, disperse 200 mg tablet in 10 mL of water to obtain 20 mg/mL mixture, and then give 1.5 mL.
Administration	IV Infusion: Infuse via syringe driver over 60 minutes. Turbidity or crystallisation may occur even when mixed with compatible fluids. Discard preparation if this occurs before or during the infusion. Oral: Dose can be given with feed.
Monitoring	Periodic full blood count, renal function, bilirubin, and hepatic transaminases. IV site for phlebitis — prepare a more dilute infusion solution if phlebitis occurs.
Contraindications	Known hypersensitivity to aciclovir, valganciclovir or any component of the product.
Precautions	Increased risk of renal impairment if there is concomitant use of other nephrotoxic drugs, pre-existing renal disease or dehydration. Administration interval may be lengthened to minimise renal effects. Refer to the renal adjustment dose in the dose adjustment section.
Drug interactions	Concurrent use with other nephrotoxic drugs may cause renal impairment (gentamicin, furosemide). Concurrent use with ceftriaxone may cause renal impairment.
Adverse reactions	Neutropenia, thrombocytopenia may occur. May cause • neurotoxicity with lethargy, tremor, and agitation. • transient renal impairment which is minimised by a slow administration rate. • transient rise in AST and total bilirubin. • phlebitis at IV injection site (highly alkaline solution). The solution can be made more dilute.
Compatibility	Fluids: sodium chloride 0.45%, sodium chloride 0.9% Compatible via Y-site : Amikacin, ampicillin, anidulafungin, cefotaxime, ceftazidime, ceftriaxone, cefazolin, chloramphenicol, clindamycin, dexamethasone, doripenem, erythromycin, fluconazole, heparin sodium, hydrocortisone sodium succinate, imipenem–cilastatin, linezolid, lorazepam, magnesium sulfate, methylprednisolone sodium succinate, metronidazole, potassium chloride, ranitidine, remifentanil, sodium bicarbonate, tobramycin, trimethoprim-sulfamethoxazole, vancomycin, zidovudine
Incompatibility	Amino acid/glucose solution, glucose-containing solutions, adrenaline (epinephrine) hydrochloride, aztreonam, caffeine citrate, cefepime, ciprofloxacin, dobutamine, dopamine, esmolol, gentamicin, hydralazine, ketamine, labetalol, lidocaine (lignocaine), midazolam, pentamidine, phenylephrine, piperacillin–tazobactam (EDTA-free), potassium phosphate, sodium nitroprusside, sodium phosphate, ticarcillin–clavulanate, vecuronium, verapamil.
Stability	Diluted solutions should be used as soon as practicable, discard unused portion.
Storage	Store below 25°C. Do NOT refrigerate (may result in precipitation).
Excipients	Sodium hydroxide
Special comments	The infusion solution may be filtered. Discard the solution if visible turbidity or crystallisation appears.
Evidence	**Efficacy** <u>High-dose versus low-dose for HSV treatment:</u> An open-label evaluation of IV aciclovir prospectively compared 16 patients receiving 45 mg/kg/day and 72 patients receiving 60 mg/kg/day in divided doses to historical controls from a previously reported trial which used 30 mg/kg/day. Survival rate for the high-dose aciclovir was found to be significantly greater than for low-dose aciclovir. Recipients of high-dose aciclovir also had a borderline significant decrease in morbidity. Neutropenia, renal dysfunction, abnormal platelet count, low haemoglobin and elevated AST were noted but the possible adverse drug reactions of high-dose aciclovir couldn't be separated from the effects of viral infection and underlying medical conditions. 20 mg/kg/dose 8 hourly aciclovir is also recommended by American Academy of Pediatrics (AAP) and Australasian Society for Infectious Diseases (ASID).[1,2,6] (LOE III-3, GOR C) <u>HSV suppression following treatment to prevent CNS sequelae:</u>

	Neonates were enrolled in two parallel, identical, double-blind, placebo-controlled studies. Neonates with central nervous system (CNS) involvement were enrolled in one study, and neonates with skin, eye, and mouth involvement only were enrolled in the other. After completing a regimen of 14 to 21 days of parenteral aciclovir, the infants were randomly assigned to immediate aciclovir suppression (300 mg per square meter of body-surface area per dose orally, three times daily for 6 months) or placebo. The Mental Development Index of the Bayley Scales of Infant Development was assessed at 12 months of age in 28 of 45 infants enrolled with HSV CNS involvement. After adjustment for covariates, infants assigned to aciclovir suppression had significantly higher mean scores than infants assigned to placebo. There was a trend toward more neutropenia in the aciclovir group (1,5) (LOE II, GOR B). VZV (Varicella zoster virus) treatment: 20 mg/kg/dose 8 hourly is recommended by ASID guidelines but is not supported by data from any trial. **Safety** Safety data from studies on aciclovir use in HSV infections would apply (1). **Pharmacokinetics** A study of 28 infants evaluated the pharmacokinetics of aciclovir in neonates with postmenstrual age (PMA) 25–41 weeks and 1–30 postnatal days. Aciclovir pharmacokinetics was described by a 1-compartment model and the study proposed dosing: 20 mg/kg 12 hourly in PMA < 30 weeks; 20 mg/kg 8 hourly in PMA 30 to < 36 weeks and 20 mg/kg 6 hourly in PMA 36–41 weeks.[4] (LOE III-3) Another pharmacokinetic study of 16 neonates born at gestational ages of 27–40 weeks, postnatal age 1–56 days, described aciclovir pharmacokinetics as two-compartment and found a relationship between clearance and serum creatinine concentration. Dosing recommendations are given based on creatinine, with a "standard dose" being 10 mg/kg /dose 8 hourly for a neonate with normal renal function.[3] (LOE III-3, GOR C).
Practice points	
References	1. Palasanthiran P, Starr M, Jones C, Giles M. Management of Perinatal Infections, Australasian Society for Infectious Diseases (ASID), 2014 2. Kimberlin DW, Lin CY, Jacobs RF, Powell DA, Corey L, Gruber WC, Rathore M, Bradley JS, Diaz PS, Kumar M, Arvin AM. Safety and efficacy of high-dose intravenous acyclovir in the management of neonatal herpes simplex virus infections. Pediatrics. 2001;108(2):230-8. 3. Englund JA, Fletcher CV, Balfour HH. Acyclovir therapy in neonates. The Journal of pediatrics. 1991;119(1):129-35. 4. Sampson MR, Bloom BT, Lenfestey RW, Harper B, Kashuba AD, Anand R, Benjamin Jr DK, Capparelli E, Cohen-Wolkowiez M, Smith PB. Population pharmacokinetics of intravenous acyclovir in preterm and term infants. The Pediatric infectious disease journal. 2014;33(1):42. 5. Kimberlin DW, Whitley RJ, Wan W, Powell DA, Storch G, Ahmed A, Palmer A, Sánchez PJ, Jacobs RF, Bradley JS, Robinson JL. Oral acyclovir suppression and neurodevelopment after neonatal herpes. New England Journal of Medicine. 2011;365(14):1284-92. 6. Australian Injectable Drugs Handbook, 6th Edition, 2016 7. The Paediatric Injectable Medicines Handbook, The Children's Hospital at Westmead, accessed 22/11/2016 8. Micromedex online. Accessed on 22/11/2016.

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