MONOGRAPH

Valganciclovir Monograph - Paediatric

Scope (Staff):	Medical, Pharmacy, Nursing
Scope (Area):	All Clinical Areas – Perth Children's Hospital (PCH)

Child Safe Organisation Statement of Commitment

CAHS commits to being a child safe organisation by applying the National Principles for Child Safe Organisations. This is a commitment to a strong culture supported by robust policies and procedures to reduce the likelihood of harm to children and young people.

This document should be read in conjunction with this DISCLAIMER

HIGH RISK MEDICINE

QUICKLINKS			
Dosage/Dosage Adjustments	Administration	Compatibility	Monitoring

DRUG CLASS

Guanine analogue antiviral.[1, 2]

Valganciclovir is a High Risk Medicine.

INDICATIONS AND RESTRICTIONS

- Valganciclovir is used in the treatment and prophylaxis of cytomegalovirus (CMV) in immunosuppressed patients.[2, 3]
- Valganciclovir may also be recommended for neonates and infants diagnosed with moderate to severe symptomatic congenital cytomegalovirus (CMV) infection given potential benefits to long-term audiological and neurodevelopmental outcomes. Refer to the CMV Neonatal Pathway for further information.[3-5]

Oral: Monitored (orange) antiviral

As per indications stipulated in Formulary One. For any other use, phone approval must be obtained from ChAMP before prescribing as per the Antimicrobial Stewardship Policy.

CONTRAINDICATIONS

- Hypersensitivity to valganciclovir, ganciclovir or any component of the formulation.[2, 4, 6-9]
- Caution should be used in patients with a history of allergy to other guanine analogues (aciclovir, famciclovir, penciclovir and valaciclovir).[4]

PRECAUTIONS

- Patients with bone marrow suppression, receiving myelosuppressive drugs or irradiation may be more susceptible to the myelosuppressive effects of valganciclovir. Dose adjustment may be required.

  Consider the need for valganciclovir and use with caution if:

  - neutrophil count is <0.5 x 10^9 cells/L **or**
  - platelet count is <25 x 10^9 cells/L **or**
  - haemoglobin is < 80g/L.[2, 8, 9]
- Valganciclovir is category D in pregnancy and has the potential to cause birth defects. Sexually active adolescent females should use effective contraception whilst taking valganciclovir and for at least 30 days after ceasing therapy. Sexually active males are recommended to use barrier contraception during and for a minimum of 90 days after treatment with valganciclovir.[2, 4, 8-10]
- Valganciclovir **must** be treated as a cytotoxic agent with the appropriate handling precautions. Refer to;
  - Antineoplastic (Cytotoxic) Agents – Safe Handling and Administration for further information.[7, 9]
  - Chemotherapy Safety in the Home (Health Facts)
  - Valganciclovir should not be disposed of via wastewater or household waste. Unused/expired medicines should be returned to pharmacy for disposal.[4]

FORMULATIONS

Listed below are products available at PCH, other formulations may be available, check with pharmacy if required:

- 450mg tablets
- 50mg/mL powder for oral solution 100mL

  Note: After reconstitution, the minimum usable volume is 88mL, this volume should be considered when determining the quantity to prescribe.[4]

Imprest location: Formulary One

DOSAGE & DOSAGE ADJUSTMENTS

- Valganciclovir **tablets** can be considered if the calculated dose is within 10% of the available tablet strength of 450mg.[4, 9]
- Valganciclovir **solution** doses should be rounded to the nearest 25mg to achieve an accurate deliverable volume of the liquid.[4, 9]

Neonates: **Refer to Neonatal Medication Protocols** AND **Cytomegalovirus (CMV) Neonatal Pathway**

***Oral - Treatment*:**

Symptomatic congenital CMV disease in neonates (≥32 weeks gestation and ≥1.8kg) and infants:

- 16mg/kg/dose (to a maximum of 900mg) given 12 hourly for 6 months (inclusive of any period treated with IV ganciclovir).[1, 7, 9]

INDICATION	AGE	ORAL DOSE	DURATION
Continuation treatment – congenital CMV[3]	≥ 4 weeks to < 12 months	16 mg/kg/dose given 12 hourly	Variable – discuss with Infectious diseases. Generally a maximum of 6 months inclusive of any IV ganciclovir treatment
	The efficacy of valganciclovir commenced after 4 weeks of age is uncertain. Dose should be adjusted monthly to account for weight gain.[11, 12]		
Active CMV disease	≥ 4 weeks to < 12 months	16 mg/kg/dose given 12 hourly	Variable – discuss with Infectious diseases
Active CMV disease[2-4, 7, 8]	≥ 12 months	7 x BSA x eGFR (to a maximum of 900mg per dose) given twice daily.	Variable – discuss with Infectious diseases
	$BSA\ (m^2) = \sqrt{\frac{Height\ (cm) \times Weight\ (kg)}{3600}}$ eGFR calculator[2-4, 7, 8]		

Oral – Prophylaxis:

INDICATION	AGE	ORAL DOSE	DURATION
Secondary CMV prophylaxis (maintenance) after induction therapy for CMV retinitis or CMV disease in an immunocompromised host[3, 9]	Initial treatment is generally commenced with IV ganciclovir, oral switch to valganciclovir may be appropriate in consultation with Infectious Diseases for those at ongoing risk of CMV reactivation.		
	≥ 4 weeks to < 12 months	16mg/kg/dose (to a maximum of 900mg) given once daily.	Variable - until CMV viral load is undetectable.
	≥ 12 months	7 x BSA x eGFR (to a maximum of 900mg per dose) given once daily calculated using the equations and links below.	
CMV prophylaxis post solid organ transplant[2, 9]	≥ 4 weeks to < 16 years	7 x BSA x eGFR (to a maximum of 900mg per dose) given once daily calculated using the equations and links below.	Kidney transplant – at least 200 days post transplant Other organ transplant – at least 100 days post transplant.[2, 4]
	≥ 16 years	900mg once daily	
	$BSA\ (m^2) = \sqrt{\frac{Height\ (cm) \times Weight\ (kg)}{3600}}$ eGFR calculator[2-4, 7, 8]		

Note: Use a value of 150mL/minute/1.73m^2 to calculate the dose if the calculated eGFR exceeds this value.[1, 2]

Renal impairment:

- eGFR calculator
- Dosage adjustment may be required in cases of impaired renal function (with creatinine clearance of less than 60mL/minute/1.73m^2).[2]
- For patients on doses using the dose: 7 x BSA x eGFR, this calculation takes into account renal function and no further dose adjustments are required.[7]
- See following page for specific recommendations.

Patients < 12 months old and adolescents 16 to 18 years of age:

- The following dose adjustments are to be applied to adolescents with a recommended dose in normal renal function of 900mg and those patients using a 16mg/kg/dose.

Valganciclovir <u>induction</u>:

- eGFR ≥60mL/ minute/1.73m^2= normal dosing
- eGFR 40-59 mL/minute/1.73m^2= 50% of the standard dose given12 hourly
- eGFR 25-39mL/minute/1.73m^2= 50% of the standard dose given 24 hourly
- eGFR 10-24mL/minute/1.73m^2= 50% of the standard dose given 48 hourly
- eGFR <10mL/minute/1.73m^2= avoid use, consider dose adjusted IV ganciclovir.[7, 8]
- Intermittent haemodialysis or peritoneal dialysis: valganciclovir is not recommended.[7]

Valganciclovir <u>maintenance</u>:

- eGFR ≥60mL/minute/1.73m^2= normal dosing
- eGFR 40-59 mL/minute/1.73m^2= 50% of the standard dose given 24 hourly
- eGFR 25-39mL/minute/1.73m^2= 50% of the standard dose given 48 hourly
- eGFR 10-24mL/minute/1.73m^2= 50% of the standard dose given twice weekly
- eGFR <10mL/minute/1.73m^2= avoid use, consider dose adjusted IV ganciclovir.[7, 8]
- Intermittent haemodialysis or peritoneal dialysis: valganciclovir is not recommended.[7]

Dosage adjustment required in hepatic impairment:

- There is no specific information available, no adjustments appear to be required.[7, 9]

Dosage adjustment required in haematologic toxicity:

- Patients with bone marrow suppression, receiving myelosuppressive drugs or irradiation may be more susceptible to the myelosuppressive effects of valganciclovir.[2, 7, 9]
- Neutropenia is often dose dependent and usually occurs within the first one to two weeks of therapy.[2]
- Dose adjustment may be required. Consider the need for valganciclovir and use with caution if:
    - neutrophil count is <0.5 x 10^9 cells/L **or**
    - platelet count is <25 x 10^9 cells /L **or**
    - haemoglobin is < 80g/L.[2, 7, 9]

Contact Infectious Diseases for advice.

- If bone marrow suppression occurs while on treatment (particularly neutropenia with a neutrophil count of < 0.5 x10^9 cells/L), valganciclovir may need to be ceased temporarily to enable bone marrow recovery. Cell counts typically begin to recover 3 to 7 days following interruption of therapy.[2, 7]

RECONSTITUTION & ADMINISTRATION

Valganciclovir must be handled as a cytotoxic agent[9]

- Valganciclovir is a potential teratogen and carcinogen. Proper procedures for the handling and disposal of cytotoxic agents should be followed.[2, 4, 7]
- Refer to Antineoplastic (Cytotoxic) Agents – Safe Handling and Administration for further information.

Reconstitution:

- Valganciclovir powder for oral solution should be reconstituted in Pharmacy within a Powder Enclosure Cabinet to avoid exposure through powder inhalation.[7]
- Store reconstituted solution in the refrigerator between 2 and 8 degrees and discard any remaining suspension 49 days after reconstitution.[4]
- **Note:** After reconstitution, the minimum usable volume is 88mL, this volume should be taken into account when determining the quantity to prescribe.[4]

Administration:

Valganciclovir **must** be treated as a cytotoxic agent with the appropriate handling precautions. Refer to Antineoplastic (Cytotoxic) Agents – Safe Handling and Administration for further information.[7, 9]

- Patients, parents, and carers should be instructed not to crush or break the oral tablets and to use gloves when handling both the tablets and/or oral solution.[7-9, 13]
- Parents and carers should be instructed to wash any skin or mucous membrane that is accidently exposed to valganciclovir with soap and water. If ocular exposure occurs, the eye should be washed with plain water.[4, 7, 9]
- Shake the oral solution well before administration and do not use the measuring device for any other medications.[4, 7]
- Best taken with food to aid absorption.[1, 2, 7, 8]

MONITORING

- Haematological function, electrolytes and renal function should be measured at baseline and then regularly (two to three times a week during induction and weekly during maintenance) throughout treatment. Liver function should be measured prior to commencement of therapy and monthly throughout treatment.[2, 7, 9]
- Neutropenia is usually dose dependent and usually occurs within the first one to two weeks of therapy.
    - Aim to maintain a neutrophil count of > 0.5 $x10^9$ cells/L throughout treatment.
    - In the event of severe neutropenia or thrombocytopenia, treatment can be temporarily interrupted as neutrophil counts tend to return to normal range within 3 to 7 days.[7]
    - Dose reduction should be considered if significant anaemia or leucopenia recurs following treatment interruption. Contact Infectious Diseases for advice.[2]
- Monitoring for neonates and infants with congenital CMV should follow the Cytomegalovirus (CMV) Neonatal Pathway.

Therapeutic drug monitoring

- Valganciclovir is a pro-drug of ganciclovir.[2, 14]
- Ganciclovir levels may be monitored on the advice of Infectious Diseases or Clinical Microbiology Consultants.
- Contact the duty Biochemist **prior** to collection of the sample.[14]

Collection tube:

- **Paediatric and neonatal –** Lithium Heparin (Dark Green top) 1 mL (No Gel) or Serum (Red top) 1 mL (No Gel).
- **Minimum volume required:** 0.5mL[14]
- Send samples chilled and within 2 hours of collection.

ADVERSE EFFECTS

As valganciclovir is rapidly converted to ganciclovir any side effect seen with ganciclovir may also occur with valganciclovir.[2, 7]

Common: anaemia, anxiety, arthralgia, asthenia, neutropenia, thrombocytopenia, fever, local and systemic infection, diarrhoea, vomiting, abdominal pain, abdominal distention, dyspepsia, decreased appetite, weight loss, chest pain, constipation, dyspnoea, diarrhoea, headache, insomnia, depression, dizziness, ear pain, seizures, confusion, itch, dermatitis, sweating, cough, decreased creatinine clearance, eye pain, electrolyte abnormalities, abnormal hepatic function, peripheral neuropathy.[2, 7, 10]

Infrequent: alopecia, arrhythmia, deafness, haematuria, hallucination, oral ulceration, pancreatitis, psychotic disorder, tremor, visual impairment, hypotension.[2, 10]

Rare: allergic reaction.[2, 7, 10]

STORAGE

- **Tablets:** Store below 30°C.[4]
- **Powder for oral solution:** Store below 30°C prior to reconstitution, after reconstitution store in the refrigerator between 2°C and 8°C and discard 49 days after reconstitution.[4]

INTERACTIONS

This medication may interact with other medications; consult PCH approved references (e.g. Clinical Pharmacology), a clinical pharmacist or PCH Medicines Information Service on extension 63546 for more information.

Please note: The information contained in this guideline is to assist with the preparation and administration of **valganciclovir**. Any variations to the doses recommended should be clarified with the prescriber prior to administration

Related CAHS internal policies, procedures and guidelines

Antimicrobial Stewardship Policy

ChAMP Empiric Guidelines and Monographs

KEMH Neonatal Medication Protocols
Cytomegalovirus CMV Neonatal Pathway
Cytotoxic/Biotherapy Agents Administration
Chemotherapy Safety in the Home (Health Facts)
Chemotherapy Safety in the Home – Keeping our Mob healthy (Health Facts)

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