Guideline

Antiviral Prophylaxis and Treatment in Haematopoietic Stem Cell Transplant and Immunocompromised children

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HUMAN RIGHTS

This governance document has been human rights compatibility assessed. No limitations were identified indicating reasonable confidence that, when adhered to, there are no implications arising under the *Human Rights Act 2019.*

PURPOSE

This guideline provides recommendations regarding best practice for Antiviral Prophylaxis and Treatment primarily in children undergoing Haematopoietic Stem Cell Transplantation (HSCT), and can also be applied to management of other immunocompromised children.

SCOPE

This guideline applies to all Children's Health Queensland (CHQ) staff caring for paediatric immunocompromised or HSCT patients.

GUIDELINE

BASELINE SCREENING

- All donors and recipients should have baseline serology and viral PCR prior to conditioning for HSCT:
- If blood viral PCR (qualitative test) is positive request quantitative PCR (viral load)

Serology blood	PCR blood	PCR stool
HSV1 and HSV2 IgG	CMV	Adenovirus (request generic adenovirus PCR) Viral PCR
CMV IgG	adenovirus	
EBV IgG	EBV	
VZV IgG	HHV6	

- Risk assessment:
  - The risk of viral reactivation is highest if the recipient is seropositive
  - Other risk factors include
    - Acute or chronic GvHD
    - ATG during conditioning
    - Alemtuzumab during conditioning

Antiviral prophylaxis

Valaciclovir or aciclovir are recommended if either donor or recipient is seropositive for HSV or CMV.

Table 1: Antiviral prophylaxis in HSCT

Serostatus	Timing of prophylaxis	Recommended prophylaxis	Alternative if recommended agent contraindicated (eg no oral absorption)
Donor and recipient ***both seronegative*** for all herpes viruses	-	Nil required	-
Either donor or recipient seropositive for HSV or CMV	At commencement of conditioning until 1 year post transplant or 6 months after discontinuation of systemic immunosuppression	Valaciclovir PO	Aciclovir IV

CMV-SPECIFIC PROPHYLAXIS (HIGH RISK)

Given the toxicities associated with targeted anti-CMV agents, a **pre-emptive treatment** (Table 2) approach is standard of care for children at QCH. Letermovir is licenced for use in adult CMV-seropositive recipients [R+] of an allogeneic HSCT and is increasingly being used (but not PBS reimbursed) in adult HSCT patients.

Letermovir prophylaxis may be considered on a case-by-case basis in children undergoing allogenic transplants at very high risk of CMV reactivation.

- CMV-seropositive recipients, seronegative donors (CMV R+/D-)
- CMV seronegative recipients, seropositive donors (CMV R-/D+) receiving a non-MSD transplant.

Oncology/BMT/ID SMO discussion required prior to consider relative risk and benefit.
Letermovir does not cover HSV/VZV, valaciclovir/aciclovir should also be continued as per Table 1.

Duration of prophylaxis

- Prophylaxis is continued until Day+100 post HSCT, unless otherwise specified.

Investigations and monitoring during HSCT

All patients:

- **Once weekly** (Monday) – CMV blood qualitative PCR, EBV blood PCR, adenovirus blood PCR
- Weekly CMV, adenovirus, EBV monitoring should continue until Day+100
    - Monitoring should continue for longer in patients considered to be at increased risk, including acute or chronic GvHD, previous viral reactivation or high risk HSCT (mismatched, cord blood or haploidentical)

Following a positive PCR result:

- Increase testing to **twice weekly** (Monday and Thursday) for detected virus
- Further investigations
    - CMV detected:
        - CMV quantitative PCR blood
        - Additional testing based on symptoms or evidence of CMV disease (e.g. pneumonitis, colitis, hepatitis, retinitis, encephalitis)
        - Ophthalmology review recommended when persistent CMV viraemia (>10^2) for more than 3 weeks
    - EBV detected:
        - EBV quantitative PCR
    - Adenovirus detected:
        - Adenovirus CT value
        - Adenovirus quantitative PCR blood.
        - Respiratory viral PCR on nasal swab or NPA, for adenovirus DNA
        - Adenovirus PCR on urine
        - Adenovirus PCR on stool (**N.B** This is NOT the routine faeces PCR which looks for Adenovirus 40/41; when ordering on iEMR select "Adenovirus PCR", then select "faeces" for specimen type, and in reason for order write "BMT patient, generic adenoviral PCR")

TREATMENT OF VIRAL REACTIVATION

Treatment of viral reactivation depends on several factors including the virus type, the child's immune status and evidence of disseminated disease. **Table 2** outlines first line treatment options and factors to consider when deciding to commence treatment.
Earlier commencement of pre-emptive therapy may be considered where the following risk factors are present (on discussion with Infectious Diseases and oncology)*:

- Pre-engraftment phase
- Poor engraftment with lymphocyte count <0.2
- T cell depleted graft
- GvHD (grade III/IV)
- CMV or adenovirus viral load (VL) > $1x10^5$

Table 2: Antiviral treatment in HSCT

Virus	Clinical	When to commence	Recommended treatment	Alternative treatment	Comments
CMV Infection **Pre-emptive treatment (PET)**	Viraemia without evidence of disease	Blood CMV VL > 1000 (1.0×10^3) IU/mL for two consecutive tests	valganciclovir PO OR ganciclovir IV	foscarnet IV Reduce immunosuppression where able. Maribavir PO	Consider Ophthalmology assessment for CMV retinitis. Please note that in cases of persistent viraemia that repeated examinations are required.
		One positive blood CMV VL > $1x10^5$			
		Low level blood CMV detection in a child with significant risk of disease consider earlier commencement on case-by-case basis*			
CMV Disease **Treatment**	Persistent otherwise unexplained fever **And /or** End organ CMV disease	Evidence of CMV disease **And** CMV PCR positive in blood or organ affected (eg BAL, pneumonitis, CSF, encephalitis). Note - retinitis may be present in absence of positive blood CMV PCR	ganciclovir IV OR valganciclovir PO Reduce immunosuppression where able	foscarnet IV cidofovir IV CMV specific CTLs Maribavir PO Intravitreal injections of ganciclovir or foscarnet for severe CMV retinitis combined with systemic therapy	Ophthalmology assessment for CMV retinitis is recommended. Please note that in cases of persistent viraemia that repeated examinations are required. Reduce immunosuppression where able.

Table 3: Antiviral treatment in HSCT (continued)

Virus	Clinical	When to commence	Recommended treatment	Alternative treatment	Comments
Adenovirus Infection Asymptomatic **Pre-emptive treatment (PET)**	**High risk patient** Haplo or mismatched donor T cell depletion cord donor Previous adenovirus PCR positive Lymphocytes < 0.3	2 consecutive positive blood PCR with increasing viral load < 30 days post allo HSCT (no minimum viral load)	cidofovir IV	Adenovirus specific CTLs Brincidofovir (IV or PO) (when available)	Reduce immunosuppression where able.
		Blood Adenovirus VL > $1x10^3$ copies/ml for two consecutive tests			
		One blood Adenovirus VL >10^5 copies/ml			
		One or more blood PCR positive **and** detected in one other site (urine, stool, resp)			
		Low level blood adenovirus detection in a child with significant risk of disease consider earlier commencement on case-by-case basis*			
	Low risk. > 1 month post HSCT and Lymphocytes >0.3	Blood Adenovirus VL > $1x10^4$ copies/ml for two consecutive tests			
Adenovirus Disease Symptomatic (Disease)	Persistent, otherwise unexplained fever **And/or** Organ involvement eg any of: Hepatitis, haemorrhagic cystis, diarrhoea, rash	Adenovirus PCR detection in blood or affected organ/site **AND** Evidence of adenovirus disease	cidofovir IV	Adenovirus specific CTLs Brincidofovir (IV or PO) (when available)	Reduce immunosuppression where able

Table 4: Antiviral treatment in HSCT (continued)

Virus	Clinical	When to commence	Recommended treatment	Alternative treatment	Comments
EBV		EBV re-activation / PTLD as per oncologist	No antiviral treatment currently recommended Rituximab	Reduce immunosuppression where able.	
HHV6	Persistent otherwise unexplained fever Encephalitis Pericarditis	Blood HHV6 VL > $1x10^4$ copies/ml for two consecutive tests **AND** Evidence of compatible disease	valganciclovir PO OR ganciclovir IV	foscarnet IV	Consider integrated HHV (iHHV6). Discuss with ID re testing

Duration of treatment

CMV

Pre-emptive treatment

- Continue treatment dosing for minimum 14 days until CMV VL decreased < 600.
- Continue at least 2 weeks maintenance until CMV PCR undetectable. Repeat pre-emptive courses may be required.

Disease Treatment

- Continue treatment dosing for minimum 21 days until resolution of clinical symptoms and 2 consecutive CMV VL decreased < 100 then at least 2 weeks maintenance until CMV PCR undetectable.
- Ensure (val)ganciclovir TDM performed

If no improvement or increase in viral load at 14 days (Possible refractory infection or disease)

- Ensure ganciclovir TDM performed and dose optimised
- Consider refractory / resistant disease. Discuss CMV Genotypic Resistance Testing with ID. Testing is recommended when CMV viral loads fail to decline by >1 log10 after more than 2 weeks of appropriately dosed antivirals (13).
  - Plasma viral loads >1000 IU/ml are generally needed for genotype testing.
  - Send CMV resistance testing from the relevant compartment when feasible, as mutations may differ between plasma and various body compartments such as vitreous or spinal fluids
- Please ensure that a recent ophthalmology assessment for CMV retinitis has been completed.

Treatment of refractory or resistant CMV

- Clinical resistance depends on host factors, whereas viral resistance is due to mutations in the viral genome.
- Resistant CMV infection is defined as the presence of a known viral genetic mutation(s) that decrease the susceptibility to one or more anti-CMV medications
- Upon clinical suspicion of CMV resistance, consider switching drug class, confirming genotypic resistance mutations and reducing immunosuppression if feasible.
- Antiviral selection is individualized based on a combination of known or suspected resistance genotype mutations, previous drug exposure and acceptable toxicity profile in consultation with Infectious Diseases Team. (13)

Adenovirus

Pre-emptive treatment

- cidofovir 5mg/kg/week for 2 weeks then 5mg/kg every 2 weeks until adenovirus PCR VL < 400 copies/ml.

Adenovirus Disease treatment

- cidofovir 5mg/kg/week for 3-6 weeks then 5mg/kg every 2 weeks until adenovirus PCR VL < 400 copies/ml
- [Alternative dosing in renal impairment: cidofovir 1mg/kg three times per week]

Indication for cidofovir should be reviewed weekly based on clinical status, viral load and lymphocyte count. Lymphocyte counts > 0.3x10^9/L are significantly associated with viral clearance.

Antiviral dosing summary.

Table 3: Antiviral dosing summary recommendations

Drug	Dose	Frequency	TDM	Notes
Ganciclovir IV	5mg/kg	Every 12 hours	Trough (30 minutes before morning dose) – level 1-4 mg/L Peak (2-hour post start of infusion) – level 7-9 mg/L	Induction dose (not neonates)
		Once daily		maintenance or prevention dose
Valganciclovir PO	**< 12 months old:** 16mg/kg **> 12 months old:** (7 x CrCl x BSA) mg (to max 900mg) **> 16 yrs:** 900mg	Every 12 hours	Trough (30 minutes before morning dose) – level 1-4mg/L Peak (2 hour post morning dose) – level 7-9 mg/L	Induction treatment dose
		Once daily		maintenance or prevention dose
Foscarnet IV	60mg/kg	Every 8 hours		Induction 180mg/kg/day continuous infusion may minimise toxicity
	90mg/kg	Every 12 hours		Induction alternate regimen
	90mg/kg	Once daily		maintenance or prevention dose
Letermovir PO Non PBS SAS	> 30kg – 480mg > 18kg – <30kg 240mg 15--< 18kg 120mg	Once Daily		Prophylaxis Reduce dose by 50% if receiving concomitant cyclosporine
Cidofovir IV	5mg/kg	Once Weekly		Induction dose To minimise nephrotoxicity, give in conjunction with probenecid and IV fluids
	5mg/kg	Once every 2 weeks		maintenance dose

Cidofovir IV alternative regimen	1mg/kg	3 times per week		Renal impairment (CrCl < 55 mL/min/1.73m2) or concomitant nephrotoxic agents
Maribavir PO	> 12 years of age and >35 kg - 400mg	Every 12 hours		Treatment; resistant or refractory CMV disease TGA approval: Treatment of adults with post-transplant cytomegalovirus (CMV) infection and disease resistant, refractory or intolerant to one or more prior therapies
Aciclovir IV	**< 12 years:** 500 mg/m^2 (or 20mg/kg) **> 12 years:** 10mg/kg	every 8 hours	-	Treatment
Valaciclovir PO	20 mg/kg	Every 8 hours		Treatment
	20 mg/kg	Every 12 hours		Prophylaxis

Consideration for dosing:

Renal function:

Use Modified Schwartz formula to calculate Paediatric Creatinine Clearance (CrCl)

Modified Schwartz formula is not validated for use in neonates and infants (less than 1 year of age).

If creatinine is reported as less than 30 micromol/L, use 30 micromol/L in the Modified Schwartz formula.

Cap the calculated Creatinine Clearance at 150mL/min/1.73m2 for the purposes of calculating the oral valGANciclovir dose.

CrCl (mL/min/1.73m2) = [36.5 x Height (cm)] / Creatinine (micromol/L) = _____ mL/min/1.73m2 **Not validated to be used in children under 1 year of age

Obesity:

- In patients with a BMI > 95th centile for age, for some antiviral agents, please use adjusted body weight for dose calculation (See Antiviral monograph)
- A child's ideal body weight (IBW) can be estimated using the corresponding weight for the height percentile on the growth chart (https://www.cdc.gov/growthcharts/) or if the child's height cannot be determined, the average weight-for-age (50th centile) on the growth chart.

Adjusted body weight (kg) = Ideal body weight + 0.4 X (Measured Weight – Ideal body weight)

Body surface area:

$$Body\ Surface\ Area\ (BSA)m^2 = \sqrt{\frac{height\ (cm)\ x\ weight\ (kg)}{3600}}$$

Table 4. Complete Antiviral Drug Monographs

Aciclovir Intravenous
Indications: Aciclovir is used in the treatment and prevention of herpes simplex virus (HSV), varicella zoster virus (VZV) and cytomegalovirus (CMV)
Restrictions: Amber restricted antimicrobial – see CHQ AMS formulary and QLD Health List of approved medicines (LAM) for pre-approved indications. Use outside of these indications, require AMS approval from CHQ ID Service
Contra indications, precautions, adverse effects and drug-drug interactions Refer to the Product information, UpToDate or Micromedex via CKN for more information
Formulations and administration Aciclovir 250 mg injection **For preparation, administration and IV compatibility information**, consult the RCH Paediatric injectable guidelines , SHPA AIDH and Micromedex on CKN. Infuse dose over at least 60 minutes. Dilute dose appropriately. Avoid extravasation (pH approximately 11)
Dosage and dose adjustments Dose based on actual body weight. If weight for height exceeds 95th centile, use adjusted body weight using paediatric formula - – seek ID advice. Dose reduction required in renal impairment Ensure adequate hydration to prevent renal toxicity **Prophylaxis (during bone marrow transplant conditioning):** **Infants, children and adolescents:** 10 mg/kg/dose (Maximum 500 mg/dose) IV 8 hourly **Treatment:** **Normal renal function:** **Neonates:** IV Aciclovir neonatal dosing monograph (ANMF) **Infants and children <12 years of age:** 500 mg/m2/dose (Maximum 1 g/dose) IV 8 hourly (**or** 20 mg/kg/dose (Maximum 1g/dose) IV 8 hourly) **Adolescents >12 years of age:** 10 mg/kg/dose (Maximum 1 g/dose) IV 8 hourly **Renal impairment** **Use Modified Schwartz formula to calculate renal function in children 1 to 18 years of age:** CrCl ≥ 50 mL/min/1.73m2: Normal dose CrCl 30-49 mL/ min/1.73m2: 100 % of dose given twice daily CrCl 10-29 mL/ min/1.73m2: 100 % of dose given once daily CrCl < 10 mL/ min/1.73m2: 50 % of dose given once daily **Renal replacement therapy / ECMO– seek Pharmacist advice.** Additional resources: The Renal drug database and Renal drug handbook on CKN
Monitoring required for long term treatment or when pre-existing renal impairment FBC and CHEM20 – monitor renal function, liver function. Aciclovir TDM available – ID specialist approval and guidance on appropriate targets required.
Penetration - Aciclovir is widely distributed in all tissues including CSF and ocular tissue.

Valaciclovir (oral/enteral)
Indications: Valaciclovir is used in the treatment and prevention of herpes simplex virus (HSV), varicella zoster virus (VZV) and cytomegalovirus (CMV)
Restrictions: Amber restricted antimicrobial – see CHQ AMS formulary and QLD Health List of approved medicines (LAM) for pre-approved indications. Use outside of these indications, require AMS approval from CHQ ID Service and if non-LAM, a CHQ Individual patient approval.
Contra indications, precautions, adverse effects and drug-drug interactions Refer to the Product information, UpToDate or Micromedex via CKN for more information
Formulations and administration Valaciclovir 500 mg tablets No commercially available Valaciclovir suspension registered in Australia Tablets can be crushed/dispersed to allow aliquot dosing (prepare each dose fresh) – seek Pharmacist advice on appropriate dose preparation and masking agents to improve palatability.
Dosage and dose adjustments Dose based on actual body weight. Dose adjustment required in renal impairment. Ensure adequate hydration to prevent renal toxicity **Neonates:** IV Aciclovir neonatal monograph - preferred for empiric or directed HSV treatment in neonates. Neonatal monograph - Oral aciclovir (dispersible tablets) - preferred for HSV suppression after completion of IV treatment course. Seek ID advice. **Infants, children and adolescents:** Valaciclovir is a prodrug of aciclovir and preferred in this age group for its more convenient dosing schedule and greater bioavailability. **HSV/CMV Prophylaxis:** 20 mg/kg/dose (Maximum 500mg/dose) twice daily **HSV/VZV Treatment:** 20 mg/kg/dose (Maximum 1 g/dose) three times daily Treatment duration vary by indication and if patient is immunocompetent/immunocompromised– seek ID advice **Renal impairment** **Use Modified Schwartz formula to calculate renal function in children 1 to 18 years of age:** **Immunocompetent patient:** CrCl ≥ 50 mL/min/1.73m2: Normal dose CrCl 30-49 mL/ min/1.73m2: 20 mg/kg/dose given twice daily CrCl 10-29 mL/ min/1.73m2: 20 mg/kg/dose given once daily CrCl < 10 mL/ min/1.73m2: 10 mg/kg/dose given once daily **Immunocompromised patient:** Seek ID specialist/ pharmacist advice on dose adjustment **Renal replacement therapy – seek Pharmacist advice.** Additional resources: The Renal drug database and Renal drug handbook on CKN
Monitoring required for long term treatment or when pre-existing renal impairment FBC and CHEM20 – monitor renal function, liver function. Aciclovir TDM available – ID approval required.
Penetration - Aciclovir is widely distributed in all tissues including CSF and ocular tissue.

Ganciclovir Intravenous

Indications: Ganciclovir is used in the treatment and prevention of cytomegalovirus (CMV). Is effective against other herpes viruses, including HSV and to some extent HHV-6.
Resistance to ganciclovir likely if CMV UL54 and UL97 mutant genes detected – seek ID advice for alternative treatment options

Restrictions: Red restricted antimicrobial. AMS approval from CHQ ID Service required prior to commencement of treatment

Contra indications, precautions, adverse effects and drug-drug interactions
Refer to the Product information, UpToDate or Micromedex via CKN for more information

Formulations and administration
Intravenous (IV) Ganciclovir doses are aseptically manufactured by the Pharmacy Aseptic Production unit.
For administration and IV compatibility information, consult the RCH Paediatric injectable guidelines , SHPA AIDH and Micromedex on CKN. Cytotoxic handling precautions required.
Infuse each dose over at least 60 minutes via Central venous access device.

Dosage and dose adjustments
Dose based on actual body weight. If weight for height exceeds 95th centile, use adjusted body weight using paediatric formula – seek ID advice.
Dose adjustment required in renal impairment. Caution with concomitant nephrotoxic agents.
Normal renal function:
Neonates:
Induction: 6 mg/kg IV 12 hourly
Switch to oral ValGANciclovir when enteral absorption is established.
Maintenance: Seek ID specialist advice

Infants, children and adolescents:
Induction: 5 mg/kg IV 12 hourly
Maintenance: 5 mg/kg IV 24 hourly
Switch to oral ValGANciclovir when enteral absorption is established.
Treatment duration vary by indication and response to treatment – seek ID advice

Renal impairment
Use Modified Schwartz formula to calculate renal function in children 1-18 years of age:
Induction dose (infants, children and adolescents):
CrCl ≥ 50 mL/min/1.73m2: Normal dose
CrCl 30-49 mL/ min/1.73m2: 2.5 mg/kg/dose 12 hourly
CrCl 10-29 mL/ min/1.73m2: 2.5 mg/kg/dose 24 hourly
CrCl < 10 mL/ min/1.73m2: 1.25 mg/kg/dose 24 to 48 hourly (guided by TDM and ID specialist)
Maintenance dose (infants, children and adolescents):
CrCl ≥ 50 mL/min/1.73m2: Normal dose
CrCl 30-49 mL/ min/1.73m2: 2.5 mg/kg/dose 24 hourly
CrCl 10-29 mL/ min/1.73m2: 1.25 mg/kg/dose 24 hourly
CrCl < 10 mL/ min/1.73m2: 0.625 mg/kg/dose 24 to 48 hourly (guided by TDM and ID specialist)

Renal replacement therapy/ ECMO – seek Pharmacist advice.
Additional resources: The Renal drug database and Renal drug handbook on CKN

Monitoring FBC and CHEM20 – monitor neutrophil count, platelet count, haemoglobin, renal & liver function.
Ganciclovir TDM available – ID approval required.
Time to steady state 24 to 48 hours (Levels on day 2 or 3 of therapy)
Treatment: Peak (2 hours from start of infusion) = 7 to 9 mg/L, Trough (30 minutes pre dose) = 1 to 4 mg/L. AUC 80 to 120
Prophylaxis: Trough (30 minutes pre dose) = 1 to 3mg/L. AUC 40 to 80
Research into AUC monitoring is ongoing – seek ID / AMS pharmacist advice.

Penetration – Ganciclovir is widely distributed in all tissues including CSF and ocular tissue.

CMV retinitis – Local treatment with Intravitreal Ganciclovir (2 mg/0.1 mL) possible in sight threatening disease. AMS approval from ID specialist required prior to Pharmacy APU compounding of doses.

ValGANciclovir (oral/enteral)

Indications: ValGANciclovir is a prodrug of Ganciclovir which is used in the treatment and prevention of cytomegalovirus (CMV). Is effective against other herpes viruses, including HSV and to some extent HHV-6. Resistance to ganciclovir likely if CMV UL54 and UL97 mutant genes detected – seek ID advice for alternative treatment options.

Restrictions: Amber restricted antimicrobial – see CHQ AMS formulary and QLD Health List of approved medicines (LAM) for pre-approved indications.

Contra indications, precautions, adverse effects and drug-drug interactions
Refer to the Product information, UpToDate or Micromedex via CKN for more information

Formulations and administration
ValGANciclovir 450 mg tablets and 50 mg/mL oral suspension. Cytotoxic handling precautions required

Dosage and dose adjustments
Dose based on actual body weight. Dose adjustment required in renal impairment.
Caution with concomitant nephrotoxic agents.
Normal renal function:
Neonates and infants up to 12 months of age:
Induction: 16 mg/kg oral (or via naso-gastric tube) 12 hourly (twice daily)
Maintenance: 16 mg/kg oral (or via naso-gastric tube) 24 hourly (once daily)

Children and adolescents:
Formula*: Dose (mg) = 7 X BSA X CrCl
(Use Modified Schwartz formula to calculate renal function in children 1-18 years of age.
Cap CrCl at 150 mL/min/1.73m2)
Induction: Administer calculated dose TWICE daily (Maximum 900 mg/dose twice daily)
Maintenance: Administer calculated dose ONCE daily (Maximum 900 mg/dose once daily)
*Studies have reported higher incidence of haematological toxicity using BSA dosing method compared to weight-based dosing (mg/kg). Seek ID specialist advice on dosing. Treatment durations vary by indication and response to treatment.

Renal impairment
Neonates and infants < 12 months of age: Seek ID / Pharmacist advice.
Children and adolescents < 16 years of age: Use Formula* (see above) to calculate adjusted dose.
Adolescents ≥16 years of age (adult dose):
Use Modified Schwartz formula to calculate renal function in children 1-18 years of age:
Induction dose (adult):
CrCl ≥ 60 mL/min/1.73m2: 900 mg/dose 12 hourly (normal adult dose)
CrCl 40-59 mL/ min/1.73m2: 450 mg/dose 12 hourly
CrCl 25-39 mL/ min/1.73m2: 450 mg/dose 24 hourly
CrCl 10-24 mL/ min/1.73m2: 450 mg/dose 48 hourly
CrCl < 10 mL/ min/1.73m2: Seek ID specialist advice on alternative treatment options.
Maintenance dose (adult):
CrCl ≥ 60 mL/min/1.73m2: 900 mg/dose 24 hourly (normal adult dose)
CrCl 40-59 mL/ min/1.73m2: 450 mg/dose 24 hourly
CrCl 25-39 mL/ min/1.73m2: 450 mg/dose 48 hourly
CrCl < 24 mL/ min/1.73m2: Seek ID specialist advice on alternative treatment options.

Renal replacement therapy – seek Pharmacist advice.
Additional resources: The Renal drug database and Renal drug handbook on CKN

Monitoring FBC and CHEM20 – monitor neutrophil count, platelet count, haemoglobin, renal & liver function.
Ganciclovir TDM available – ID approval required.
Time to steady state 24 to 48 hours (Levels on day 2 or 3 of therapy)
Treatment: Peak (2 hours from dose) = 7 to 9 mg/L, Trough (30 minutes pre dose) = 1 to 4 mg/L. AUC 80 to 120
Prophylaxis: Trough (30 minutes pre dose) = 1 to 3mg/L. AUC 40 to 80
Research into AUC monitoring is ongoing – seek ID / AMS pharmacist advice.

Penetration – Ganciclovir is widely distributed in all tissues including CSF and ocular tissue.

Cidofovir intravenous	
Indications: Cidofovir is used in the treatment of cytomegalovirus (CMV) (including UL97 resistance) and adenovirus. It also has activity against herpes simplex, varicella zoster and possibly BK virus.	
Restrictions: Red restricted antimicrobial. AMS approval from CHQ ID Service required prior to commencement of treatment	
Contra indications, precautions, adverse effects and drug-drug interactions Refer to the Product information, UpToDate or Micromedex via CKN for more information	
Formulations and administration Intravenous (IV) Cidofovir doses are aseptically manufactured by the Pharmacy Aseptic Production unit. **For administration and IV compatibility information**, consult the RCH Paediatric injectable guidelines , SHPA AIDH and Micromedex on CKN. Cytotoxic handling precautions required. Pre-hydration, probenecid and post-hydration required to reduce renal toxicity.	
Dosage and dose adjustments for CMV and Adenoviremia Dose based on actual body weight. If weight for height exceeds 95th centile, use adjusted body weight using paediatric formula – seek ID specialist advice. Dose adjustment required in renal impairment. Caution with concomitant nephrotoxic agents. Pre-hydration, probenecid and post-hydration required to reduce renal toxicity. **Normal renal function:** Neonates – limited information. Seek ID specialist advice. Infants, children and adolescents: 5 mg/kg IV once a week (induction) or once every 2 weeks (maintenance) **Renal impairment (CrCl < 55 mL/min/1.73m2) or concomitant nephrotoxic agents:** Neonates – limited information. Seek ID specialist advice. Infants, children and adolescents: 1 mg/kg/dose IV three times a week Treatment duration vary by indication and response to treatment – seek ID advice **Renal replacement therapy/ ECMO – seek Pharmacist advice.** Additional resources: The Renal drug database and Renal drug handbook on CKN	
Cidofovir infusion timeline (including pre-hydration, probenecid and post-hydration) **If charting in ieMR, use Paediatric Cidofovir PowerPlan**	
3 hours pre-infusion	Administer oral Probenecid 25 to 40 mg/kg/dose (Maximum 2 gram)
1 hour pre-infusion	Commence pre-hydration: Sodium chloride 0.9% 10 mL/kg to 20 mL/kg (to maximum 1000 mL) over 1 hour
Commence cidofovir infusion (1 hour infusion)	Continue hydration: Sodium chloride 0.9% 10 mL/kg to 20 mL/kg (to maximum 1000 mL) over 1 hour
Immediately post cidofovir infusion	Continue maintenance fluids for 2 hours after completion of the cidofovir infusion
3 hours after commencement of cidofovir infusion (2 hours post completion of infusion)	Administer oral Probenecid 10 to 20 mg/kg/dose (Maximum 1 gram)
9 hours after commencement of cidofovir infusion (8 hours post completion of infusion)	Administer oral Probenecid 10 to 20 mg/kg/dose (Maximum 1 gram)
Monitoring FBC and CHEM20 – monitor neutrophil count, renal & liver function, electrolytes. Urinalysis - proteinuria **Cidofovir assay and TDM is not currently available.** **Resistance to cidofovir likely if CMV UL54 mutant gene detected** – seek ID advice for alternative treatment options. Cidofovir suitable alternative to Ganciclovir if CMV UL97 mutant gene detected.	
Penetration - CSF penetration of Cidofovir is not well studied.	

Foscarnet intravenous

Indications: Foscarnet is used in the treatment of cytomegalovirus (CMV) (including UL97 resistance) and aciclovir-resistant herpes simplex, herpes zoster infections and possibly HHV-6 virus.

Restrictions: Red restricted antimicrobial. AMS approval from CHQ ID Service required prior to commencement of treatment. Non-LAM - CHQ Individual patient approval required

Contra indications, precautions, adverse effects and drug-drug interactions
Refer to the Product information, UpToDate or Micromedex via CKN for more information

Formulations and administration
Intravenous (IV) Foscarnet doses are aseptically manufactured by the Pharmacy Aseptic Production unit.
For administration and IV compatibility information, consult the RCH Paediatric injectable guidelines , SHPA AIDH and Micromedex on CKN. Cytotoxic handling precautions required. Pre-hydration required to reduce renal toxicity. Maximum infusion rate 1 mg/kg/minute. Case reports suggest that renal toxicity may be reduced by administering foscarnet as extended infusions or continuous infusions. Seek ID advice.

Dosage and dose adjustments
Dose based on actual body weight. If weight for height exceeds 95th centile, use adjusted body weight using paediatric formula – seek ID advice.
Dose adjustment required in renal impairment. Caution with concomitant nephrotoxic agents or electrolyte abnormalities (consider ECG monitoring and electrolyte supplementation).
Pre-hydration:
Give 10 mL/kg to 20 mL/kg sodium chloride 0.9% (Maximum 1000 mL pre 1st dose, Maximum 500 mL from 2nd dose onwards) as pre-hydration 1 hour pre-foscarnet dose.
CMV disease - Normal renal function:
Neonates – limited information. Seek ID advice.
Infants, children and adolescents:
Induction: 60 mg/kg/dose IV 8 hourly (CMV disease, with CNS involvement: 90 mg/kg IV 12 hourly)
Maintenance: 90 mg/kg to 120 mg/kg IV 24 hourly
Aciclovir-resistant HSV infection - Normal renal function:
Infants and children: 40 mg/kg/dose IV 8 hourly
Adolescents: 40 mg/kg/dose IV 12 hourly or 8 hourly
Treatment duration vary by indication and response to treatment – seek ID advice

Renal impairment:
Use Modified Schwartz formula to calculate renal function in children 1-18 years of age.
Divide calculated CrCl by patient's weight for mL/minute/kg.

CrCl (mL/minute/kg)	Recommended dose adjustment			
> 1.4 (normal renal function)	**40 mg/kg 8 hrly**	**60 mg/kg 8 hrly**	**90 mg/kg 24 hrly**	**120 mg/kg 24 hrly**
> 1 to 1.4	30 mg/kg 8 hrly	45 mg/kg 8 hrly	70 mg/kg 24 hrly	90 mg/kg 24 hrly
> 0.8 to 1	35 mg/kg 12 hrly	50 mg/kg 12 hrly	50 mg/kg 24 hrly	65 mg/kg 24 hrly
> 0.6 to 0.8	25 mg/kg 12 hrly	40 mg/kg 12 hrly	80 mg/kg 48 hrly	105 mg/kg 48 hrly
> 0.5 to 0.6	40 mg/kg 24 hrly	60 mg/kg 24 hrly	60 mg/kg 48 hrly	80 mg/kg 48 hrly
> 0.4 to 0.5	35 mg/kg 24 hrly	50 mg/kg 24 hrly	50 mg/kg 48 hrly	65 mg/kg 48 hrly
≤ 0.4	**Not recommended – seek ID specialist advice on alternative treatment option**			

Monitoring FBC and CHEM20 – monitor neutrophil count, renal & liver function, electrolytes (magnesium, calcium, potassium, phosphate). Urinalysis - proteinuria
Foscarnet assay and TDM is not currently available. Seek ID specialist advice.
Resistance to foscarnet likely if CMV UL54 mutant gene detected – seek ID specialist advice for alternative treatment options.
Foscarnet suitable alternative to Ganciclovir if CMV UL97 mutant gene detected.

CMV retinitis – Local treatment with Intravitreal Foscarnet (2.4 mg/0.1 mL) possible in sight threatening disease.
AMS approval from ID service required prior to Pharmacy APU compounding of doses.

Penetration Foscarnet is widely distributed in all tissues including CSF.

Letermovir (oral/enteral/intravenous)
Indications: Letermovir is used in the prevention of cytomegalovirus (CMV) infection in seropositive recipients of an allogeneic HSCT. Originally, Letermovir demonstrated little cross-resistance due to its novel inhibition of the CMV terminase complex. However, the emergence of Letermovir resistant HCMV UL56 mutant has been reported in recent case reports. Letermovir is not active against HSV or VZV. Additional valaciclovir/aciclovir prophylaxis is required.
Restrictions: Red restricted antimicrobial. AMS approval from CHQ ID Service required prior to commencement of treatment Non-LAM - CHQ Individual patient approval required
Contra indications, precautions, adverse effects and drug-drug interactions For more information, refer to the Product information, UpToDate or Micromedex via CKN. Letermovir is a strong inhibitor of CYP3A4 – likely to increase Ciclosporine levels. Ciclosporin also increases Letermovir concentrations through inhibition of OATP1B1/1B3 transporters. Please contact Pharmacist to review drug-drug interactions prior to commencement of treatment
Formulations Letermovir 240 mg/ 12mL and 480 mg/ 24 mL concentrated injection for infusion Letermovir 240 mg and 480 mg film-coated tablets
Intravenous administration **For administration and IV compatibility information**, consult the RCH Paediatric injectable guidelines , SHPA AIDH and Micromedex on CKN. Cytotoxic handling precautions required. Pre-hydration required to reduce renal toxicity. Administer through a sterile 0.2 or 0.22 micron polyethersulfone (PES) in-line filter. Dose can be administered via peripheral or central intravenous access over at least 60 minutes
Dosage and dose adjustments Oral and IV dose equivalence has not been established in the paediatric population. **Oral dosing in children (film-coated tablets):** **Without co-administration of ciclosporine:** 15 to <18 kg: Give 120 mg Letermovir orally once daily 18 to <30 kg: Give 240 mg Letermovir orally once daily > 30kg: Give 480 mg Letermovir orally once daily **With co-administration of ciclosporine:** 15 to <18 kg: Give 60 mg Letermovir orally once daily 18 to <30 kg: Give 120 mg Letermovir orally once daily > 30kg: Give 240 mg Letermovir orally once daily **Intravenous dosing** (with or without co-administration of ciclosporine) **IV dosing in adolescents >12 years of age:** Give 480 mg Letermovir IV once daily **IV dosing in children <12 years of age and >30kg:** Give 120mg Letermovir IV once daily **Renal impairment:** No dose adjustment for patients with mild renal impairment. Letermovir AUC was increased 1.9 and 1.4-fold in patients with moderate to severe renal impairment (CrCl < 59 mL/min/1.73m2 and CrCl <30 mL/min/1.73m2 respectively). The IV formulation contains an excipient SBECD, that may accumulate in ESRD. Use with caution. **Hepatic impairment:** No dose adjustment for patients with mild hepatic impairment. Use in severe hepatic impairment is not recommended. Letermovir AUC was increased 1.6 and 3.8-fold in patients with moderate to severe hepatic impairment.
Monitoring FBC and CHEM20 – monitor neutrophil count, renal & liver function, electrolytes **Letermovir assay and TDM is not currently available.**
Penetration - CSF penetration of Letermovir is not well studied.

Maribavir (oral/enteral)

Indications:
Maribavir is used in the treatment in adults and children >12 years (and >35 kg) of cytomegalovirus (CMV) refractory to treatment (with or without genotypic resistance) with ganciclovir, valganciclovir, cidofovir or foscarnet.
Maribavir is not active against HSV or VZV. Additional valaciclovir/aciclovir prophylaxis is required.

Restrictions: Red restricted antimicrobial.
AMS approval from CHQ ID Service required prior to commencement of treatment
Non-LAM - CHQ Individual patient approval required

Contra indications, precautions, adverse effects and drug-drug interactions

Maribavir is a major substrate for CYP 3A4, minor substrate for CYP 1A2 and a weak inhibitor for CYP 3A4
Maribavir concentration is significantly reduced when co-administered with CYP 3A4 inducer.
Please contact Pharmacist to review drug-drug interactions prior to commencement of treatment

Maribavir antagonize the antiviral activity of ganciclovir and valganciclovir through inhibition of CMV encoded kinase pUL97. Do not co-administer with ganciclovir and valganciclovir.

Maribavir may cause taste disturbances, nausea, vomiting, diarrhoea, neutropenia and acute kidney injury.
For more information, refer to the Product information, UpToDate or Micromedex via CKN.

Use cytotoxic handling precautions – Maribavir is considered teratogenic.

Formulations
Maribavir 200 mg tablets

Dosage, administration and dose adjustments

Standard dose for children > 12 years of age and >35 kg:
400 mg twice daily (with or without food)

Renal impairment:
No dose adjustment for patients with mild, moderate or severe renal impairment.
Use in patients with end stage renal disease has not been studied

Hepatic impairment:
No dose adjustment for patients with mild or moderate hepatic impairment.
Use in patients with severe hepatic impairment has not been studied.

To prepare dose for naso-gastric administration:
Use cytotoxic handling precautions – Maribavir is considered teratogenic.
Disperse 400 mg dose (two 200 mg tablets) in 30 mL of water in an oral dispenser. Shake oral dispenser well for 30 to 45 seconds until tablet is fully dispersed, before administering the full dose (30 mL volume) via naso-gastric tube (≥10 french size). Flush tube well after dose is administered. Prepare each dose fresh.

Monitoring
FBC and CHEM20 – monitor neutrophil count, haemoglobin and platelet count, renal & liver function, electrolytes.
Maribavir assay and TDM is not currently available.

Penetration Maribavir does not penetrate into CSF.

SUPPORTING DOCUMENTS

Standards:

- Guidelines for the management of cytomegalovirus infection in patients with haematological malignancies and after stem cell transplantation from the 2017 European Conference on Infections in Leukaemia (ECIL7). Lancet Infect Dis, 19: e260-272.
- National Safety and Quality Health Service (NSQHS) Standards

Supporting documents:

- CHQ-GDL-0129 Management of Fever in a Paediatric Oncology Patient- Febrile Neutropaenia and Febrile Non-neutropaenia
- CHQ-GDL-01075 Antifungal Prophylaxis and Treatment in Paediatric Oncology Patients and other Immunocompromised Children (when published)
- CHQ Procedure 01035 Antimicrobial Restriction Procedure
- CHQ Antimicrobial Restriction list

CONSULTATION

Key stakeholders who reviewed this version:

• Paediatric Infection Management Consultant team (CHQ) • Director BMT (CHQ) • Paediatric Oncology Consultant team (CHQ) • Pharmacist Advanced – Antimicrobial Stewardship (CHQ) • Pharmacy Team leader – Oncology (CHQ)	• Senior Clinical Pharmacist – Oncology (CHQ) • Medicines Advisory Committee endorsed

DEFINITIONS

Term	Definition
CMV viraemia	CMV detection in blood without evidence of disseminated disease
CMV disease	Signs and symptoms suggestive of specific site disease (pneumonia, colitis, hepatitis, retinitis, encephalitis etc) with CMV detection in site-specific specimen
Probable refractory CMV infection	is defined as persistent CMV DNA in the blood or plasma at the same level or <1 log10 increase, after at least 2 weeks of an appropriately dosed anti-CMV medication
Refractory CMV infection	is an increase by >1 log10 CMV DNA levels in blood or plasma after at least 2 weeks of an appropriately dosed anti-CMV medication
Refractory CMV disease	is defined as the worsening of clinical signs and symptoms and/or progression to CMV end-organ disease after at least 2 weeks of appropriately dosed anti-CMV medication
Resistant CMV infection	is defined as the presence of a known viral genetic mutation(s) that decreases the susceptibility. to one or more anti-CMV medications

ABBREVIATIONS

Term	Definition
BSA	Body surface area
CMV	Cytomegalovirus
CrCl	Creatinine clearance
EBV	Epstein Barr virus
GvHD	Graft-versus-Host disease
HHV6	Human herpes virus 6
HSCT	Haematopoietic stem cell transplant
HSV1	Herpes simplex virus 1
HSV2	Herpes simplex virus 2
ID	Infectious Diseases
IgG	Immunoglobulin G
IV	Intravenous
NPA	Nasopharyngeal aspirate
PCR	Polymerase chain reaction
PO	Per oral
TDM	Therapeutic drug monitoring
VZV	Varicella zoster virus
D -/+	Donor (- = negative; + = positive)
R -/+	Recipient (- = negative; + = positive)

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GUIDELINE REVISION AND APPROVAL HISTORY

Version No.	Modified by	Amendments authorised by	Approved by	Comments
1.0 19/11/2024	Director, IMPS Paediatric infectious diseases fellow, CHQ Paediatric infection specialist team, CHQ Pharmacist Advanced, Antimicrobial stewardship	Divisional Director Medicine	Executive Director Clinical Services	New endorsed document

Key words	Antiviral, prophylaxis, treatment, oncology, immunocompromised, HSCT, aciclovir, cidofovir, foscarnet, ganciclovir, valaciclovir, valganciclovir, maribavir, letermovir, cytomegalovirus, CMV, adenovirus, EBV, 02219
Accreditation references	NSQHS Standards (1-8): • ACSQHC Standard 3 – Healthcare associated infections • ACSQHC Standard 4 – Medication safety