Management of CMV Reactivation and Infection in Allogeneic Blood and Marrow Transplant Recipients

This document provides information on the use of ganciclovir, valganciclovir, foscarnet and cidofovir in the management of cytomegalovirus (CMV) reactivation and infection in allogeneic blood and marrow transplant (BMT) recipients.

INTRODUCTION

Cytomegalovirus (CMV) infection or reactivation is a frequent cause of morbidity and mortality in recipients of allogeneic BMT. Some patients with CMV reactivation are asymptomatic; others will have clinical disease manifested as fever, leukopaenia, hepatitis, oesophagitis, gastroenteritis or pneumonia. Approximately 85% of patients with CMV pneumonia will die of the infection.

Risk factors for CMV infection or reactivation include recipient age, the histocompatibility of donor and recipient, the CMV antibody status of the donor and recipient and the severity of GvHD.

CMV reactivation is more common in seropositive recipients, and among the seronegative recipients CMV infection is more frequent where the donor is seropositive. CMV seropositive patients have a poorer outcome than seronegative patients. The use of CMV seronegative donor for CMV seronegative patient reduces the risk of non-relapse mortality. Several studies have shown that the use of CMV-seronegative donor over seropositive donors for seropositive patients has negative effects including delayed CMV-specific immune reconstitution repeated reactivations, higher peak virus load, late CMV recurrence, CMV disease and a decreased in survival.

PREVENTION OF CMV REACTIVATION AND DISEASE

The use of CMV screened blood products is not required. Leukocyte-depleted blood products should be used.

Table 1 - Overview of CMV prophylaxis

<table>
<thead>
<tr>
<th>Recipient CMV status</th>
<th>Donor CMV status</th>
<th>CMV Prophylaxis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seropositive (+)</td>
<td>Seropositive (+)</td>
<td>Letermovir 480mg OD PO/IV (240mg OD in patients taking ciclosporin) from day 0 to day +100.</td>
</tr>
<tr>
<td>Seropositive (+)</td>
<td>Seronegative (-)</td>
<td>Letermovir 480mg OD PO/IV (240mg OD in patients taking ciclosporin) from day 0 to day +100</td>
</tr>
<tr>
<td>Seronegative (-)</td>
<td>Seropositive (+)</td>
<td>Aciclovir 500mg/m² IV TDS or 800mg PO QDS from start of conditioning till day +30 then 800mg PO QDS for 3 months*</td>
</tr>
<tr>
<td>Seronegative (-)</td>
<td>Seronegative (-)</td>
<td>Aciclovir 250mg/m² IV TDS or 200mg PO TDS</td>
</tr>
</tbody>
</table>

Patients taking letermovir for CMV prophylaxis still require aciclovir 200mg TDS for HSV/VZV prophylaxis for 12 months post-transplant.

* Longer treatment should be considered if CMV reactivation has occurred or if immunosuppression is used for a prolonged period (discuss with consultant).

For full information on letermovir see drug treatment summaries further in document.
MONITORING OF CMV REACTIVATION

CMV seropositive recipients are screened pre transplant, at work up, for evidence of CMV viraemia by polymerase chain reaction (PCR) testing of peripheral blood. If there is evidence of CMV reactivation the transplant may be postponed on instruction of the transplant consultant.

All transplant recipients are screened by PCR testing post-transplant starting from day +14 and continuing weekly until day +100.

CMV reactivation is indicated by a virus load of >10^3 copies/ml (3 log_{10}). The chief “at risk” period for CMV reactivation post-transplantation is the first 100 days. Later reactivation has been noted in recipients of reduced intensity transplants particularly those receiving T cell depletion with Campath (alemtuzumab).

After +100 days post-transplant CMV PCR testing can usually be discontinued although testing should continue for up to one year in high-risk patients:

- (a) Patients with CMV reactivation in the first 100 days post BMT
- (b) Patients on prolonged immunosuppression e.g., steroid therapy for GVHD

How to request a CMV PCR

CMV PCR is performed in the Microbiology Laboratory at the John Radcliffe Hospital. Please request on EPR and send a minimum of 4mls EDTA blood (lavender topped tube) with a blue microbiology request form. Testing is usually performed on Tuesdays and Thursdays. Samples must be received in the lab by the end of the day before testing.

Where to find results

PCR results will be available on EPR by the end of the day on Tuesdays and Thursdays. CMV PCR results are reported as a quantitative virus load, either ‘NOT detected’ where the limit of detection is 600 copies/ml, or as log(10) copies/ml (e.g. 3.0 log(10) copies/ml equates to a viral load of 10^3 = 1000 copies/ml).

TREATMENT OF CMV INFECTION AND DISEASE

Initiating pre-emptive treatment for CMV viraemia

A patient with a CMV viral load of ≥10^4 copies/ml (4.0 log(10) copies/ml) should be commenced on pre-emptive treatment even in the absence of symptoms. A virus load of ≥10^4 copies/ml (4.0 log(10) copies/ml) correlates strongly with risk of CMV disease.

Consider treatment when levels are >10^3 copies/ml in asymptomatic high-risk individuals (as defined in introduction above), especially when serial testing shows that CMV load is increasing by over 10-fold per week.

If patient is asymptomatic with normal LFT’s and has a low CMV virus load (<10^4 copies/ml) which is stable on repeat testing, it is reasonable to observe for symptoms and continue to monitor weekly until negative on two consecutive weeks (discuss with consultant).

Treatment of CMV Disease
TREATMENT SUMMARIES

1. Letermovir – prophylaxis only
2. Valganciclovir
3. Ganciclovir
4. Foscarnet
5. Cidofovir
6. Maribavir

1. LETERMOVIR - Blueteq required.

**Indication:** Prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive [R+] recipients of an allogeneic haematopoietic stem cell transplant [NICE TA591]

**Treatment dose:** Refer to Table 1. The recommended dose is 480 mg (2 x 240mg tablets) PO once daily, unless used in combination with ciclosporin as described below.

**Dose modifications:** No renal or hepatic dose adjustments are required. If letermovir is co-administered with ciclosporin, the dosage of letermovir should be decreased to 240 mg (1 x 240mg tablet) PO once daily.

- If ciclosporin is initiated after starting letermovir, the next dose of letermovir should be decreased to 240 mg once daily.
- If ciclosporin is discontinued after starting letermovir, the next dose of letermovir should be increased to 480 mg once daily.
- If ciclosporin dosing is temporarily interrupted due to high ciclosporin levels, no dose adjustment of letermovir is needed.

**Patients unable to swallow or absorb enterally:** An intravenous form of letermovir is available (240mg/12mL vial). Conversion from PO to IV dosing is 1:1. Dilute dose in 250mL sodium chloride 0.9% or glucose 5% and infuse IV over 60 minutes with a 0.2micron filter.

**Treatment duration:** Start on day 0 (stem cell infusion day), if delayed may be started up to 28 days post-infusion. Continue until day +100 post-transplant, unless stopped earlier due to CMV reactivation. Treatment beyond 100 days may be considered in some patients at high risk for late CMV reactivation. There should be clear documentation of this decision in the patient notes.

**Monitoring:** CMV monitoring as described above and routine bloods. No additional specific requirements. Prophylaxis should be continued unless evidence of CMV reactivation. On reactivation, the drug should be stopped, and pre-emptive therapy initiated.
Letermovir prophylaxis should not be restarted following treatment failure unless there are exceptional circumstances. In some situations, this may be justified - note that 20% of cases of CMV reactivation through letermovir prophylaxis have clones of CMV that carry mutations conferring drug resistance.

**Cautions/Side-effects:** [Common - Nausea, diarrhoea, vomiting]. [Uncommon - Hypersensitivity, decreased appetite, dysgeusia, headache, vertigo, abdominal pain, ALT/AST derangements, muscle spasm, fatigue, peripheral oedema, creatinine derangements].

**Interactions:** Caution, numerous significant drug interactions - refer to the full summary of product characteristics (SmPC) and ensure a pharmacist has been consulted. In combination with ciclosporin, concomitant use of dabigatran, atorvastatin, simvastatin, rosuvastatin or pitavastatin is contraindicated.

Letermovir is not recommended with drugs that are strong and moderate inducers of transporters (e.g., P-gp) and/or enzymes (e.g., UGTs). This may result in subtherapeutic exposure, examples of problematic drugs include carbamazepine, phenytoin and efavirenz.

Use cautiously in combination with drugs that are CYP3A substrates (e.g., midazolam, amiodarone). Close monitoring and/or dose adjustment of the co-administered CYP3A substrates are recommended.

**Increased monitoring of ciclosporin, tacrolimus, sirolimus is recommended for the first 2 weeks after initiation of and when stopping letermovir as well as after changing route of administration. Therapeutic drug monitoring is recommended for voriconazole.**

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2. **VALGANCICLOVIR**

**Indication:** Valganciclovir is an oral pro-drug of ganciclovir. It is used first line for pre-emptive treatment. It should not be used to treat CMV infection if the patient is acutely unwell and in patients with severe gastrointestinal GvHD.

It is the drug of choice for patients at risk of relapse of CMV retinitis. Dose and duration should be defined in consultation with the infectious diseases team and a consultant ophthalmologist. Because it results in greater drug levels in the eye, the placement of a ganciclovir implant in a patient who has relapsed while receiving systemic treatment is generally recommended.

**Treatment dose:** Valganciclovir PO 900mg twice daily PO with food (unless renally impaired).

**Treatment duration:** Induction dosing - Continue until 2 consecutive negative PCR results >72 hours apart. Prescriptions should be written weekly, to avoid costly wastage. Maintenance dosing – total duration is patient dependent.

**Monitoring:** FBC and renal function twice a week during treatment.

**Dose adjustment in renal impairment:** Monitor serum creatinine / creatinine clearance (CrCl) carefully. Adjust dose as per Table 2 based on renal clearance calculated via Cockcroft and Gault (C&G) CrCl formulae, as below.

\[
\text{Male patient}^* = \frac{(140 – \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (0.011 \times \text{serum creatinine [micromol/L]})}
\]

*Female patients = 0.85 × male value

Alternatively, the **MDCalc C&G online calculator** is fit for use. Note that for overweight patients (actual weight >120% Devine IBW), it is standard practice to calculate clearance with an ideal body weight.
Table 2 – Valganciclovir dose modifications for renal function

<table>
<thead>
<tr>
<th>C&amp;G CrCl</th>
<th>Induction/Treatment dose</th>
<th>Maintenance/Prophylaxis dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 60 ml/min</td>
<td>900 mg (2 tablets) twice daily</td>
<td>900 mg (2 tablets) once daily</td>
</tr>
<tr>
<td>40 – 59 ml/min</td>
<td>450 mg (1 tablet) twice daily</td>
<td>450 mg (1 tablet) once daily</td>
</tr>
<tr>
<td>25 – 39 ml/min</td>
<td>450 mg (1 tablet) once daily</td>
<td>450 mg (1 tablet) once a day, on ALTERNATE days</td>
</tr>
<tr>
<td>10 – 24 ml/min</td>
<td>450 mg (1 tablet) once a day, on ALTERNATE days</td>
<td>450 mg (1 tablet) twice WEEKLY</td>
</tr>
<tr>
<td>&lt; 10 ml/min</td>
<td>Not recommended</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

**Dose adjustments for bone marrow suppression:** If neutrophils < 0.5 x 10⁹/L or platelets < 25 x 10⁹/L - consider dose modification or interruption of treatment. If there is isolated neutropenia, G-CSF support may be given when neutrophils < 0.5 x 10⁹/L.

**Cautions/ Side Effects:** Neutropenia and anaemia (very common), thrombocytopenia (common), renal dysfunction, fever, rash, abnormal liver function, anaphylaxis, decreased appetite, psychiatric disorders (depression, anxiety, confusion, abnormal thinking), nervous system disorders (headache, insomnia, taste disturbance, hypoesthesia, paraesthesia, peripheral neuropathy, convulsions, dizziness (excluding vertigo).Visual problems (macular oedema, retinal detachment, vitreous floaters, eye pain, vision abnormal, conjunctivitis), ear pain, deafness, dyspnoea, cough, phlebitis (high pH – irritant to veins), Gl upset (nausea, vomiting, abdominal pain, abdominal pain upper, constipation, flatulence, dysphagia, dyspepsia).

**Cautions/ Contraindications:** Pregnancy, hypersensitivity to aciclovir and valaciclovir. Mutagenicity, teratogenicity, carcinogenicity: valganciclovir should, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers. Valganciclovir causes temporary or permanent inhibition of spermatogenesis. Women of childbearing potential must be advised to use effective contraception during and for at least 30 days after treatment. Men must be advised to practise barrier contraception during treatment, and for at least 90 days thereafter, unless it is certain that the female partner is not at risk of pregnancy.

**Handling:** Valganciclovir is a potential teratogen and carcinogen, caution is advised when handling of broken tablets. If a broken tablet makes contact with skin or mucosa wash off immediately with water. The tablets must not be handled by women of childbearing potential.

### 3. GANCICLOVIR

**Indication:** Ganciclovir should be considered first-line treatment for CMV disease. It can also be used for pre-emptive treatment when the patient is unable to tolerate oral valganciclovir.

**Dosage and administration**

Induction dose: 5mg/kg* (adjusted according to renal function) in sodium chloride 0.9% or glucose 5% as an intravenous infusion over 1 hour BD (every 12 hours) via central venous access device (CVAD).
There were patients where actual body weight is more than 120% ideal body weight (IBW, Devine formula) use adjusted body weight (ABW40) as follows:

- ABW40 = IBW + 0.4(ABW - IBW) – or see MDCalc ABW40 calculator

Administer via a central venous access device to avoid venous irritation (the preparation has a high pH). If clinically urgent, it can be infused (short-term) peripherally into a large vein with adequate blood flow whilst awaiting line insertion.

**Switching from valganciclovir**: IV ganciclovir 5mg/kg/bd is equivalent to valganciclovir 900mg bd.

**Treatment duration**: Continue until 2 consecutive negative PCR results >72 hours apart. In practice treatment duration is usually 14-21 days. In some cases, the IV course may need to be further extended, with weekly monitoring, until the CMV virus load is undetectable.

Prescription can be written for 21-day course but dispensed to patient weekly.

**Supply via Baxter**: Baxter will aseptically reconstitute and dilute the product. Contact the ward pharmacist to order from Baxter.

**Out of hours supply**: Contact on-call pharmacist via switchboard. Ready made bags are available in the emergency drug cupboard (500mg ganciclovir in 110ml sodium chloride 0.9%).

**Monitoring**: FBC and renal function should be monitored twice each week during treatment and dose adjusted according to Table 3 below.

### Table 3 – Ganciclovir dose modifications for renal function

<table>
<thead>
<tr>
<th>Creatinine Clearance</th>
<th>Induction dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥70ml/min</td>
<td>5 mg/kg every 12 hours</td>
</tr>
<tr>
<td>50 - 69ml/min</td>
<td>2.5 mg/kg every 12 hours</td>
</tr>
<tr>
<td>25 - 49ml/min</td>
<td>2.5 mg/kg every 24 hours</td>
</tr>
<tr>
<td>10 - 24ml/min</td>
<td>1.25 mg/kg/ every 24 hours</td>
</tr>
<tr>
<td>&lt; 10ml/min</td>
<td>Haemodiafiltration (HDF) - 1.25mg/kg/three times per week, after HDF (on dialysis days only)</td>
</tr>
<tr>
<td></td>
<td>Continuous Ambulatory Peritoneal Dialysis (CAPD) - 1.25mg/kg three times a week.</td>
</tr>
<tr>
<td></td>
<td>Continuous renal replacement therapy (i.e. Haemofiltration in Critical Care - CVVH) = 1.25 mg/kg every 24 hours.</td>
</tr>
</tbody>
</table>

**Dose modification for bone marrow suppression**: Consider dose modification or interruption of treatment if neutrophils < 0.5 x 10^9/L or platelets < 25 x 10^9/L. If there is isolated neutropenia, then G-CSF support may be given when neutrophils < 0.5 x 10^9/L.

**Cautions/ side effects/ contraindications**: The most common adverse effects of ganciclovir are haematological and include neutropenia and thrombocytopenia. Other adverse effects include dyspnoea, headache, fever, rash, pruritus, asthenia, CNS and gastrointestinal disturbances, infection, increased serum-creatinine concentration, and abnormal liver function tests.

**Handling**: Handle as for cytotoxics. Personnel should be adequately protected during handling and administration: if the solution makes contact with skin or mucosa, wash off immediately with soap and water.
4. FOSCARNET SODIUM

**Indication:** Treatment of CMV disease, in patients who are intolerant of ganciclovir. It is also recommended as an alternative first-line agent if neutropenia is present or for ganciclovir treatment failure. It should be used at the discretion of the consultant looking after the patient (unlicensed indication).

**Dosage:** Dose according to renal function (see Table 4), dose should be adjusted throughout treatment in response to creatinine fluctuation. Round dose **down** to nearest dose band. Monitor renal function daily and adjust the dose accordingly.

Where severe toxicity, consider reducing to twice daily frequency if used for pre-emptive therapy, in with dosing recommendation by ECIL17 guideline.

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/kg/min)</th>
<th>Foscarnet dose and frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1.6</td>
<td>60mg/kg every 8 hours</td>
</tr>
<tr>
<td>1.6 – 1.4</td>
<td>55mg/kg every 8 hours</td>
</tr>
<tr>
<td>1.4 – 1.2</td>
<td>49mg/kg every 8 hours</td>
</tr>
<tr>
<td>1.2 – 1.0</td>
<td>42mg/kg every 8 hours</td>
</tr>
<tr>
<td>1.0 – 0.8</td>
<td>35mg/kg every 8 hours</td>
</tr>
<tr>
<td>0.8 – 0.6</td>
<td>28mg/kg every 8 hours</td>
</tr>
<tr>
<td>0.6 – 0.4</td>
<td>21mg/kg every 8 hours</td>
</tr>
<tr>
<td>&lt;0.4</td>
<td>Not recommended</td>
</tr>
</tbody>
</table>

**Administration:** Administer **pre-hydration** with 500mL to 1 litre of sodium chloride 0.9% with each dose to reduce the risk of foscarnet nephrotoxicity.

Foscarnet dose should be diluted (1:1 ratio) in sodium chloride 0.9% or glucose 5% bag. Administer via IV infusion **over at least one hour** ideally via central venous access device, or peripherally.

**Supply via Baxter:** Infusion bags are supplied via Baxter - contact the ward pharmacist to order. Foscarnet will be diluted to 12mg/ml using equal part (1:1 ratio) in sodium chloride sodium chloride 0.9% or glucose 5% bag.
Out of hours supply: In exceptional situations where urgent treatment is indicated, foscarnet 24mg/ml undiluted intravenous solution will be supplied (containing 6g in 250mL).

Undiluted foscarnet MUST be administered CENTRALLY via a central venous access device (CVAD).

Due to the risk of wrong dose being administered, the exact dose and volume must be checked by TWO nurses. The infusion should be run under the supervision nurse who must ensure the infusion is stopped once the exact prescribed dose and corresponding volume has been administered from the bottle (clearly and securely attach a label on the administration pump to indicate this and intervene immediately if the pump alarms).

Monitoring: Creatinine, U&Es (especially calcium, magnesium, potassium and phosphate) baseline and throughout treatment - correct any electrolyte deficiencies daily.

Cautions/ Side Effects: Nephrotoxicity and electrolyte disturbances including hypocalcaemia, hypomagnesaemia; maintain adequate hydration to maintain renal function & prevent genital irritation, avoid concurrent nephrotoxic drugs. Other potential adverse effects: Convulsions, thrombophlebitis if given undiluted via peripheral vein, fatigue, pyrexia, nausea (reduce infusion rate), vomiting, abdominal pain, headache, dizziness, pins and needles sensation (reduce infusion rate), rash, pruritus, changes in blood pressure and ECG, palpitation, aggression, agitation, anxiety, confusion, depression and flushing. Anaemia.

5. CIDOFOVIR - Micro approval required.

Indication: Treatment of CMV disease as an alternative to ganciclovir and foscarnet (unlicensed).

Dosage: In patients with creatinine clearance >55ml/min; cidofovir 5mg/kg ONCE A WEEK via intravenous infusion over 1 hour. Dose adjusted according to renal function and in case of proteinuria or bone marrow suppression- see Table 5. Each dose must be given concurrently with probenecid and hydration to reduce the risk of nephrotoxicity.

Treatment duration: Continue ONCE WEEKLY until 2 consecutive negative PCR results >72 hours apart.

Hydration: Prescribe 1 litre of sodium chloride 0.9% over 1 hour prior to cidofovir infusion. Prescribe a further litre of sodium chloride 0.9% over 1-3 hours, beginning simultaneously with, or immediately after, the cidofovir infusion.

Probenecid is given to reduce the risk of nephrotoxicity as follows. In order to reduce the potential for nausea, patients should be encouraged to eat food prior to each dose of probenecid. The use of an antiemetic may be necessary.

Table 5 – Probenecid weight and time-based dosing

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Probenecid dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose at 3 hrs pre-cidofovir infusion</td>
</tr>
<tr>
<td>Adult or &gt; 60kg</td>
<td>2g</td>
</tr>
</tbody>
</table>
Renal dose modification
If creatinine clearance < 55ml/min, the data sheet states that the drug should not be given. However, the dose reductions in Table 6 can be used.

Table 6 – Cidofovir renal dose modifications

<table>
<thead>
<tr>
<th>Creatinine clearance (ml/min)</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>41-55</td>
<td>3mg/kg*</td>
</tr>
<tr>
<td>30-40</td>
<td>2mg/kg*</td>
</tr>
<tr>
<td>20-29</td>
<td>1mg/kg</td>
</tr>
<tr>
<td>&lt;19</td>
<td>0.5mg/kg</td>
</tr>
</tbody>
</table>

*CConsider renal sparing regimen (split doses e.g. 3 x week or 2 x week)

Renal sparing regimen – There is limited evidence supporting this dosing schedule. Splitting doses reduces peak cidofovir concentrations and may limit toxicity. Disadvantages include the logistical challenge with delivery of doses (limited expiry of 24hrs) and increased cost of treatment along with additional vial use which can be a concern with stock shortages.

Example regimens: 3mg/kg = 1mg THREE times a week, 2mg/kg= 1mg TWICE a week.

Cidofovir dose according to bone marrow suppression
- Neutrophils < 1 x 10^9/L - consider reducing dose to 3mg/kg (discuss with consultant).
- Neutrophils < 0.6 x 10^9/L - contraindicated

Administration
To reduce the risk of nephrotoxicity, the following procedure must be followed:
1. Ensure patient has received the first dose of probenecid 3 hours prior to cidofovir.
2. Give 1 litre of sodium chloride 0.9% over 1 hour prior to cidofovir infusion.
3. Give cidofovir dose in 100ml sodium chloride 0.9% via intravenous infusion over 1 hour (aseptically prepared via Baxter)
4. Give a further 1 litre of sodium chloride 0.9%over 1-3 hours, beginning simultaneously with, or immediately after, the cidofovir infusion.
5. Test urine for protein:
   - if negative, give normal dose.
   - if positive – proteinurea ≥ (1g/litre), reduce dose to 3mg/kg.
   - proteinurea ≥ 3+ or more (3g/litre), do not administer cidofovir
6. Remind patient to take the rest of the probenecid course.
7. Remind patient to drink plenty of fluids over the next 48 hours.

Supply via Baxter: Cidofovir must be diluted in 100ml sodium chloride 0.9%, aseptically prepared and supplied via Baxter. Cidofovir is unlicensed in the UK and will normally need to be imported as a named-patient product.

Monitoring: Creatinine clearance, FBC, urine protein levels.
**Cidofovir side effects:** Nephrotoxicity, neutropenia, headaches, metabolic acidosis, nausea, vomiting, diarrhoea, fever, rash, alopecia. Ocular disorders: regular ophthalmological examinations recommended; iritis & uveitis have been reported which may respond to topical corticosteroids with or without a cycloplegic drug.

**Probencid side-effects:** Nausea, vomiting (may require antiemetics), rashes & fever (may require prophylactic antihistamines +/- paracetamol), headaches.

**Cautions/ Contraindications:** Cidofovir is nephrotoxic and special precautions must be taken to reduce the risk – see procedure for administration. Caution in diabetes mellitus (increased risk of ocular hypotony). Concomitant treatment of cidofovir with products containing tenofovir disoproxil fumarate may give rise to increased risk of Fanconi Syndrome; it must not be given concurrently.

Hypersensitivity to probencid or other sulphactually-containing medication – in this situation, only consider giving probencid if the potential benefits outweigh the risks. Caution in G6PD deficiency.

**Handling:** cidofovir is toxic and personnel should be adequately protected during handling and administration, if solution makes contact with skin or mucosa, wash off immediately with soap and water.

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6. **MARIBAVIR - Bluteq required. Micro approval required.**

**Indication:** Treatment of CMV disease, in patients who are intolerant or refractory* to at least ONE prior therapy [NICE TA860]. Note in practice this would be considered last line treatment.

*Refractory defined as documented failure to achieve >1 log10 (common logarithm to base 10) decrease in CMV DNA level in whole blood or plasma after a 14 day or longer treatment period with IV cidofovir, IV foscarnet or IV ganciclovir/oral valganciclovir.

**Dosage:** Maribavir 400mg (2 x 200mg tablets) PO twice a day with, or without food.

**Treatment duration:** Continue until 2 consecutive negative PCR results >72 hours apart. Treatment duration should be individualised based on clinical situation.

**Administration via enteral tube:** [Licensed] Crush and disperse in 10mL water, flush the enteral feeding tube before and after administration to avoid blockage. There is no intravenous formulation.

**Monitoring:** CMV monitoring as clinically indicated. Routine bloods, nil other specific to drug.

**Precautions** - Maribavir does not readily penetrate the CNS and is not recommended in CMV CNS infections.

Virologic failure can occur during and after treatment. Virologic relapse during the post-treatment period usually occurred within 4 - 8 weeks after treatment discontinuation. Some maribavir pUL97 resistance-associated substitutions confer cross-resistance to ganciclovir and valganciclovir. Treatment should be discontinued if maribavir resistance mutations are detected.

**Cautions/Side-effects:** [Very Common – Taste disturbance, diarrhoea, nausea, vomiting]. [Common – Headache, upper abdominal pain, decreased appetite, weight decreased, immunosuppressant drug level increased].

**Dose modifications:** No renal or hepatic dose adjustments are required. There is no data to support dosing in dialysed patients. Maribavir is highly-protein bound so it is theorised that no dose adjustments would be required. Data is lacking in patients meeting Child-Pugh Class C criteria and therefore caution and close treatment monitoring is recommended.

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**Department of Clinical Haematology**
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Authorised by: Dr Andy Peniket

This is a controlled document and therefore must not be changed
Dose modifications are required in case of some drug interactions – see below.

**Interactions:** Co-administration of maribavir with valganciclovir and ganciclovir is contraindicated. Maribavir may antagonise the antiviral effect of ganciclovir and valganciclovir.

There are several clinically relevant drug interactions, consult the SmPC and discuss with a pharmacist. Co-administration with strong CYP3A4 enzyme inducers (e.g., rifampicin, rifabutin, St. John’s wort) is not recommended due to potential decreased efficacy of maribavir. Where co-administration is unavoidable (e.g., with carbamazepine, efavirenz, phenobarbital and phenytoin), the dose should be increased to 1200 mg (6 x 200mg tablets) PO twice daily.

Immunosuppressants- Maribavir potentially increases concentrations of CYP3A4/P-gp substrates with narrow therapeutic ranges. **Increased monitoring of ciclosporin, tacrolimus, sirolimus is recommended for the first 2 weeks after initiation of and when stopping letermovir as well as after changing route of administration.**

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11. Summary of Product Characteristics Foscavir (Foscarnet), Clinigen Healthcare Limited, Last updated on eMC: 21 Feb 2019
Audit
These processes are subject to the OxBMT/IEC audit programme.

Authors
Tim Littlewood, BMT Programme Director, Version 1, 2006
Specialist Pharmacist, Claire Humphries, Version 1, 2006
Andy Peniket, Consultant Haematologist – Version 2, 2010,
Denise Wareham, BMT Co-ordinator – Version 2, 2010
Katie Jeffery, Consultant Virologist – Version 2, 2010

Circulation
NSSG Haematology Website

Review

<table>
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<th>Name</th>
<th>Revision</th>
<th>Date</th>
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<tr>
<td>Cheuk-Kie Cheung, Specialist Cancer Pharmacist; Paolo Polzella, Specialist Haematology Registrar; Denise Wareham, BMT Nurse Coordinator</td>
<td>Minor drug amendments, references. Minor changes. Valganciclovir/ganciclovir amendments.</td>
<td>Feb 2017</td>
<td>3.0</td>
<td>Feb 2019</td>
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<td>James Davies, BMT consultant; Nadjoua Maouche, Lead Haematology Pharmacist</td>
<td>Inclusion of Letemovir for CMV prophylaxis. PCR logs monitoring. Major drug amendments; administration and supply of foscarnet, ganciclovir, cidofovir. References</td>
<td>Jul 2019</td>
<td>4.0</td>
<td>July 2021</td>
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