Management of cytomegalovirus (CMV) reactivation and infection in allogeneic blood and marrow transplant (BMT) recipients

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Contents

Introduction

Cytomegalovirus (CMV) infection or reactivation is a frequent cause of morbidity and mortality in recipients of allogeneic bone marrow transplant (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 graft versus host disease (GvHD).

CMV reactivation is more common in CMV seropositive recipients. Among the seronegative recipients CMV infection is more frequent where the bone marrow, or stem cell, donor is seropositive.

CMV seropositive patients have a poorer outcome than seronegative patients. The use of a CMV seronegative donor for a seronegative patient reduces the risk of non-relapse mortality. However, several studies have shown that the use of CMV seronegative donors (over seropositive donors) for seropositive patients has negative effects including delayed CMV-specific immune reconstitution, repeated CMV reactivations, higher peak virus load, late CMV recurrence, clinical CMV disease and a decrease in survival rates.

CMV infection is generally seen in the immediate to late post-engraftment period. In the past, prevention of CMV disease was based on initiation of pre-emptive therapy which required regular weekly CMV monitoring by PCR for the first 100 days post-transplant to identify rising trends in viral load and patients at risk of manifesting full disease.

Since late 2019, patients at high risk of CMV reactivation (from D0 onwards) receive prophylactic therapy with letermovir. This means that the majority of reactivation cases will occur in the period following cessation of letermovir prophylaxis.

Prevention of CMV disease

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

Prophylaxis should be prescribed in accordance with recipient-donor CMV status as shown in Table 1.

(Table 1 can be found on page 3)

Table 1 - Overview of CMV prophylaxis recommendations

Recipient CMV status	Donor CMV status	CMV Prophylaxis
Seropositive (+)	Seropositive (+)	Letermovir* 480mg OD PO/IV from day 0 to day +100. Reduce to 240mg OD in patients taking concurrent ciclosporin .
Seropositive (+)	Seronegative (-)	Letermovir* 480mg OD PO/IV from day 0 to day +100. Reduce to 240mg OD in patients taking concurrent ciclosporin.
Seronegative (-)	Seropositive (+)	Aciclovir 500mg/m^2 IV TDS or 800mg PO QDS from start of conditioning till day +30, then 800mg PO QDS for 3 months**
Seronegative (-)	Seronegative (-)	Aciclovir 250mg/m^2 IV TDS or 200mg PO TDS from start of conditioning till day +30

* Patients taking letermovir for CMV prophylaxis 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 during the pre-transplant work up for evidence of CMV viraemia using 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 $>10^3$ IU/ml (3 $\log_{10}$). The chief “at risk” period for CMV reactivation post-transplantation is in the weeks following cessation of antiviral prophylaxis. 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

Requesting CMV PCR testing

CMV PCR is performed in the Microbiology Laboratory at the John Radcliffe Hospital. Testing is usually performed daily Monday to Friday.

Please request on EPR and send a minimum of 4mL EDTA blood (lavender topped tube) with a blue microbiology request form.

Where and when you can find CMV PCR results

PCR results will usually be available on EPR within 24 - 48 hours Monday to Friday. Samples can be run urgently during office hours on request.

CMV PCR results are reported as a quantitative virus load, either 'NOT detected' where the limit of quantitation is <1.48 Log(10) IU/mL, DETECTED at <1.48 log(10) IU/ml, equivalent to <30 IU/ml or reported quantitatively as log(10) IU/ml (e.g. 3.0 log(10) IU/ml equates to a viral load of 10^3= 1000 IU/ml).

Treatment of CMV infection and disease

Initiating pre-emptive treatment for CMV viraemia

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

Consider treatment when levels are $>10^3$ IU/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 ($<10^4$ IU/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

If there is clinical evidence of CMV disease and a detectable CMV virus load by PCR, patients must be treated with antiviral agents, the choice of which is guided by the clinical scenario and any prior treatments given.

Treatment summaries

Letermovir - Blueteq® form 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 above. 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 reduced to 240 mg (1 x 240mg tablet) PO 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 equivalent. 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.

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.

Cautions/Contra-indications: Hypersensitivity letermovir or to any of the excipients. Concomitant administration with pimozide, ergot alkaloids, St John's Wort (hypericum perforatum).

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**.

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.

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.

C&G renal clearance calculation:

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

*__Female patient__ = 0.85 × male value

Alternatively, the MDCalc C&G online calculator is fit for use.

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

C&G CrCl	Treatment dose
≥ 50 ml/min	900 mg (2 tablets) twice daily
25 – 49 ml/min	450 mg (1 tablet) twice daily
10 – 24 ml/min	450 mg (1 tablet) once a day
< 10 ml/min	Consider 450 mg (1 tablet) 3 times a WEEK if no alternative

The above recommended doses deviate from the product licence. However, dosing has been widely accepted in clinical practice and complements practice in renal transplant.

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

Side Effects: Very common - Neutropenia and anaemia. Common - thrombocytopenia, 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), GI upset (nausea, vomiting, abdominal pain, abdominal pain upper, constipation, flatulence, dysphagia, dyspepsia).

Cautions/ Contraindications: Pregnancy**,** hypersensitivity to ganciclovir or valganciclovir or to any of the excipients.

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.

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: 5mg/kg* 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).

*In overweight 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

Administration: Administer via a central venous access device (CVAD) due to venous irritation. 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 (Oxford): Baxter will aseptically reconstitute and dilute the product. Contact the ward pharmacist to order from Baxter.

Out of hours supply (Oxford): 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.

Renal impairment:

Table 3 – Ganciclovir dose modifications for renal function

GFR (mL/min)	Recommended renal dose
≥ 50 ml/min	5 mg/kg every 12 hours
25 – 49 ml/min	2.5 mg/kg every 12 hours
10 – 24 ml/min	2.5 mg/kg every 24 hours

< 10 ml/min	Haemodiafiltration (HDF) -1.25mg/kg/three times per week, after HDF (on dialysis days only) Continuous Ambulatory Peritoneal Dialysis (CAPD) - 1.25mg/kg three times a week. Continuous renal replacement therapy (i.e. Haemofiltration in Critical Care - CVVH) = 1.25 mg/kg every 24 hours.

The above recommended doses deviate from the product licence. However, dosing has been widely accepted in clinical practice and complements practice in renal transplant.

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 isolated neutropenia, GCSF support may be considered 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.

Foscarnet Sodium (off-label)

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.

CMV resistance testing is now available with a short turnaround time – if ganciclovir resistance suspected please discuss with microbiology SpR/Consultant.

Dosage: 60mg/kg IV every 8 hours. Round dose down to nearest measurable dose – each mL is 24mg. Monitor renal function daily and adjust the dose accordingly.

In obesity (BMI >30kg/m^2) there is limited evidence to guide dosing, however it is sensible to use the weight calculated with the ABW40 formulae:

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

Renal impairment:

Table 4 – Foscarnet dose modifications for renal function

Creatinine clearance (ml/kg/min)	Foscarnet dose and frequency
>1.6	60mg/kg every 8 hours
1.6 – 1.4	55mg/kg every 8 hours
1.4 – 1.2	49mg/kg every 8 hours
1.2 – 1.0	42mg/kg every 8 hours
1.0 – 0.8	35mg/kg every 8 hours

0.8 – 0.6	28mg/kg every 8 hours
0.6 – 0.4	21mg/kg every 8 hours
<0.4	Not recommended
CrCl per kilo (ml/min/kg) = (140-age) x 1.23 (males) **or** 1.04 (females) / Serum creatinine (micromol)	

Administration: Pre-hydration with 500mL to 1 litre of sodium chloride 0.9% is recommended with each dose to reduce the risk of foscarnet nephrotoxicity. Total daily fluid volume should be considered to avoid overload.

Administer as an IV infusion via central line over one hour. Symptomatic hypocalcaemia during infusion can be ameliorated by increasing the infusion duration to 2 hours.

Peripheral infusion should be avoided where possible – the undiluted product must never be given via this route.

Supply via Baxter (Oxford): Baxter will aseptically reconstitute and dilute the product in sodium chloride 0.9%. Contact the ward pharmacist to order from Baxter.

Out of hours supply (Oxford): In exceptional situations where urgent treatment is indicated, foscarnet 24mg/ml undiluted intravenous solution can be supplied (containing 6g in 250mL).

In emergency treatment out of hours only - undiluted foscarnet MUST be administered CENTRALLY via a central venous access device (CVAD).

The exact dose and volume for administration must be carefully checked by TWO nurses. The infusion must be run via an infusion pump (clearly and securely attach a label on the administration pump to indicate the indicated dose and corresponding administration volume. Intervene immediately if the pump alarms). The supervising nurse must check the correct infusion has run through to time and should avoid handing over to prevent communication errors. Immediately disconnect the bottle and discard any remaining solution as soon as the infusion has completed.

Monitoring: Creatinine, U&Es, calcium, magnesium and phosphate at baseline and throughout treatment. Correct any electrolyte deficiencies daily.

Cautions / Contra-indications: Hypersensitivity to foscarnet or to any of the excipients. Caution in patients with existing cardiac conditions or seizure disorders.

Side Effects: Nephrotoxicity and profound hypocalcaemia, hypomagnesaemia, hypophosphataemia and/or hypokalaemia are very common and require close monitoring with prompt replacement**.** Symptomatic hypocalcaemia (e.g. nausea, paraesthesia) during infusion can be ameliorated by increasing the infusion duration to 2 hours. Genital irritation can be avoided through adequate hydration.

Other potential adverse effects - Hypokalaemia, thrombophlebitis if given undiluted via peripheral vein, fatigue, pyrexia, nausea, vomiting, abdominal pain, headache, dizziness, paraesthesia, rash, pruritus, changes in blood pressure and ECG, palpitation, aggression, agitation, anxiety, confusion, depression and flushing, convulsions. Anaemia. Uncommon **–**

Acidosis, pancytopenia, urticaria, angioedema, nephrotic syndrome, glomerulonephritis, raised creatine kinase, raised amylase.

Cidofovir (off-label) - Micro approval required.

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

Dosage: 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.

Prescribing: Oxford clinicians are advised to prescribe doses using the "Cidofovir (Adult) Powerplan" for accurate prescribing. Other local centres are recommended to create order sets to facilitate prescribing with supportive care measures where possible. Hydration and probenecid should be prescribed as below:

Hydration: Administer 500 – 1000mL sodium chloride 0.9% prior to cidofovir infusion. Prescribe a further 1000mL over 1-3 hours to begin simultaneously with, or immediately following the cidofovir infusion. The total quantity of fluid given is discretional and should be based on total daily fluid requirements to avoid overload; however, this should not be completely omitted.

Probenecid (off-label) must be given to reduce the risk of nephrotoxicity. To reduce nausea, patients should be encouraged to eat food prior to each dose. The use of an antiemetic may be necessary.

Table 5 – Probenecid weight and time-based dosing

Weight (kg)	**3 hours prior to infusion**	**2 hours post completion**	**8 hours post completion**
More than 60kg	2g	1g	1g
Less than 60kg	1.5g	750mg	750mg

Renal impairment: Administration in renal impairment is not covered by the product licence. The recommendations in Table 6 are based on clinical practice and have been amalgamated from several examples of international and national clinical practice.

Table 6 – Cidofovir renal dose modifications

Creatinine clearance (ml/min)	**Dose**
41-55	3mg/kg*
30-40	2mg/kg*
20-29	1mg/kg
<19	0.5mg/kg

*Consider 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, increased cost of treatment along with additional vial wastage which is a concern with stock shortages.

Cidofovir dose according to bone marrow suppression

- Neutrophils < 1 x 10^9/L - consider reducing dose to 3mg/kg (discuss with consultant).
- Neutrophils < 0.5 x 10^9/L – contra-indicated.

Monitoring: FBC, creatinine, urine protein as below. Regular ophthalmic examination.

Proteinuria: Proteinuria appears to be an early and sensitive indicator of cidofovir-induced nephrotoxicity. Patients must have their serum creatinine and urine protein levels determined on specimens obtained within 24 hours prior to the administration of each dose of cidofovir.

- In patients exhibiting ≥ 2+ proteinuria, further IV hydration should be given, and the test repeated. If following hydration, a ≥ 2+ proteinuria is still observed, cidofovir should be reduced to at least 3mg/kg (unlicensed) and a decision to go ahead or delay administration carefully considered.
- In patients with ≥ 3+ proteinuria the dose should not be administered.
- Continued administration of cidofovir to patients with persistent ≥ 2+ proteinuria following hydration and/or dose reduction may result in further evidence of proximal tubular injury, including glycosuria, decreases in serum phosphate, uric acid and bicarbonate, and elevations in serum creatinine.

Supply via Baxter (Oxford): Baxter will aseptically reconstitute and dilute the product in sodium chloride 0.9%. Contact the ward pharmacist to order from Baxter.

There is a limited 24-hour expiry for each dose from the time of manufacture.

Out of hours supply (Oxford): Limited availability (Saturday) - orders can be placed if received by the duty cancer pharmacist prior to 11am if stock available. There is no dose availability on Sundays and after 4pm Monday to Friday.

Administration:

1) Ensure patient has received the first dose of probenecid 3 hours prior to infusion.
2) Give 500 – 1000mL sodium chloride 0.9% over 1 hour prior to infusion.
3) Test urine for protein:
    a. Negative - proceed with dosing.
    b. Positive - discuss with medical team (see advice above)
4) Administer cidofovir via intravenous infusion over 1 hour.
5) Give a further 1 litre of sodium chloride 0.9%over 1-3 hours, beginning simultaneously with, or immediately after, the cidofovir infusion.
6) Administer 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 side effects: Nephrotoxicity, neutropenia, headaches, metabolic acidosis, nausea, vomiting, diarrhoea, fever, rash, alopecia.

Ocular disorders - uveitis/iritis and ocular hypotony. Cidofovir should be discontinued if uveitis/iritis does not respond to treatment with a topical corticosteroid or the condition worsens, or if iritis/uveitis reoccurs after successful treatment.

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

Cautions/ Contraindications: Cidofovir is nephrotoxic and special precautions must be taken to reduce the risk. 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 probenecid or other sulpha-containing medication – in this situation, only consider giving probenecid if the potential benefits outweigh the risks. Caution in G6PD deficiency.

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

Maribavir- Blueteq® form 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.

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 CYP34A/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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Audit

These processes are subject to the OxBMT/IEC audit programme.

Authors

Tim Littlewood, BMT Programme Director. Claire Humphries, Specialist Pharmacist, Version 1, 2006

Andy Peniket, Consultant Haematologist. Denise Wareham, BMT Co-ordinator. Katie Jeffery, Consultant Virologist – Version 2, 2010

Circulation

NSSG Haematology Website

Review

Name	Revision	Date	Ver	Review
Cheuk-Kie Cheung, Specialist Cancer Pharmacist Paolo Polzella, Specialist Haem Registrar. Denise Wareham, BMT Nurse Coordinator	Minor drug amendments, references. Minor changes. Valganciclovir/ganciclovir amendments.	Feb 2017	3.0	Feb 2019
James Davies, BMT consultant; Nadjoua Maouche, Lead Haematology Pharmacist	Inclusion of Letermovir for CMV prophylaxis. PCR logs monitoring. Major drug amendments; administration and supply of foscarnet, ganciclovir, cidofovir. References	Jul 2019	4.0	Jul 2021
Katrina Fordwor, Specialist Haematology Registrar; Donna Constantine, Advanced Cancer Pharmacist	Addition of letermovir IV availability. Clarification of IVIg commissioning status and upcoming online portal. Clarify ABW40 for ganciclovir and dialysis/filtration recc. Addition of Maribavir. Some trimming of content. Adjustments to cidofovir renal dosing.	Jun 2023	5.0	Jun 2025
Katie Jeffries, Consultant Virologist; Rob Danby, Consultant Haematologist; Donna Constantine, Advanced Cancer Pharmacist	Valganciclovir / ganciclovir renal dose rec. simplified and aligned with Oxford renal unit practice. Removal of IVIg. Adjustments to CMV monitoring and advice re: major reactivation risk periods Adjustments to cidofovir monograph. New foscarnet renal dosing.	Oct 2024	6.0	Oct 2026