Maribavir in Solid Organ Transplants

April 2025

Introduction

Maribavir is an orally bioavailable antiviral drug approved by Health Canada to treat refractory/resistant forms of post-transplant cytomegalovirus (CMV) infection[1].

Mechanism of Action

Maribavir competitively inhibits the CMV UL97 protein kinase, which inhibits the phosphorylation of proteins[2] needed for DNA replication, encapsidation, and nuclear egress of viral capsids[3].

Therapeutic use

Maribavir is approved for the treatment of adults with post-transplant CMV infection/disease who are refractory (with or without genotypic resistance) to one or more prior antiviral therapies including cidofovir, foscarnet, ganciclovir or valganciclovir[3, 4]. It is available on the BC Transplant formulary on a restricted basis - please see authorization form below for criteria and approval process. Maribavir should be discontinued if there is no change or an increase in CMV viral load after at least 2 weeks of maribavir treatment, or if there is confirmed CMV genetic mutation associated with resistance to maribavir[5].

Maribavir has not been studied for central nervous system (CNS) infections with CMV and is expected to have poor blood-brain barrier penetration based on the results from the whole-body autoradiography study in rats. Therefore, it is not expected to be effective in treating CNS infections with CMV. If this type of infection is suspected, coverage with another CMV anti-viral agent is recommended[6].

Due to maribavir's lack of activity against herpes simplex virus (HSV) or varicella-zoster virus (VZV) additional antiviral therapy may be necessary to prevent these infections[7].

Contraindications

Maribavir is contraindicated for co-administration with ganciclovir or valganciclovir[3], since these two medications need the UL97 kinase to be active.

Warnings/precautions

Virologic failure with maribavir can occur during and after treatment due to resistance in the UL97 enzyme. Recurrence may happen within 4 to 8 weeks after discontinuing treatment. Cross-resistance with ganciclovir and valganciclovir has been observed in some cases, but emerging CMV resistance to maribavir is more common[8]. Regular monitoring of CMV levels is recommended to ensure the patient responds to treatment[9].

Dose and Administration

400 mg (two 200 mg tablets) orally twice daily with or without food[3]. If patients miss a dose and the next dose is due within the next 3 hours, they should skip the missed dose and continue with the regular schedule[3]. Patients are not to double their next dose or take more than the prescribed dose[3].

Pharmacokinetics

Maribavir is rapidly absorbed following oral administration with peak plasma concentrations (Cmax) occurring 1 to 3 hours post-dose. Plasma exposure (Cmax and AUC) increases dose-proportionally between 50 mg and 1600 mg, reaching steady state within 2 days when taken twice daily. Its pharmacokinetics are time independent. A moderate-fat meal decreases the AUC by 13.6% and Cmax by

27.8%. The approved 400 mg twice-daily dosing achieves a steady-state AUC of 128 h*µg/mL and a trough concentration of 4.90 µg/mL[1, 3, 9].

Maribavir is 40% bioavailable[3], 98% bound to plasma proteins, and has a volume of distribution of 27.3 L. It is primarily metabolized by CYP3A4, with some involvement of CYP1A2, and its inactive metabolite (VP44669) is excreted in urine and feces. Following oral administration, 61% is excreted in urine (<2% unchanged) and 14% in feces (5.7% unchanged). In transplant patients, it has a clearance of 2.85 L/h, and an elimination half-life of 4.32 hours[1, 3, 9].

Special Populations

Pregnancy: There is insufficient human data to determine the risk of maribavir on pregnancy outcomes. In animal studies, decreased embryo-fetal survival was observed in rats at maribavir exposures lower than those seen in humans at the recommended dose, while no such effects were noted in rabbits. Maribavir is not recommended during pregnancy and in women of childbearing potential not using contraception[3, 4, 6, 9].

Lactation: It is unknown if maribavir or its metabolites are present in human or animal milk, or if they affect milk production or the breastfed infant. A risk to the breastfeeding child cannot be excluded; Breastfeeding should be discontinued during treatment[3].

Pediatric use (< 18 years): Health Canada has not authorized an indication for pediatric use due to lack of data[3].

Geriatric Use: No dosage adjustment is needed for patients over 65. Clinical studies showed similar safety, effectiveness, and pharmacokinetics in elderly (≥65 years) and younger patients[3, 4, 9].

Impaired Renal Function: No dose adjustment is required for patients with mild to severe renal impairment. However, maribavir has not been studied in patients with end-stage renal disease (ESRD) or those on dialysis[3, 4, 9].

Impaired Hepatic Function: No dose adjustment is needed for mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment, but maribavir has not been studied in patients with severe hepatic impairment (Child-Pugh Class C)[3, 4, 9].

Adverse Drug Reactions

Side Effects (>10%)[(3, 10)]

Area of Effect	**Adverse Effects**
Nervous system	Fatigue & **taste disturbance**
Gastrointestinal	Nausea, vomiting, diarrhea, abdominal pain
Hematologic & oncologic	Decreased hemoglobin, platelets, neutrophils
Infection	Infection including CMV
Renal	Increased serum creatinine

Drug Interactions

Maribavir is metabolized by CYP-3A4 (70-85%) and CYP-1A2 (15-30%). It is also a substrate of P-glycoprotein (P-gp) and uridine diphosphate glucuronosyltransferases (UGTs). Maribavir is a weak inhibitor of CYP3A4, and an inhibitor of P-gp and breast cancer resistance protein (BCRP).

The table below outlines major drug interactions[3, 9, 12] only and is not all-inclusive. For a complete list of drug interactions and management, refer to tertiary references or consult the transplant clinic.

Drug	Possible mechanism, onset, and severity	Adverse effects	Management
Pharmacodynamic interactions with maribavir			
Immunosuppressants:			
tacrolimus (tacrolimus stable daily dose between 1.5 and 16 mg, maribavir 400 mg twice daily)	CYP3A/P-gp inhibition: ↑ tacrolimus C_{max} 38% and AUC 51%[12]	↑ toxicity including renal impairment and neurotoxicity[12]	Frequently monitor immunosuppressant levels throughout treatment with maribavir, especially following initiation and after discontinuation up to 48 hours of maribavir and adjust dose, as needed.
cyclosporine, everolimus, sirolimus	CYP3A/P-gp inhibition: interactions not studied	Expected: ↑ cyclosporine, everolimus, sirolimus	
Antivirals:			
ganciclovir, valganciclovir	CMV pUL97 kinase inhibition: interactions not studied	Expected: ↓ ganciclovir ↓ valganciclovir	Co-administration of maribavir with ganciclovir or valganciclovir is contraindicated.
HMG-CoA reductase inhibitors:			
rosuvastatin	BCRP inhibition: interaction not studied	Expected: ↑ rosuvastatin	The patient should be closely monitored for rosuvastatin-related events, especially the occurrence of myopathy and rhabdomyolysis. A rosuvastatin dose reduction may be necessary.
Antiarrhythmics:			
digoxin (0.5 mg single dose, 400 mg twice daily maribavir)	P-gp inhibition: ↑digoxin C_{max} 26% and AUC 22%[14]	↑ digoxin	Monitor serum digoxin concentrations. The dose of digoxin may need to be reduced when co-administered with maribavir
Drugs that DECREASE maribavir levels			
Anticonvulsants:			
carbamazepine	CYP3A induction: ↓ maribavir C_{max}23% and AUC 29%[12]	↓ maribavir levels: reduced virologic response	Adjust maribavir dose to 800 mg BID.

phenobarbital	CYP3A induction: ↓ maribavir C_{max}27% and AUC 39%[12]		Adjust maribavir dose to 1200 mg BID and caution in phenobarbital doses higher than 100 mg due to potential decreased efficacy of maribavir.
phenytoin	CYP3A induction: ↓ maribavir C_{max}31% and AUC 42%[12]		Adjust maribavir dose to 1200 mg BID.
Antimycobacterials:			
rifampin	CYP3A and CYP1A2 induction: ↓ maribavir C_{max} and AUC 61%[12]	↓ maribavir levels: reduced virologic response	Co-administration is not recommended due to potential decreased efficacy of maribavir.
rifabutin	CYP3A induction: interaction not studied	Expected: ↓ maribavir	
Herbal products:			
St. John's wort (hypericum perforatum)	CYP3A induction: interaction not studied	Expected: ↓ maribavir	Co-administration is not recommended due to potential decreased efficacy of maribavir.
Drugs that INCREASE maribavir levels			
Antifungals:			
ketoconazole (400 mg single dose, maribavir 400 mg single dose)	CYP3A/P-gp inhibition: ↑ maribavir C_{max} 17% and AUC 54%	↑ maribavir	No dose adjustment is required.
Calcium-channel blockers:			
diltiazem	CYP3A/P-gp inhibition: ↑maribavir C_{max} 6% and AUC 9%	↑ maribavir	No dose adjustment is required.
Macrolide antibiotics:			
erythromycin	CYP34A inhibition: ↑maribavir C_{max}26% and AUC 44%	↑ maribavir	No dose adjustment is required.
Protease inhibitors:			
Ritonavir	CYP3A/P-gp inhibition: ↑ maribavir C_{max} 37% and AUC 63%	↑ maribavir	No dose adjustment is required.

No clinically significant interactions were observed in clinical drug-drug interaction studies of maribavir and voriconazole, antacids, caffeine, warfarin, dextromethorphan, or midazolam[9, 12, 13].

References

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Maribavir Authorization Request Form *April 2025*

1. Transplant ID must be consulted and usage approved. Provider/clinic to then complete form and prescription, and fax to BC Transplant Pharmacy Manager Fax: 604-877-2111 (please call 604-833-6297 for urgent cases)

2. BC Transplant Pharmacy Manager to indicate authorization and fax form back to provider/clinic

3. Provider/clinic to fax form to relevant BC transplant pharmacy

BCT ID:

Name:

PHN:

A. Organ group: ☐ Heart ☐ Kidney ☐ Liver ☐ Lung ☐ Pancreas/Islet Requesting clinic: _____

B. ☐ Transplant Infectious Disease has been consulted and usage approved: Yes – Dr. _____

C. Indication(s) for maribavir treatment – Adult patient with CMV infection:

☐ 1. Refractory with suspected resistance to valganciclovir, ganciclovir, foscarnet, or cidofovir – must meet all criteria below:
- ☐ CMV viral load has plateaued or increased after at least 21 days of treatment, AND
- ☐ CMV viral load above 1000 IU/mL requiring treatment, AND
- ☐ Resistance testing ordered

OR

☐ 2. Genotypic resistance mutation to valganciclovir/ganciclovir – specify: _____, AND
- ☐ CMV viral load above 1000 IU/mL requiring treatment

OR

☐ Renewal due to persistent viremia if CMV viral load above 200 IU/mL. Only 1 renewal per treatment course.
Date of treatment initiation: _____ CMV viral load level & date: _____

OR

☐ Other: _____

NOTE: Discontinue maribavir if no change or an increase in CMV viral load after at least 2 weeks of maribavir treatment, and/or confirmed CMV genetic mutation associated with resistance to maribavir

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Prescription: Maribavir (LIVTENCITY®)
- **Ensure BCT has authorized prior to dispensing**

☐ Treatment initiation: maribavir 400 mg PO twice daily for 8 weeks

☐ Renewal: maribavir 400 mg PO twice daily for 4 weeks
(only 1 renewal per treatment course)

Pharmacy (fax):

☐ SPH (604-806-8675)

☐ VGH (604-875-4475)

Prescriber signature Print Name College ID Date

Please fax completed form to BC Transplant office for authorization: Fax: 604-877-2111 Attn: Pharmacy Manager
BCT Authorization: ☐ Yes ☐ No Date _____ Notes: _____ Signature: _____