Summary of risk management plan for Letermovir (PREVYMIS) Oral Tablet (240 mg and 480 mg)s and Concentrate for Solution for Infusion (20mg/mL, 240 mg and 20mg/mL, 480 mg)

This is a summary of the risk management plan (RMP) for PREVYMIS™ oral tablets and concentrate for solution for infusion. The RMP details important risks of PREVYMIS™ how these risks can be minimised, and how more information will be obtained about the risks and uncertainties (missing information) regarding PREVYMIS.

The Summary of Product Characteristics (SmPC) for PREVYMIS and its package leaflet give essential information to healthcare professionals and patients on how PREVYMIS™ should be used.

Important new concerns or changes to the current ones will be included in updates of the RMP for PREVYMIS™.

I. The Medicine and What it is Used For

PREVYMIS™ is authorised for prophylaxis of cytomegalovirus (CMV) reactivation and disease in adult CMV-seropositive recipients [R+] of an allogeneic hematopoietic stem cell transplant (HSCT). (see SmPC for the full indication). It contains letermovir as the active substance and it is given by oral and/or intravenous infusion.

Further information about the evaluation of PREVYMIS™ and its benefits can be found in the EPAR for PREVYMIS™, including in its plain-language summary, available on the EMA website, under the medicine's webpage:
https://www.ema.europa.eu/en/medicines/human/EPAR/Prevymis.

II. Risks Associated With the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of PREVYMIS™, together with measures to minimise such risks and the proposed studies for learning more about the risks of PREVYMIS™, are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine's legal status — the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A List of Important Risks and Missing Information

Important risks of PREVYMIS™ are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered and taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of PREVYMIS™ Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

Table II.A.1: List of Important Risks and Missing Information

Important identified risks	Pharmacokinetic Drug Interactions (effects on drug transporters and several drug metabolizing enzymes)
Important potential risks	None.
Missing information	None

II.B Summary of Important Risks

Table II.B.1: Important Identified Risk: Pharmacokinetic Drug Interactions (Effects on Drug Transporters and Several Drug Metabolizing Enzymes)

Evidence for linking the risk to the medicine	Clinical DDI studies have identified the following important drug-drug interactions for the target patient population in the approved indication: *Effect of other Medicinal Products on Letermovir:* Letermovir is a substrate of organic anion-transporting polypeptide 1B1/3 (OATP1B1/3) and P-glycoprotein (P-gp) transporters and UGT1A1/3 enzymes. Co-administration of letermovir with drugs that are potent inhibitors of OATP1B1/3 transporters (e.g., cyclosporine and other OATP1B1/3 inhibitors) may result in a clinically relevant increase in letermovir plasma concentration. Co-administration of letermovir with strong and moderate inducers of drug transporters (e.g. P-gp) and or drug metabolizing enzymes (e.g. UGTs) has the potential to decrease letermovir plasma concentrations. Rifampicin co-administration resulted in an initial increase in letermovir plasma concentrations that is not clinically relevant (due to OATP1B inhibition) followed by clinically relevant decreases in letermovir plasma concentration with continued rifampicin co-administration.

Table II.B.1: Important Identified Risk: Pharmacokinetic Drug Interactions (Effects on Drug Transporters and Several Drug Metabolizing Enzymes)

	Effect of other Medicinal Products on Letermovir: Letermovir is a net moderate inhibitor of CYP3A and can increase plasma concentrations of co-administered substrates of CYP3A with the potential to increase the chance for adverse reactions associated with increased concentrations of those substrates with narrow therapeutic ranges. Letermovir is an inhibitor of OATP1B1/3 transporters. Co-administration of letermovir with drugs that are substrates of OATP1B1/1B3 transporters (e.g., atorvastatin or other HMG-CoA reductase inhibitors which are OATP1B1/3 and/or CYP3A substrates and glyburide, etc.) may result in a clinically relevant increase in plasma concentrations of OATP1B1/3 substrates, with the potential to increase the chance for adverse reactions associated with these products. Letermovir co-administration with voriconazole results in a reduction in voriconazole exposure, potentially leading to reduced therapeutic effect of voriconazole. Voriconazole is eliminated primarily by CYP2C9 and CYP2C19 and to a minor extent via CYP3A. The observed effect of letermovir on voriconazole could be attributed to induction of CYP2C9 and CYP2C19 by letermovir. This interaction may also impact other CYP2C9 and/or CYP2C19 substrates (e.g., warfarin, tolbutamide, and proton pump inhibitors e.g., omeprazole, esomeprazole, lansoprazole, or pantoprazole) which have not been evaluated in clinical studies. The following DDI were predicted based on simulation and modeling: A physiologically-based pharmacokinetic (PBPK) approach was used to predict the risk of letermovir to inhibit CYP2C8 in vivo. In this prospective DDI simulation, letermovir increased the exposure of the CYP2C8 substrates such as repaglinide by 2.4 and 3.6-fold after oral and IV dosing, respectively. The simulations suggest that letermovir has the potential to increase the plasma concentration of CYP2C8 substrates *in vivo* with the potential to increase adverse reactions associated with repaglinide such as hypoglycemia. Co-administration of letermovir with dabigatran has not been studied in clinical trials and there is limited postmarketing experience in adults with HSCT.
Risk factors and risk groups	Patients receiving inhibitor or inducers of these various drug transporters or drug metabolizing enzymes concurrently with letermovir prophylaxis are at risk for these interactions Patients receiving substrates of these various drug transporters or drug metabolizing enzymes concurrently with letermovir prophylaxis are at risk for these interactions.
Risk minimisation measures	Routine risk minimisation measures Posology and method of administration, Contraindications, Special warnings and precautions for use, Interaction with other medicinal products and other forms of interaction, pharmacological properties, Pharmacodynamic properties, Pharmacokinetic properties and incompatibilities section of the summary of product characteristics (SPC) and in the Package Leaflet (“What you need to know before you use PREVYMIS”).
Additional pharmacovigilance activities	Drug interaction study of the effect of a strong P-gp/BCRP inhibitor, itraconazole, on letermovir PK

II.C Post-Authorisation Development Plan

II.C.1 Studies Which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of PREVYMIS™.

II.C.2 Other Studies in Post-Authorisation Development Plan

The following additional DDI study (P039) is an ongoing PAM:

Short Name: The effect of a strong P-gp/BCRP inhibitor, itraconazole, on letermovir PK

Rationale and Study Objectives:

Rationale: Itraconazole is an inhibitor of CYP3A, P-gp and BCRP. The effects of a P-gp/BCRP inhibitor on letermovir is not known. This study will evaluate MK-8228 pharmacokinetics at steady-state following the administration of itraconazole administration.

Objectives:

1. To evaluate the effect of multiple doses of oral itraconazole on oral MK-8228 steady state pharmacokinetics (PK) (e.g., AUC0-24, Cmax, C24, Tmax, and apparent terminal t1/2).

2. To evaluate the effect of oral MK-8228 at steady-state on the multiple dose PK of oral itraconazole (e.g., AUC0-24, Cmax, C24, Tmax, and apparent terminal t1/2).