PREVYMIS

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
X/0037/G	This was an application for a group of variations. Annex I_2.(d) Change or addition of a new pharmaceutical form C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or	27/02/2025	25/04/2025	SmPC, Labelling and PL	Please refer to Scientific Discussion 'Prevymis-H-C-004536-X-37'.

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	modification of an approved one Annex I_2.(c) Change or addition of a new strength/potency				
II/0036	B.II.g.4.a - Changes to an approved change management protocol - Major changes	26/09/2024	n/a		
II/0033/G	This was an application for a group of variations. C.I.6.a: Extension of indication to include prophylaxis of CMV disease in CMV-seronegative adults who have received a kidney transplant from a CMV-seropositive donor [D+/R-], based on the final results from study P002MK8228; this is Phase III, Randomized, Double-Blind, Active Comparator- Controlled Study to Evaluate the Efficacy and Safety of MK-8228 (Letermovir) Versus Valganciclovir for the Prevention of Human Cytomegalovirus (CMV) Disease in Adult Kidney Transplant Recipients. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 5.3 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor editorial changes to the product information. C.I.4: Update of section 4.2, 4.8, 5.1, 5.2 and 5.3 of the SmPC to reflect a longer duration of treatment recommendation based on the final results from study P040MK8228; this is a Phase 3 randomized, double-blind, placebo-controlled clinical trial to evaluate the safety and efficacy of letermovir (LET)	12/10/2023	15/11/2023	SmPC and PL	Please refer to Scientific Discussion 'Prevymis-H-C-004536-II-0033/G.

	prophylaxis when extended from 100 days to 200 days post-transplant in cytomegalovirus (CMV) seropositive recipients (R+) of an allogeneic hematopoietic stem cell transplant (HSCT). The Package Leaflet is updated in accordance. Version 4.1 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IA/0035	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	22/06/2023	n/a		
IG/1623	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	16/06/2023	15/11/2023	Annex II and PL	
IAIN/0032	B.II.a.1.a - Change or addition of imprints, bossing or other markings including replacement, or addition of inks used for product marking - Changes in imprints, bossing or other markings	07/03/2023	15/11/2023	PL	
IB/0030	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	24/11/2022	15/11/2023	SmPC	

IAIN/0031/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	17/11/2022	15/11/2023	Annex II and PL	
II/0028/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	10/11/2022	n/a		

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.g - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new manufacturer of the AS that is not supported by an ASMF and requires significant update to the relevant AS section in the dossier				
IA/0029	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	05/10/2022	n/a		
R/0027	Renewal of the marketing authorisation.	23/06/2022	24/08/2022	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of PREVYMIS in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10660 /202111	Periodic Safety Update EU Single assessment - letermovir	10/06/2022	n/a		PRAC Recommendation - maintenance
WS/2193	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	02/06/2022	n/a		
IB/0024	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	04/01/2022	24/08/2022	SmPC and PL	

IB/0023	B.II.g.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	22/06/2021	16/12/2021	Annex II	To introduce minor changes to the approved management protocol intended to implement a terminal sterilisation (TS) process.
PSUSA/10660 /202011	Periodic Safety Update EU Single assessment - letermovir	10/06/2021	n/a		PRAC Recommendation - maintenance
IA/0022	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	11/02/2021	n/a		
IA/0020	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	13/01/2021	n/a		
IB/0019	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	22/12/2020	16/12/2021	SmPC and PL	
IA/0018	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	29/10/2020	n/a		
II/0016/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/05/2020	03/07/2020	SmPC, Annex II, Labelling and PL	The SmPC sections 4.2, 4.4, 6.2 and 6.6 for Prevymis contrate for solution for infusion have been updated to include the requirement to administer the diluted solution through a sterile 0.2 micron or 0.22 micron polyethersulfone (PES) in-line filter as the medicinal product may contain a few product-related small translucent or white particles. The SmPC was also updated

	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				with relevant information on preparation and handling of the medicinal product and its incompatibility intravenous bags and infusion set materials containing polyurethane or the plasticizer diethylhexyl phthalate (DEHP). Materials that are phthalate free are also DEHP-free. The Labelling and package leaflet have been updated accordingly, to highlight that the medicinal product must be administered through a sterile 0.2 micron or 0.22 micron PES in-line filter. The due date for completing the Annex II condition (Step 2) is extended from 31 May 2020 to 31 May 2021.
PSUSA/10660 /201911	Periodic Safety Update EU Single assessment - letermovir	11/06/2020	n/a		PRAC Recommendation - maintenance
II/0013	Update of section 5.1 of the SmPC in order to update the viral resistance profile that may be associated with a change in susceptibility to letermovir considering new intro pharmacology data based on the analysis of the patients' samples included in the study MK-8228.This study is a Phase III Randomized, Placebo-Controlled Clinical Trial to Evaluate the Safety and Efficacy of MK-8228 (Letermovir) for the Prevention of Clinically Significant Human Cytomegalovirus (CMV) Infection in Adult, CMV Seropositive Allogeneic Hematopoietic Stem Cell. This variation follows the recommendation dated on 9th November 2017 that asked for the submission when available of the results to update the CMV phenotypic resistance analyses of all clinical isolates for subjects failing letermovir treatment and to explore the possibility to obtain	27/02/2020	03/07/2020	SmPC	The purpose of this application is to update the letermovir (Prevymis) product information on viral resistance. Additional genotypic resistance data, both from in vitro selection studies and from clinical samples have been provided in order to identify CMV variants that may be associated with a change in susceptibility to letermovir.

	additional pre-failure CMV genotypic data from available samples. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0014	Update of section 4.5 of the SmPC in order to update the safety information with regard to the drug interaction information following the results from study MK-8228-039, a clinical pharmacology trial entitled "A Study to Assess the Effect of P-gp/BCRP Inhibition, following Multiple Oral Doses of Itraconazole, on the Steady-State Pharmacokinetics of MK-8228 in Healthy Adult Subjects" listed as a category 3 study in the RMP. The RMP version has not been submitted. In addition, the Marketing authorisation holder (MAH) took the opportunity to submit the protein binding report as part of the rifampin study MK-8228-038 as it was requested within the previous type II variation (EMEA/H/C/004536/II/0011) . C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	13/02/2020	03/07/2020	SmPC	The safety information regarding drug-drug interaction of this product is updated following the results from the study to assess the Effect of P-gp/BCRP Inhibition, following Multiple Oral Doses of Itraconazole (perpetrator), on the steady-state pharmacokinetics of Letermovir (victim) in healthy adult subjects. The presently observed increase in letermovir exposure as a consequence of DDI with itraconazole is not considered clinically relevant. Additionally, exposure of itraconazole decreased in the presence of letermovir, with AUC dropping to 76% and Cmax to 84% of its initial value (value in the absence of letermovir). This change in itraconazole exposure was not considered clinically relevant, but its exposure was still considered sufficiently high for the purpose of the present DDI study. In addition, the protein binding of letermovir was evaluated using equilibrium dialysis in plasma samples from 15 healthy female subjects after co-administration of an oral dose of 480 mg MK-8228 with a single oral dose of 600 mg rifampin. Letermovir was highly bound to human plasma proteins and that the fraction unbound was independent of letermovir plasma concentrations. Data from this study

					were consistent with plasma protein binding data obtained from previous studies. Therefore, potential SmPC updates in this regard are not considered necessary.
PSUSA/10660 /201905	Periodic Safety Update EU Single assessment - letermovir	28/11/2019	n/a		PRAC Recommendation - maintenance
IA/0015/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	10/10/2019	n/a		
II/0011	Update of sections 4.3, 4.4 and 4.5 of the SmPC in order to update the safety information following the final results of a clinical pharmacology trial entitled "A Study to Assess the Effect of Rifampin on the Single-Dose and Steady-State Pharmacokinetics of MK-8228 in Healthy Adult Subjects" (MK-8228-038) listed as a category 3 study in the RMP; the Package Leaflet is updated accordingly. The RMP version 2.1 has also been submitted. This submission fulfils the post-authorisation measure MEA 001.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/07/2019	26/08/2019	SmPC and PL	The MAH submitted final results from a clinical DDI study with rifampicin. Inducers of p-gp/UGT may substantially reduce exposure of letermovir (85% decrease in AUC) leading to subtherapeutic levels. Whether such co-administrations should be strictly contraindicated or not recommended shall be discussed on a case by case basis in the light of the medical need of the co-administration. However, in any case, co-administration with St. John's wort must be a contra-indication rather than a not recommended combination. As a result of this variation, sections 4.3, 4.4 and 4.5 of the SmPC are being updated accordingly.

PSUSA/10660 /201811	Periodic Safety Update EU Single assessment - letermovir	16/05/2019	n/a		PRAC Recommendation - maintenance
II/0009	Update of section 4.5 of the SmPC in order to update the information on drug-drug interaction between letermovir and fluconazole based on the results from study MK-8228-037; this is an open-label, 3-period, fixed-sequence trial to evaluate the effect of single-dose administration of letermovir on the single-dose PK of fluconazole, and the effect of single dose administration of fluconazole on the single-dose PK of letermovir in healthy females. Moreover, the median time to maximum plasma concentration was updated in section 5.2 of the SmPC. In addition, the Marketing authorisation holder (MAH) took the opportunity include minor editorial changes in the SmPC and package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/03/2019	26/08/2019	SmPC	The results from the pharmacokinetic drug-drug interaction study MK-8228-037 with fluconazole (400 mg single dose) and letermovir (480 mg single dose) have shown that no dose adjustment of letermovir is required. Interaction at steady state was not studied; however clinically relevant interactions are not expected at steady-state.
PSUSA/10660 /201805	Periodic Safety Update EU Single assessment - letermovir	29/11/2018	n/a		PRAC Recommendation - maintenance
IA/0008/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	12/11/2018	n/a		

	B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS				
II/0005	B.II.g.4.a - Changes to an approved change management protocol - Major changes	08/11/2018	26/08/2019	Annex II	
IA/0007/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	26/10/2018	n/a		
IA/0006	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	18/09/2018	n/a		
IAIN/0004/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer	17/08/2018	n/a		

	responsible for batch release B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
T/0002	Transfer of Marketing Authorisation	27/06/2018	23/07/2018	SmPC, Labelling and PL	
IB/0001	B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation	08/03/2018	n/a		