Vemlidy

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
IB/0046	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/09/2024	n/a		
IG/1722/G	This was an application for a group of variations.	04/04/2024	n/a		

[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).

	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
II/0043/G	This was an application for a group of variations. Grouped application consisting of: C.I.13: Submission of the final report from study GS-US-320-0108 listed as category 3 studies in the RMP. This is a Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Negative, Chronic Hepatitis B. The RMP version 11.0 has also been submitted. C.I.13: Submission of the final report from study GS-US-320-0110 listed as category 3 studies in the RMP. This is a is a Phase 3, Randomized, Double-Blind Study to Evaluate the Safety and Efficacy of Tenofovir Alafenamide (TAF) 25 mg QD versus Tenofovir Disoproxil Fumarate (TDF) 300 mg QD for the Treatment of HBeAg-Positive, Chronic Hepatitis B. The RMP version 11.0 has also been submitted.	11/01/2024	n/a		Vemlidy 25 mg tenofovir alafenamide (TAF) film-coated tablets are indicated for the treatment of chronic hepatitis B (CHB) in adults and paediatric patients 6 years of age and older weighing at least 25 kg. The recommended dose is one tablet daily. With this group of variations, the MAH submitted the final study reports of studies GS-US-320-0108 and GS-US-320-0110 listed as category 3 studies in the RMP, which contain efficacy and safety data, including long-term resistance, on up to 384 weeks (i.e., 8 years) of TAF treatment. Also were included final integrated safety data for participants who completed the treatment phase of the study and entered the 24 week treatment-free follow-up (TFFU) phase or those who prematurely discontinued study drug and entered the TFFU phase. No concerns with respect to efficacy or safety result emerged from the presented data. No changes to the SmPC were considered necessary by the Committee. An updated RMP (version 11.0) was endorsed accordingly.

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
WS/2540	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	14/12/2023	n/a		
IG/1626/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size 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	23/06/2023	n/a		

II/0040	Extension of indication to include treatment of chronic hepatitis B-infected children from 6 years and older and weighing at least 25 kilograms for Vemlidy, based on the interim results from Week 24 clinical study report (CSR) for Cohort 1 and Cohort 2 Group 1 and supporting modular summaries for the category 3 study GS-US-320-1092, 'A Randomized, Double-Blind Evaluation of the Pharmacokinetics, Safety, and Antiviral Efficacy of Tenofovir Alafenamide (TAF) in Children and Adolescent Subjects with Chronic Hepatitis B Virus Infection'. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity to update the wording in section 4.6 of the SmPC related to breastfeeding and pregnancies exposed to TAF, and to update the list of local representatives in the Package Leaflet. An updated RMP version 9.1 has been provided. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/04/2023	26/05/2023	SmPC and PL	
WS/2315/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a	10/11/2022	n/a		

	starting material/reagent/intermediate for AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the 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				
II/0038	Submission of the final Week 192 report from study GS-US-320-3912; 'A Phase 2, Randomized, Open Label Study to Evaluate the Efficacy and Safety of Tenofovir Alafenamide (TAF) versus Tenofovir Disoproxil Fumarate (TDF)–containing Regimens in Subjects with Chronic HBV Infection and Stxage 2 or Greater Chronic Kidney Disease Who Have Received a Liver Transplant', listed as a category 3 study in the RMP. The RMP version 9.0 has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	01/09/2022	n/a		
PSUSA/10575 /202111	Periodic Safety Update EU Single assessment - tenofovir alafenamide	23/06/2022	17/08/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10575/202111.
IA/0039/G	This was an application for a group of variations. B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient	30/03/2022	n/a		

	- Minor changes to an approved test procedure				
R/0035	Renewal of the marketing authorisation.	14/10/2021	16/12/2021	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Vemlidy in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IA/0036/G	This was an application for a group of variations. 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 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	18/11/2021	n/a		
II/0032	Update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to add new information on efficacy and safety based on final results from study GS-US-320-4035. This was a phase 2, open-label study to evaluate the safety and efficacy of switching to tenofovir alafenamide from tenofovir disoproxil fumarate and/or other oral antiviral treatment in virologically suppressed chronic hepatitis B subjects with renal and/or hepatic impairment. C.I.4 - Change(s) in the SPC, Labelling or PL due to	30/09/2021	16/12/2021	SmPC	SmPC new text […] 4.4 Special warnings and precautions for use Renal impairment Patients with creatinine clearance < 30 mL/min The use of Vemlidy once daily in patients with CrCl ≥ 15 mL/min and < 30 mL/min is based on Week 96 data on the efficacy and safety of switching from another antiviral regimen to tenofovir alafenamide in an open label clinical study of virologically suppressed chronic HBV-infected patients (see sections 4.8 and 5.1). There are very limited

	new quality, preclinical, clinical or pharmacovigilance data				data on the safety and efficacy of Vemlidy in HBV-infected patients with CrCl < 15 mL/min on chronic haemodialysis (see sections 4.8, 5.1 and 5.2). […] 4.8 Undesirable effects […] In the open-label Phase 2 study (GS-US-320-4035; "Study 4035") to evaluate the efficacy and safety of switching from another antiviral regimen to tenofovir alafenamide in virologically suppressed chronic HBV infected patients, small median increases in fasting total cholesterol, direct LDL, HDL, and triglycerides from baseline to Week 96 were observed in subjects with moderate or severe renal impairment (Part A Cohort 1) and subjects with moderate or severe hepatic impairment (Part B), consistent with changes observed in Studies 108 and 110. Small median decreases in total cholesterol, LDL and triglycerides were observed in subjects with ESRD on hemodialysis in Part A Cohort 2, while small median increases were observed in HDL from baseline to Week 96. Median (Q1, Q3) change from baseline at Week 96 in total cholesterol to HDL ratio was 0.1 (-0.4, 0.4) in the moderate or severe renal impairment group, and -0.4 (-0.8,-0.1) in subjects with ESRD on hemodialysis and 0.1 (-0.2, 0.4) in subjects with moderate or severe hepatic impairment. Metabolic parameters Body weight and levels of blood lipids and glucose may increase during therapy. Other Special Populations In Study 4035 in virologically suppressed patients with moderate to severe renal impairment (eGFR by Cockcroft-Gault method 15 to 59 mL/min; Part A, Cohort 1, N = 78),

					end stage renal disease (ESRD) (eGFR < 15 mL/min) on haemodialysis (Part A, Cohort 2, N = 15), and/or moderate to severe hepatic impairment (Child-Pugh Class B or C at screening or by history; Part B, N = 31) who switched from another antiviral regimen to tenofovir alafenamide, no additional adverse reactions to tenofovir alafenamide were identified through Week 96. […] For more information, please refer to the Summary of Product Characteristics.
II/0030	Update of sections 4.8 and 5.1 to include new information on safety and pharmacodynamic properties based on the final report from study GS-US-320-4018, listed as a category 3 study in the RMP. This was a phase 3, randomized, double blind study to evaluate the efficacy and safety of switching from tenofovir disoproxil fumarate 300 mg once daily to tenofovir alafenamide 25 mg once daily in subjects with chronic hepatitis B who are virologically suppressed. The RMP (v 8.0) has also been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	08/07/2021	29/09/2021	SmPC	The results showed that at Week 48, switching to tenofovir alafenamide 25 mg once daily was non-inferior to continued treatment with tenofovir disoproxil fumarate 300 mg in patients with chronic hepatitis B that were virologically suppressed. The clinical virology data at Week 96 did not implicate a higher risk for the development of resistance or virological failure for subjects switching from tenofovir disoproxil fumarate to tenofovir alafenamide. At Week 96, increases in fasting total cholesterol, direct LDL, HDL and triglycerides were observed in patients who switched from tenofovir disoproxil to tenofovir alafenamide at Week 48.
PSUSA/10575 /202011	Periodic Safety Update EU Single assessment - tenofovir alafenamide	10/06/2021	n/a		PRAC Recommendation - maintenance
IB/0031	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	21/05/2021	n/a		

	authorisation, including the RMP - Other variation				
IA/0033	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	27/04/2021	n/a		
N/0034	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/04/2021	29/09/2021	PL	
IA/0028	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	26/11/2020	n/a		
II/0023	Update of sections 4.4, 4.8, 5.1 and 5.2 of the SmPC based on interim analysis data at Week 24 from study GS-US-320-4035. This is a Phase 2, open-label study evaluating the efficacy and safety of tenofovir alafenamide (TAF) in virologically suppressed chronic hepatitis B subjects with renal and/or hepatic impairment who switch from tenofovir disoproxil fumarate and/or other oral antiviral agents to TAF 25 mg once daily. Supportive safety and pharmacokinetic data are also provided from Study GS-US-292-1825 (phase 3b trial in which Elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide a fixed-dose TAF containing combination indicated for the treatment of HIV-1 infection, was evaluated in HIV-1 infected subjects with end stage renal disease). Study GS-US-320-4035 is included in the RMP version 4.2 under additional PhV activities. In addition, the MAH took the opportunity to make some editorial changes to bring Annex II and IIIA in	24/09/2020	29/09/2021	SmPC	SmPC new text: At week 24 , these results demonstrate that antiviral efficacy is maintained in virally suppressed chronic hepatitis B (CHB) subjects with pre-existing renal and/or hepatic decompensation switching to TAF from TDF and/or other oral antiviral therapy. In addition, it was well tolerated with a low proportion of subjects experiencing severe adverse event (AEs) or AEs leading to premature discontinuation of study drug.

	line with the latest QRD guidelines. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/1278	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	27/08/2020	n/a		
PSUSA/10575 /201911	Periodic Safety Update EU Single assessment - tenofovir alafenamide	25/06/2020	25/08/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10575/201911.
WS/1745	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/05/2020	25/08/2020	PL	
IG/1247	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)	08/05/2020	n/a		
WS/1746	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	06/02/2020	n/a		

	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data				
IB/0021	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	28/01/2020	n/a		
II/0020	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/12/2019	01/04/2020	SmPC and PL	The interim efficacy data of the submitted study demonstrated that at 48 weeks switching to Tenofovir alafenamide (TAF) 25 mg given once daily was non-inferior to continued treatment Tenofovir disoproxil fumarate (TDF) 300 mg given once daily in patients with CHB that are virologically suppressed and it did not implicate a higher risk for the development of resistance or virological failure. The safety profile of TAF is considered to be similar to TDF with some exceptions. It appears to be a beneficial effect for patients switched from TDF to TAF in terms of renal and bone events, however, the lipid profile changes, weight gain, cardiac events and alopecia are cause of concern and require monitoring by routine pharmacovigilance activities.
PSUSA/10575 /201811	Periodic Safety Update EU Single assessment - tenofovir alafenamide	14/06/2019	n/a		PRAC Recommendation - maintenance
WS/1566	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.8 of the SmPC following a safety review by the MAH assessing the clinical evidence of	02/05/2019	01/04/2020	SmPC, Annex II, Labelling and PL	Based on post-marketing surveillance data, there is sufficient evidence to consider that a causal association between tenofovir alafenamide-containing products and two adverse events, angioedema and urticaria, with the frequency uncommon. The Product information is updated accordingly.

	a causal association between tenofovir alafenamide-containing products and two adverse events, angioedema and urticaria. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to implement minor linguistic amendments and editorial changes to the Odefsey and Vemlidy products information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/1009	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	18/12/2018	n/a		
PSUSA/10575 /201805	Periodic Safety Update EU Single assessment - tenofovir alafenamide	29/11/2018	n/a		PRAC Recommendation - maintenance
WS/1441	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	04/10/2018	n/a		

WS/1430	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	04/10/2018	n/a		
PSUSA/10575 /201711	Periodic Safety Update EU Single assessment - tenofovir alafenamide	14/06/2018	n/a		PRAC Recommendation - maintenance
T/0013	Transfer of Marketing Authorisation	25/04/2018	28/05/2018	SmPC, Labelling and PL	
IB/0012	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/04/2018	n/a		
WS/1310	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.5 of the Descovy, Genvoya, Odefsey and Vemlidy SmPCs in order to include information on the drug-drug interaction with sofosbuvir/velpatasvir/voxilaprevir fixed dose combination based on the results of study GS-US0367-1657, listed as a category 3 in the Vemlidy RMP, in order to fulfil MEA 006 for Vemlidy. Study GS-US0367 is a phase I multiple dose study to evaluate the drug-drug interaction potential between	22/03/2018	28/05/2018	SmPC	

	sofosbuvir/velpatasvir/voxilaprevir fixed dose combination and HIV anti-retrovirals in healthy subjects. In addition, the Worksharing applicant (WSA) took the opportunity to make some small corrections to section 4.5 of the SmPC for Descovy, Genvoya, Odefsey and Vemlidy and to make corrections to the DE, ES, HU, IS, IT, LV, NO, PT, SL and SV translations for Vemlidy. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0010	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)	18/01/2018	28/05/2018	SmPC	
WS/1305	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	18/01/2018	n/a		
IG/0877	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	21/12/2017	n/a		

PSUSA/10575 /201705	Periodic Safety Update EU Single assessment - tenofovir alafenamide	30/11/2017	n/a		PRAC Recommendation - maintenance
IG/0861	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	17/11/2017	n/a		
II/0004	Update of sections 4.8 and 5.1 of the Vemlidy SmPC in order to provide 96 week data from Studies GS-US-320-0108 and GS-US-320-0110, listed as category 3 studies in the RMP; GS-US-320-0108 is an ongoing Phase 3, randomized, double-blind, non-inferiority study evaluating the safety and efficacy of Vemlidy 25 mg compared with tenofovir disoproxil fumarate 300 mg in HBeAg-negative subjects with Chronic hepatitis B. GS-US-320-0110 is a an ongoing Phase 3, randomized, double-blind, noninferiority study evaluating the safety and efficacy of Vemlidy versus tenofovir disoproxil fumarate for the treatment of HBeAg-positive subjects with chronic hepatitis B. The Package Leaflet is updated accordingly. The RMP version 2.0 has also been updated. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/11/2017	28/05/2018	SmPC and PL	The efficacy and safety of Vemlidy in patients with chronic hepatitis B are based on 48 and 96-week data from two randomized, double blind, active controlled studies, GS US 320 0108 (“Study 108”) and GS US 320 0110 (“Study 110”). In analyses at Week 48 (n=20) and Week 96 (n=72), no amino acid substitutions associated with resistance to Vemlidy were identified in these isolates (genotypic and phenotypic analyses). The safety of Vemlidy is also supported by pooled data from patients in Studies 108 and 110 who remained on blinded treatment from Week 96 through Week 120 and additionally from patients in the open-label phase of Studies 0108 and 0110 from Week 96 through Week 120 (N = 361 remained on Vemlidy; N = 180 switched from tenofovir disoproxil fumarate to Vemlidy at Week 96). The most frequently reported adverse reactions were headache (12%), nausea (6%), and fatigue (6%). No additional adverse reactions to Vemlidy were identified from Week 96 through Week 120 in the double-blind phase and in the subset of subjects receiving open-label Vemlidy treatment.

IG/0836	A.7 - Administrative change - Deletion of manufacturing sites	31/08/2017	n/a		
IA/0002/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	16/06/2017	n/a		
IB/0001/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	06/02/2017	n/a		