Odefsey

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
IG/1588	C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority	16/02/2023		SmPC and PL	

[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).

IG/1581/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 B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	16/12/2022	n/a		
WS/2331	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	10/11/2022		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 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	10/11/2022	n/a		

	starting material/reagent/intermediate for AS - Other variation				
IG/1456	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	08/11/2021	n/a		
IG/1412	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	28/07/2021	n/a		
WS/2030	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update section 4.4 of the SmPC and section 2 of the PL with information regarding nephrotoxicity, in alignment with the outcome of procedure EMEA/H/C/PSUSA/00010575/201911 already approved for Vemlidy. In addition, the marketing authorisation holder has taken the opportunity to introduce minor editorial changes for Biktarvy and to align the PI of all four products to the latest QRD template (v. 10.2). C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure	20/05/2021	14/06/2022	SmPC and PL	

	concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation				
IG/1396/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	18/05/2021	n/a		
IG/1387	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	18/05/2021	n/a		
R/0049	Renewal of the marketing authorisation.	12/11/2020	14/01/2021	SmPC, Annex II and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Odefsey in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10514 /202002	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir alafenamide	01/10/2020	n/a		PRAC Recommendation - maintenance
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		

IG/1236	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	04/05/2020	n/a		
WS/1718	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 4.6 of the Eviplera and Odefsey SmPCs in order to reflect rilpivirine data from the Antiretroviral Pregnancy Registry (APR) Interim Report issued in December 2019. The Eviplera Package Leaflet is updated in accordance. Furthermore, section 4.6 of the SmPC was updated to harmonise the text for breast-feeding with the already agreed text for rilpivirine, sections 4.4, 4.5 and 4.8 of the SmPC regarding the drug-drug interaction with didanosine and section 4.8 of the SmPC was updated regarding lactic acidosis, as agreed by the PRAC in the Viread procedure EMEA/H/C/PSUSA/00002892/201903. Section 4.5 was also updated to remove the reference to simeprevir. In addition, the Worksharing applicant (WSA) took the opportunity to bring the PI in line with the latest QRD template version 10.1, make minor editorial changes and update the PI in line with the Annex to the European Commission guideline on `Excipients in the labelling and package	17/04/2020	14/01/2021	SmPC, Annex II and PL	There are no adequate and well controlled studies of Eviplera/Odefsey or their components in pregnant women. A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformative or foeto/neonatal toxicity of rilpivirine (see sections 4.4, 5.1 and 5.2). Lower exposures of rilpivirine were observed during pregnancy; therefore viral load should be monitored closely. A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformative nor foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil. The use of Eviplera/Odefsey may be considered during pregnancy, if necessary. Because of both the potential for HIV transmission and the potential for adverse reactions in breastfed infants, women should be instructed not to breast feed if they are receiving Eviplera/Odefsey. Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals. Patients with predisposing factors such as patients with decompensated liver disease, or patients receiving concomitant medications known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

	leaflet of medicinal products for human use' (EMA/CHMP/302620/2017 Rev.1) regarding sodium content, for both products. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/1746	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.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	06/02/2020	n/a		
PSUSA/10514 /201902	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir alafenamide	03/10/2019	n/a		PRAC Recommendation - maintenance
WS/1627	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 4.9 of the Eviplera and Odefsey SmPCs in order to remove the recommendation to use oral activated charcoal in the event of an overdose of rilpivirine and replace it with a general guidance to contact poison control. In addition the MAH has taken the opportunity to update the lactose wording in Section 4.4 of the SmPC and Section 2 of	27/06/2019	01/04/2020	SmPC and PL	Section 4.9 of the Eviplera and Odefsey SmPCs have been updated to remove the mention of administration of activated charcoal to aid in the removal of unabsorbed rilpivirine hydrochloride, replaced by advice that further management of rilpivirine overdose should be as clinically indicated or as recommended by the national poisons centre, where available.

	the PL of Eviplera, according to the annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', as well as update Section 5.1 of the Eviplera SmPC to reflect the full waiver for the Eviplera PIP. The MAH has also taken the opportunity to introduce minor administrative updates in the product information for both for Eviplera and Odefsey. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/1429	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC of Descovy, Genvoya and Odefsey with data in patients on chronic haemodialysis from the Study GS-US-292-1825; this is a Phase 3b Open-Label Study to Evaluate the Safety, Tolerability, Pharmacokinetics and Efficacy of E/C/F/TAF Fixed Dose Combination (FDC) in HIV-1 Infected Subjects on Chronic Haemodialysis. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to remove boceprevir drug-drug interaction information in section 4.5 of the SmPC since this medicinal product has been withdrawn	26/04/2019	06/06/2019	SmPC, Labelling and PL	In study GS US 292 1825, the efficacy and safety of of emtricitabine + tenofovir alafenamide in combination with elvitegravir + cobicistat as a fixed-dose combination tablet in HIV-1 infected adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis were evaluated. There were no new safety issues identified in these patients. No clinically relevant differences in tenofovir alafenamide pharmacokinetics were observed in patients with end stage renal disease on chronic haemodialysis as compared to those with normal renal function. Efficacy was maintained through 48 weeks but emtricitabine exposure was significantly higher than in patients with normal renal function. Although there were no new safety issues identified, the implications of increased emtricitabine exposure remain uncertain. Therefore, it is recommended that Descovy, Genvoya and Odefsey should generally be avoided but may be used in

	from the EU market, as well as to introduce some minor amendments throughout the product information of Descovy, Genvoya and Odefsey. The Package Leaflet is updated accordingly. Moreover, the Package Leaflet of Genvoya and Odefsey have been updated regarding the lactose wording, as per the revised Annex to the European Commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'; as well as an administrative correction to the Genvoya Package Leaflet in order to add "lurasidone" to the second list of contra-indicated drugs. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				adults with end stage renal disease (estimated CrCl < 15 mL/min) on chronic haemodialysis if the potential benefits are considered to outweigh the potential risks. No dose adjustment is required in these patients. Based on this, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC of Descovy, Genvoya and Odefsey have been updated accordingly.
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 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.	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.

	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		
WS/1466/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. 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 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 - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	29/11/2018	n/a		
IG/1001	B.I.b.1.d - Change in the specification parameters	23/11/2018	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
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		
IG/0983	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/09/2018	06/06/2019	SmPC	
WS/1424	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	13/09/2018	n/a		

	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IAIN/0037	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	11/09/2018	n/a		
PSUSA/10514 /201802	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir alafenamide	06/09/2018	n/a		PRAC Recommendation - maintenance
T/0030	Transfer of Marketing Authorisation	25/04/2018	16/05/2018	SmPC, Labelling and PL	
IB/0029	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)	12/04/2018	16/05/2018	SmPC	
PSUSA/10514 /201708	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir alafenamide	12/04/2018	n/a		PRAC Recommendation - maintenance
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	22/03/2018	16/05/2018	SmPC	

	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 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				
II/0027/G	This was an application for a group of variations. Update of sections 4.8 and 5.1 of the SmPC to provide the 96 weeks clinical study reports for two Odefsey switch studies (GS-US-366-1216 and GS-US-366-1160), listed as category 3 studies in the Risk Management Plan, in fulfilment of post-authorisation measures (PAM) MEA 1.1 and 2.1 respectively. Study GS-US-366-1216: A Phase 3b, Randomized, Double-Blind Switch Study to Evaluate the Safety and Efficacy of Emtricitabine/Rilpivirine/Tenofovir Alafenamide (FTC/RPV/TAF) Fixed Dose	08/02/2018	16/05/2018	SmPC and Labelling	

	Combination (FDC) in HIV-1 Positive Subjects who are Virologically Suppressed on Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF). Study GS-US-366-1160: A Phase 3b, Randomized, Double-Blind Study to Evaluate Switching from a Regimen Consisting of Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF) Fixed Dose Combination (FDC) to Emtricitabine/Rilpivirine/Tenofovir Alafenamide (FTC/RPV/TAF) FDC in Virologically-Suppressed, HIV-1 Infected Subjects. In addition, the Marketing authorisation holder (MAH) took the opportunity to introduce minor administrative amendments in the Labelling and minor linguistic amendments to the Product Information in the following languages: DE, NO and SV. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/1305	This was an application for a variation following a	18/01/2018	n/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				
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		
WS/1251	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4 , 4.6, 5.1 and 5.2 of the Eviplera and Odefsey SmPCs with data from Study TMC114HIV3015, a Category 4 additional pharmacovigilance activity in the Risk Management Plan for both the Eviplera and Odefsey. This is a single-arm, open-label study to assess the pharmacokinetics of Darunavir and Ritonavir, Darunavir and Cobicistat, Etravirine, and Rilpivirine in HIV-1 infected pregnant women results for the Rilpivirine arm. The Package Leaflet is updated accordingly. In addition, the Worksharing Applicant (WSA) has taken the opportunity to introduce some minor administrative amendments and to implement some	19/10/2017	11/12/2017	SmPC, Labelling and PL	Rilpivirine (one of the components of Odefsey) in combination with a background regimen was evaluated in Study TMC114HIV3015 in 19 pregnant women during the 2nd and 3rd trimesters, and postpartum. The pharmacokinetic data demonstrate that total exposure (AUC) to rilpivirine as a part of an antiretroviral regimen was approximately 30% lower during pregnancy compared with postpartum (6-12 weeks). The virologic response was generally preserved throughout the study: of the 12 patients that completed the study, 10 patients were suppressed at the end of the study; in the other 2 patients an increase in viral load was observed only postpartum, for at least 1 patient due to suspected suboptimal adherence. No mother to child transmission occurred in all 10 infants born to the mothers who completed the trial and for whom the HIV status was available. Rilpivirine was well tolerated during pregnancy and postpartum. There were no new

	minor linguistic amendments (MLAs) to the translations of the product information annexes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				safety findings compared with the known safety profile of rilpivirine in HIV 1 infected adults. In the Phase 3 studies (C209 and C215), lower rilpivirine exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure, therefore viral load should be monitored closely. Alternatively, switching to another antiretroviral regimen could be considered.
IAIN/0025	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	17/11/2017	n/a		
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		
IB/0021	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	10/10/2017	n/a		
PSUSA/10514 /201702	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir alafenamide	28/09/2017	n/a		PRAC Recommendation - maintenance
WS/1205	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 SmPC of Genvoya, Descovy and Odefsey in order to provide the final study report for the in vitro study AD-120-2045; this is a non-clinical study on the Effect of Xanthine Oxidase Inhibitors on Metabolism of Tenofovir	14/09/2017	11/12/2017	SmPC	Based on data from the in vitro study AD-120-2045, co administration of tenofovir alafenamide and xanthine oxidase inhibitors (e.g. febuxostat) is not expected to increase systemic exposure to tenofovir in vivo.

	alafenamide fumarate in Primary Human Hepatocytes. This study is listed in the respective Risk Management Plans as an additional pharmacovigilance activity (Category 3) (Genvoya: MEA 006; Descovy: MEA 004; Odefsey: MEA 007). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/0836	A.7 - Administrative change - Deletion of manufacturing sites	31/08/2017	n/a		
IG/0799	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	14/07/2017	n/a		
WS/1136	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4, 4.8, and 5.1 of the SmPC in order to provide 48 weeks data from Study GS-US-292-1249; a Phase 3b open-label study of the efficacy and safety of elvitegravir / cobicistat / emtricitabine / tenofovir alafenamide single-tablet regimen in HIV-1/Hepatitis B co-infected adults. The Package Leaflet is updated accordingly.	06/07/2017	11/12/2017	SmPC and PL	The following existing information in the SmPC was updated to reflect the efficacy and safety of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) evaluated in 72 adult patients co infected with Human Immunodeficiency virus (HIV 1) and chronic hepatitis B (HBV) in the open label Study GS-US-29201249. Tenofovir alafenamide is active against hepatitis B virus (HBV). Of the patients who were HBeAg positive at baseline, 1/30 (3.3%) achieved seroconversion to antibodies against hepatitis B e antigen (anti HBe) at Week 48. Of the patients

	In addition, the Worksharing Applicant (WSA) took the opportunity to update the list of local representatives (Lithuania, Latvia and Estonia), update section 4.5 of the SmPC with the removal of telaprevir due to the withdrawal of the marketing authorisation in the EU and to include minor administrative changes in the SmPC and the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				who were HBsAg positive at baseline, 3/70 (4.3%) achieved seroconversion to anti HBs at Week 48. At Week 48, 92% of patients (66/72) maintained HIV 1 RNA < 50 copies/mL after switching to E/C/F/TAF. The mean change from baseline in CD4+ cell count at Week 48 was 2 cells/mm3. Ninety two percent (66/72 patients) had HBV DNA < 29 IU/mL using missing = failure analysis at Week 48. Of the 62 patients who were HBV suppressed at baseline, 59 remained suppressed and 3 had missing data. Of the 10 patients who were not HBV suppressed at baseline (HBV DNA ≥ 29 IU/mL), 7 became suppressed, 2 remained detectable, and 1 had missing data. Alanine aminotransferase (ALT) normalisation was achieved in 40% (4/10) of subjects with ALT greater than upper limit of normal (ULN) at baseline. There are limited clinical data on the use of E/C/F/TAF in HIV/HBV co infected patients who are treatment naïve. The safety profile of emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed dose combination tablet, in patients with HIV/HBV co infection, was similar to that in patients with HIV 1 monoinfection.
IG/0818	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	16/06/2017	n/a		
IB/0014	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	24/05/2017	n/a		

WS/1152	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.8 and 5.1 of the SmPC in order to amend the study duration and percentages of subjects maintaining HIV RNA <50 copies/mL at Week 144 regarding undesirable effects and pharmacodynamic properties of Genvoya, Descovy and Odefsey following Week 144 efficacy and safety data from Study GS-US-292-0112, listed as a category 4 study in the Risk Management Plan; this is a phase 3 open-label safety study of elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide single-tablet regimen in HIV-1 positive patients with mild to moderate renal impairment. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	05/05/2017	11/12/2017	SmPC and PL	The following existing information in the SmPC was updated to reflect the new study duration and the percentages of subjects maintaining HIV RNA <50 copies/mL at Week 144. The safety of emtricitabine and tenofovir alafenamide was evaluated through 144 weeks in an open-label clinical study (GS US 292 0112) in which 248 HIV 1 infected patients who were either treatment-naïve (n = 6) or virologically suppressed (n = 242) with mild to moderate renal impairment (estimated glomerular filtration rate by Cockcroft Gault method [eGFRCG]: 30 69 mL/min) received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet. The safety profile in patients with mild to moderate renal impairment was similar to that in patients with normal renal function. At Week 144, 83.1% (197/237 patients) maintained HIV 1 RNA < 50 copies/mL after switching to emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet.
WS/1133/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. Updates of sections 4.4 and 4.5 of the SmPC for the tenofovir disoproxil fumarate (TDF)-containing products (Viread, Truvada, Atripla, Stribild) which includes the results from Study GS-US-342-1167 and	21/04/2017	11/12/2017	SmPC and PL	The Marketing Authorisation Holder has submitted the results from Study GS-US-342-1167 and Study GS-US-342-1326 to update the Product Information for tenofovir disoproxil fumarate (TDF)-containing products (Viread, Truvada, Atripla, Eviplera and Stribild) and tenofovir alafenamide (TAF)-containing products (Genvoya, Descovy, Odefsey). Study GS-US-342-1167 is a Phase I Study to Evaluate the Pharmacokinetic Drug-Drug Interactions between

	Study GS-US-342-1326. The Package Leaflets and Risk Management Plans for Viread (v. 22), Truvada (v.14), Atripla (v.16) and Stribild (v.11.1) have been updated accordingly. Update of section 4.5 for the tenofovir alafenamide (TAF)-containing products (Genvoya, Descovy, Odefsey) and for Eviplera, which include the results from Study GS-US-342-1167. The Risk Management Plan for Eviplera (v.13) has been updated accordingly. Administrative update of section 4.8 of the SmPC for Viread, Atripla, Eviplera and Stribild. Study GS-US-342-1167 is a Phase I Study to Evaluate the Pharmacokinetic Drug-Drug Interactions between Sofosbuvir/GS-5815 Fixed Dose Combination (FDC) Tablets and Antiretrovirals Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF; Atripla), Emtricitabine/Riplivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF; Complera), Dolutegravir (DTG; Tivicay) o Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate (EVG/COBI/FTC/TAF) in Healthy Subjects. Study GS-US-342-1326, a Phase I Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between Sofosbuvir/GS-5816 (SOF/GS-5816) Fixed-Dose Combination (FDC) Tablet and HIV Antiretroviral Regimens Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF), Ritonavir-				Sofosbuvir/GS-5815 Fixed Dose Combination (FDC) Tablets and Antiretrovirals Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF; Atripla), Emtricitabine/Riplivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF; Complera), Dolutegravir (DTG; Tivicay) o Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate (EVG/COBI/FTC/TAF) in Healthy Subjects. The recommendation stemming from this study is that no dose adjustment of sofosbuvir/velpatasvir with Eviplera orGenvoya is warranted upon co-administration, and that Atripla should not be co-administered with sofosbuvir/velpatasvir. Study GS-US-342-1326, a Phase I Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between Sofosbuvir/GS-5816 (SOF/GS-5816) Fixed-Dose Combination (FDC) Tablet and HIV Antiretroviral Regimens Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF), Ritonavir-boosted Darunavir (DRV/r) plus Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF), Ritonavir-boosted Atazanavir (ATV/r) plus FTC/TDF, Ritonavir/boosted Lopinavir (LPV/r) plus FTC/TDF or Raltegravir plus FTC/TDF. Results showed that no dose adjustment is recommended. The increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored.

	boosted Darunavir (DRV/r) plus Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF), Ritonavir-boosted Atazanavir (ATV/r) plus FTC/TDF, Ritonavir/boosted Lopinavir (LPV/r) plus FTC/TDF or Raltegravir plus FTC/TDF. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/1010	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 5.2 of the SmPC in order to provide the final results from Study GS-US-320-1615 "A Phase 1, Open-Label, Parallel-Group, Single Dose Study to Evaluate the Pharmacokinetics of Tenofovir Alafenamide (TAF) in Subjects with Normal Hepatic Function and Subjects with Severe Hepatic Impairment". In addition, the Worksharing applicant (WSA) took the opportunity to update section 4.2 of the SmPC for Descovy. The information from the CSR for Study GS-US-320-1615 does not lead to the addition or deletion of a	23/02/2017	24/03/2017	SmPC	Results from Study GS-US-320-1615 showed that no clinically relevant changes in the pharmacokinetics of tenofovir alafenamide or its metabolite tenofovir were observed in patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, total plasma concentrations of tenofovir alafenamide and tenofovir are lower than those seen in subjects with normal hepatic function. When corrected for protein binding, unbound (free) plasma concentrations of tenofovir alafenamide in severe hepatic impairment and normal hepatic function are similar.

	safety concern in the corresponding RMPs. The requested worksharing procedure proposed amendments to the Summary of Product Characteristics. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10514 /201608	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir alafenamide	09/03/2017	n/a		PRAC Recommendation - maintenance
WS/1062	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.8 and 5.1 of the SmPC for Genvoya, Descovy and Odefsey in order to provide long-term efficacy and safety data for HIV-infected, antiretroviral therapy-naive adults with results through 144 weeks of treatment with Genvoya from studies GS-US- 292-0104 and GS-US- 292-0111; two Phase III, randomized, double-blind, multicenter, active-controlled studies to evaluate the safety and efficacy of Genvoya vs Stribild. In addition, the Worksharing applicant (WSA) took the opportunity to make minor administrative corrections to sections 4.4 and 5.1 of the SmPC for Genvoya and Descovy and linguistic amendments in Slovakian, Swedish, Polish, Latvian, Czech and Portuguese.	26/01/2017	24/03/2017	SmPC	Assessment of adverse reactions is based on safety data from across all Phase 2 and 3 studies in which 2,396 patients received Genvoya. The most frequently reported adverse reactions in clinical studies through 144 weeks were nausea (11%), diarrhoea (7%), and headache (6%) (pooled data from Phase 3 clinical studies GS-US-292-0104 and GS-US-292-0111 in 866 treatment-naïve adult patients receiving Genvoya). Cobicistat increases serum creatinine due to inhibition of tubular secretion of creatinine without affecting renal glomerular function. In clinical studies of Genvoya, increases in serum creatinine occurred by Week 2 of treatment and remained stable through 144 weeks. In treatment-naïve patients, a mean change from baseline of 0.04 ± 0.12 mg/dL (3.5 ± 10.6 µmol/L) was observed after 144 weeks of treatment. Mean increases from baseline in the Genvoya group were smaller than in the elvitegravir 150 mg/cobicistat 150 mg/emtricitabine 200 mg/tenofovir

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				disoproxil (as fumarate) 245 mg (E/C/F/TDF) group at Week 144 (difference −0.04, p < 0.001). In studies in treatment naïve patients, increases from baseline were observed in both treatment groups for the fasting lipid parameters total cholesterol, direct low density lipoprotein (LDL) and high density lipoprotein (HDL) cholesterol, and triglycerides at Week 144. The median increase from baseline for those parameters was greater in the Genvoya group compared with the E/C/F/TDF group at Week 144 (p < 0.001 for the difference between treatment groups for fasting total cholesterol, direct LDL and HDL cholesterol, and triglycerides). The median (Q1, Q3) change from baseline in total cholesterol to HDL cholesterol ratio at Week 144 was 0.2 (0.3, 0.7) in the Genvoya group and 0.1 (0.4, 0.6) in the E/C/F/TDF group (p = 0.006 for the difference between treatment groups). In a pooled analysis, genotyping was performed on plasma HIV 1 isolates from antiretroviral-naïve patients receiving Genvoya in Phase 3 studies GS US 292 0104 and GS US 292 0111 with HIV 1 RNA ≥ 400 copies/mL at confirmed virologic failure, Week 144, or time of early study drug discontinuation. Up to Week 144, the development of one or more primary elvitegravir, emtricitabine, or tenofovir alafenamide resistance-associated mutations was observed in HIV 1 isolates from 12 of 22 patients with evaluable genotypic data from paired baseline and Genvoya treatment-failure isolates (12 of 866 patients [1.4%]) compared with 12 of 20 treatment failure isolates from patients with evaluable genotypic data in the E/C/F/TDF treatment group (12 of 867 patients [1.4%]). Of the HIV 1

					isolates from 12 patients with resistance development in the Genvoya group, the mutations that emerged were M184V/I (n = 11) and K65R/N (n = 2) in RT and T66T/A/I/V (n = 2), E92Q (n = 4), Q148Q/R (n = 1) and N155H (n = 2) in integrase. Of the HIV 1 isolates from 12 patients with resistance development in the E/C/F/TDF group, the mutations that emerged were M184V/I (n = 9), K65R/N (n = 4), and L210W (n = 1) in RT and E92Q/V (n = 4), and Q148R (n = 2), and N155H/S (n = 3) in integrase. Most HIV 1 isolates from patients in both treatment groups who developed resistance mutations to elvitegravir developed resistance mutations to both emtricitabine and elvitegravir. In phenotypic analyses of patients in the final resistance analysis population, 7 of 22 patients (32%) had HIV 1 isolates with reduced susceptibility to elvitegravir in the Genvoya group compared with HIV 1 isolates from 7 of 20 patients (35%) in the E/C/F/TDF group, HIV 1 isolates from 8 patients (36%) had reduced susceptibility to emtricitabine in the Genvoya group compared with HIV 1 isolates from 7 patients (35%) in the E/C/F/TDF group. One patient in the Genvoya group (1 of 22 [4.5%]) and 2 patients in the E/C/F/TDF group (2 of 20 [10%]) had reduced susceptibility to tenofovir. Genvoya met the non inferiority criteria demonstrated statistical superiority in achieving HIV 1 RNA < 50 copies/mL when compared to E/C/F/TDF at Week 144. The difference in percentage was 4.2% (95% CI: 0.6% to 7.8%).

					Changes in measures of bone mineral density In studies in treatment naïve patients, Genvoya was associated with smaller reductions in bone mineral density (BMD) compared to E/C/F/TDF as measured by DXA analysis of hip (mean change: −0.8% vs −3.4%, p < 0.001) and lumbar spine (mean change: −0.9% vs −3.0%, p < 0.001) after 144 weeks of treatment. Improvements in BMD were noted at 96 weeks after switching to Genvoya from a TDF-containing regimen compared to maintaining the TDF-containing regimen. In studies in treatment naïve patients, Genvoya was associated with a lower impact on renal safety parameters (as measured after 144 weeks treatment by estimated glomerular filtration rate by Cockcroft Gault method, and urine protein to creatinine ratio and after 96 weeks treatment by urine albumin to creatinine ratio) compared to E/C/F/TDF (see also section 4.4). Through 144 weeks of treatment, no subject discontinued Genvoya due to a treatment emergent renal adverse event compared with 12 subjects who discontinued E/C/F/TDF (p < 0.001).
II/0008/G	This was an application for a group of variations. Update of sections 4.8, 5.1 and 5.2 of the SmPC with 48 weeks data from Study GS-US-366-1216 and Study GS-US-366-1160 in fulfilment of MEA 001 and MEA 002 respectively. Study GS-US-366-1216 is a Phase 3b, Randomized, Double-Blind Switch Study to Evaluate the Safety	26/01/2017	24/03/2017	SmPC, Annex II, Labelling and PL	The Marketing Authorisation Holder has submitted interim 48 weeks study reports for two studies conducted with Odefsey (GS-US-366-1216 and GS-US-366-1160). Sections 4.8 (Undesirable effects) of the SmPC has been updated with information regarding adverse reactions identified through Week 48 in both clinical studies. Sections 5.1 (Pharmacodynamic properties) and 5.2 (Pharmacokinetic properties) of the SmPC have been updated with information from these two studies and with

	and Efficacy of Emtricitabine/Rilpivirine/Tenofovir Alafenamide (FTC/RPV/TAF) Fixed Dose Combination (FDC) in HIV-1 Positive Subjects who are virologically suppressed on Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF) Study GS-US-366-1160 is a Phase 3b, Randomized, Double-Blind Study to Evaluate Switching from a Regimen Consisting of Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF) Fixed Dose Combination (FDC) to Emtricitabine/Rilpivirine/Tenofovir Alafenamide (FTC/RPV/TAF) FDC in virologically-suppressed, HIV-1 Infected Subjects. The Marketing Authorisation Holder took the opportunity to make minor administrative corrections in the SmPC, Annex II and Package Leaflet The requested group of variations proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				the deletion of data from two Eviplera (emtricitabine/rilpivirine/tenofovir disoproxil fumarate) 48 week switch studies (GS-US-264-0106 [switch from a PI-containing regimen to Eviplera] and GS-US-264-0111 [switch from Atripla to Eviplera].
WS/1034	This was an application for a variation following a	15/12/2016	24/03/2017	SmPC	In section 4.5 of the SmPC, the following oral

	worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.5 of the SmPC for Genvoya, Descovy and Odefsey with new information regarding interactions with oral contraceptives norgestimate and ethinyl estradiol, from the final clinical study report (CSR) for Study GS-US-311-1790: "A Phase 1, Randomized, Open Label, Drug Interaction Study Evaluating the Effect of Emtricitabine/Tenofovir Alafenamide Fixed-Dose Combination Tablet or GS-9883 on the Pharmacokinetics of a Representative Hormonal Contraceptive Medication, Norgestimate/Ethinyl Estradiol". C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				contraceptives have been listed as having an interaction with the individual components of Descovy, Genvoya and Odefsey: Norgestimate (0.180/0.215/0.250 mg once daily), ethinylestradiol (0.025 mg once daily). The recommendation concerning their co-administration with Descovy is that no dose adjustment of norgestimate/ethinylestradiol is required. Descovy should be dosed according to the concomitant antiretroviral in line with section 4.2 of the SmPC. The recommendation concerning their co-administration with Odefsey is that no dose adjustment is required. The recommendation concerning the co-administration of a hormonal contraceptive with Genvoya is that caution should be exercised. The hormonal contraceptive should contain at least 30 µg ethinylestradiol and contain norgestimate as the progestagen or patients should use an alternative reliable method of contraception. The long-term effects of substantial increases in progesterone exposure are unknown. The effect of co administration of Genvoya with oral contraceptives containing progestagens other than norgestimate is not known and therefore should be avoided.
IG/0745	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	28/11/2016	n/a		
IG/0725	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	21/10/2016	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
WS/0978	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.8 and 5.1 of the SmPC for Genvoya, Descovy and Odefsey in order to update the safety information of virologically suppressed patients with mild to moderate renal impairment with Week 96 efficacy and safety data from Study GS-US-292-0112 "A Phase 3 Open-label Safety Study of Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Single Tablet Regimen in HIV-1 Positive Patients with Mild to Moderate Renal Impairment". The Package Leaflet and Labelling are updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to update section 4.4 of the SmPC for Genvoya and section 2 of the Package Leaflet with the MITOC class labelling text (EMEA/H/C/xxxx/WS/0792) and to bring the PI for Genvoya and Descovy in line with the latest QRD template version 10. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	24/03/2017	SmPC, Labelling and PL	The safety of emtricitabine and tenofovir alafenamide was evaluated through 96 weeks in an open-label clinical study (GS US 292 0112) in which 248 HIV 1 infected patients who were either treatment-naïve (n = 6) or virologically suppressed (n = 242) with mild to moderate renal impairment (estimated glomerular filtration rate by Cockcroft Gault method [eGFRCG]: 30 69 mL/min) received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet. At Week 96, 88.4% (214/242 patients) maintained HIV 1 RNA < 50 copies/mL after switching to emtricitabine and tenofovir alafenamide given with elvitegravir and cobicistat as a fixed-dose combination tablet. Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for

					any child exposed in utero to nucleos(t)ide analogues, who present with severe clinical findings of unknown etiology, particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV. If you have taken Genvoya during your pregnancy, your doctor may request regular blood tests and other diagnostic tests to monitor the development of your child. In children whose mothers took NRTIs during pregnancy, the benefit from the protection against HIV outweighed the risk of side effects.
IG/0708	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	12/08/2016	n/a		
IG/0711	B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	27/07/2016	n/a		