Descovy

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).

IA/0060/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 - Minor changes to an approved test procedure	11/11/2022	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 starting material/reagent/intermediate for AS - Other variation	10/11/2022	n/a		
II/0057	Submission of the clinical study report and supporting modular summaries for study GS-US-311-1269 'Phase 2/3, Open Label, Multi-Cohort	07/07/2022	n/a		

	Switch Study to Evaluate Emtricitabine/Tenofovir Alafenamide (F/TAF) in HIV 1 Infected Children and Adolescents Virologically Suppressed on a 2 NRTI Containing Regimen' in fulfilment of the milestone for the Category 3 additional pharmacovigilance activity to address the safety concern of Long-term safety information in adolescents (missing information) as detailed in the Descovy EU Risk Management Plan (RMP). The RMP was amended as version 7 in line with this submission and to update the list of safety concerns. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
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		
IB/0052/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release	21/05/2021	n/a		

	arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place 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				
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 concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	20/05/2021	13/06/2022	SmPC and PL	
IG/1396/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	18/05/2021	n/a		

	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				
R/0051	Renewal of the marketing authorisation.	12/11/2020	11/02/2021	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 Descovy in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10515 /202004	Periodic Safety Update EU Single assessment - emtricitabine / tenofovir alafenamide	29/10/2020	n/a		PRAC Recommendation - maintenance
IB/0049	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/06/2020	n/a		
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	11/02/2021	PL	
IG/1236	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	04/05/2020	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IAIN/0047/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	13/03/2020	23/04/2020	SmPC, Labelling and PL	
II/0044	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	27/02/2020	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. 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/10515 /201904	Periodic Safety Update EU Single assessment - emtricitabine / tenofovir alafenamide	31/10/2019	n/a		PRAC Recommendation - maintenance

IG/1125	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	25/06/2019	n/a		
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 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	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 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.

	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				
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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	02/05/2019	23/04/2020	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.
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	18/12/2018	n/a		

	an obsolete parameter)				
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 and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	23/11/2018	n/a		
PSUSA/10515 /201804	Periodic Safety Update EU Single assessment - emtricitabine / tenofovir alafenamide	31/10/2018	n/a		PRAC Recommendation - maintenance
IA/0038	B.II.b.3.a - Change in the manufacturing process of	25/10/2018	n/a		

	the finished or intermediate product - Minor change in the manufacturing process				
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	
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		
T/0030	Transfer of Marketing Authorisation	25/04/2018	28/05/2018	SmPC, Labelling and	

				PL	
IB/0029	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	16/04/2018	n/a		
PSUSA/10515 /201710	Periodic Safety Update EU Single assessment - emtricitabine / 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 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.	22/03/2018	28/05/2018	SmPC	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0025	Update of sections 4.8, 5.1 and 5.2 of the SmPC in order to reflect week 48 results from study GS-US-311-1717, listed as a category 3 study in the RMP; this is a Phase 3b, randomized, double-blind, switch study to evaluate Descovy (F/TAF) in HIV-1 infected subjects who are virologically suppressed on regimens containing abacavir/lamivudine (ABC/3TC). In addition, the Marketing authorisation holder (MAH) took the opportunity to make administrative updates and Minor Linguistic Amendments to the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/01/2018	19/04/2018	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	21/12/2017	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
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		
PSUSA/10515 /201704	Periodic Safety Update EU Single assessment - emtricitabine / tenofovir alafenamide	26/10/2017	n/a		PRAC Recommendation - maintenance
IA/0022	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	17/10/2017	n/a		
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 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).	14/09/2017	19/04/2018	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.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0021	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)	05/09/2017	19/04/2018	SmPC	
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. 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	06/07/2017	19/04/2018	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 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

	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				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.
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	05/05/2017	19/04/2018	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

	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				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.
PSUSA/10515 /201610	Periodic Safety Update EU Single assessment - emtricitabine / tenofovir alafenamide	05/05/2017	n/a		PRAC Recommendation - maintenance
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 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.	21/04/2017	19/04/2018	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 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-342-1167 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-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				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.

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 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	23/02/2017	29/03/2017	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.
II/0013	Update of sections 4.8 and 5.1 of the Summary of Product Characteristics (SmPC) for Descovy with adverse reactions, virological outcomes and	16/02/2017	29/03/2017	SmPC	In a study of virologically suppressed patients switching from emtricitabine/tenofovir disoproxil fumarate (Truvada; FTC/TDF) to Descovy while maintaining the third

	measures of bone mineral density based on 96 week data from Study GS-US-311-1089; this is a Phase 3, randomized,double-blind, multicenter, active-controlled study of virologically suppressed patients switching from emtricitabine/tenofovir disoproxil fumarate to Descovy while maintaining the third antiretroviral agent. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				antiretroviral agent (Study GS US 311 1089), increases from baseline were observed in the fasting lipid parameters total cholesterol, direct low density lipoprotein (LDL) cholesterol and triglycerides in the Descovy arm compared with little change in the FTC/TDF arm ($p \leq 0.009$ for the difference between groups in changes from baseline). There was little change from baseline in median fasting values for high density lipoprotein (HDL) cholesterol and glucose, or in the fasting total cholesterol to HDL cholesterol ratio in either treatment arm at Week 96. None of the changes was considered clinically relevant. Improvements in bone mineral density were noted through 96 weeks after switching to Descovy from a tenofovir disoproxil fumarate (TDF) containing regimen compared to minimal changes with maintaining the TDF containing regimen as measured by dual-energy x-ray absorptiometry (DXA) analysis of hip (mean change from baseline of 1.9% vs 0.3%, $p < 0.001$) and lumbar spine (mean change from baseline of 2.2% vs 0.2%, $p < 0.001$). Virological outcomes through 96 weeks after switching to Descovy from a TDF containing regimen were also presented. The percentage of subjects with HIV-1 RNA < 50 c/mL in the FAS was 94.3% for those who switched to Descovy (+3rd Agent) and 93.0% for those who remained on Truvada (+3rd Agent), 95% CI: −2.5% to 5.1%), indicating non- inferiority at week 48. By week 96, success rates were 88.6% and 89.1%, respectively (95% CI: -5.3% to 4.4%), again indicating non- inferiority. The results of the study are in line with the data generated which supported the initial MAA.

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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/01/2017	29/03/2017	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 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 ($p < 0.001$).
WS/1034	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 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	15/12/2016	29/03/2017	SmPC	In section 4.5 of the SmPC, the following oral 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		
IA/0010	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	28/11/2016	n/a		
IA/0009	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	26/10/2016	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 intermediate used in the manufacture of the AS or manufacturer of a novel excipient	21/10/2016	n/a		
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	15/09/2016	29/03/2017	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.

	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				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.

II/0002	Update of sections 4.2, 4.8 and 5.1 of the SmPC in order to provide additional efficacy and safety data for antiretroviral therapy-naive adults from Studies GS-US-292-0104 and GS-US-292-0111 through 96 weeks of treatment. The Package Leaflet is updated accordingly. The MAH has also taken the opportunity to update the DDI table in Section 4.5 by adding a new footnote and removing another to increase clarity. In addition, the 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	15/09/2016	29/03/2017	SmPC and PL	The MAH has updated section 4.2 of the SmPC to note that there are limited data available regarding the use of Descovy (DVY) in patients with estimated CrCl < 30 mL/min; previously it stated there was no data. The summary of the safety profile in section 4.8 and the pharmacodynamic properties in section 5.1 were further updated to reflect 96 weeks data from clinical studies of treatment-naïve adult patients with Genvoya (GEN). Data from GEN clinical studies presented through 96 weeks of treatment in ART-naive adults in the current submission are consistent with the findings in the original submission. At Week 96, GEN was noninferior to Stribild. The efficacy of GEN in subgroup analyses revealed no meaningful differences in virologic success. The frequency of resistance development in ART-naive subjects taking GEN was acceptably low and comparable to that of the STB group through 96 weeks of treatment. Treatment with GEN continued to be well tolerated, as demonstrated by the incidence of SAEs considered related to study drug, or study drug discontinuation due to AEs. No new ADRs were identified. Based on the demonstrated bioequivalence between FTC/TAF from Genvoya and Descovy these results demonstrate that DVY is beneficial as a chronic treatment for ART-naive subjects.
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		
IB/0001/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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.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 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	22/06/2016	n/a		