



Genvoya

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification ¹ issued on	Commission Decision Issued ² / amended on	Product Information affected ³	Summary
X/0079/G	This was an application for a group of variations. Annex I_2.(c) Change or addition of a new strength/potency C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or	21/07/2022	03/10/2022	SmPC, Labelling 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).



	modification of an approved one				
PSUSA/10449 /202111	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir alafenamide	23/06/2022	12/08/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10449/202111.
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		
WS/2039	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of section 4.5 of the SmPC to add new information about the drug-drug interactions between cobicistat containing products (Genvoya, Tybost and Stribild) and corticosteroids, based on post-marketing data. Furthermore, the MAH took the opportunity to bring the Tybost Product Information in line with version 10.2 of the QRD template and update the list of local representatives. Moreover, minor editorial updates and corrections have been introduced throughout the Product Information of all three products.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	02/09/2021	13/05/2022	SmPC and PL	<p>Given that cobicistat is a strong CYP3A inhibitor and the possibility of systemic absorption of corticosteroids when administered cutaneously, development of Cushing's syndrome and secondary adrenal suppression from concomitant administration of cobicistat-containing products and cutaneously-administered CYP3A-metabolized corticosteroids was considered plausible.</p> <p>For coadministration of cutaneously-administered corticosteroids sensitive to CYP3A inhibition, the treating physician should refer to the prescribing information of the corticosteroid for conditions or uses that augment its systemic absorption.</p>

IG/1431	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	25/08/2021	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		
II/0077	Update of sections 4.8 and 5.1 of the SmPC based on study GS-US-292-0106. This was a phase 2/3, open-label study of pharmacokinetics, safety and antiviral activity in HIV-1 infected antiretroviral treatment-naïve adolescents and virologically suppressed children. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/07/2021	13/05/2022	SmPC	The data presented in the 4th interim clinical study report of the ongoing study GS-US-292-0106 provided an update on the use of Genvoya in the paediatric population. No emergent resistance to Genvoya was detected through Week 48. Based on the data available, the benefit-risk profile of Genvoya remains unchanged. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10449 /202011	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir alafenamide	10/06/2021	n/a		PRAC Recommendation - maintenance
WS/2030	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	20/05/2021	13/05/2022	SmPC and PL	

	<p>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.</p> <p>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).</p> <p>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</p>				
II/0070/G	<p>This was an application for a group of variations.</p> <p>Update of Section 4.5 of the SmPC to include data on the drug-drug interaction between Genvoya and the thienopyridine anti-platelet drugs clopidogrel and prasugrel, based on a MAH cumulative safety review. The Package Leaflet is updated accordingly.</p> <p>Update of Section 4.5 of the SmPC to include data on the drug-drug interaction between Genvoya and medicinal products or oral supplements containing polyvalent cations, based on a MAH cumulative safety review. The Package Leaflet is updated accordingly.</p> <p>In addition, the Marketing Authorisation Holder (MAH) took the opportunity to correct the amount of</p>	20/05/2021	13/05/2022	SmPC and PL	<p>The following information on drug-drug interactions was considered relevant to the prescriber and added to the Product Information:</p> <p>Co-administration of clopidogrel with cobicistat is expected to decrease clopidogrel active metabolite plasma concentrations, which may reduce the antiplatelet activity of clopidogrel. Co-administration of Genvoya with clopidogrel is not recommended.</p> <p>Genvoya is not expected to have a clinically relevant effect on plasma concentrations of the active metabolite of prasugrel. No dose adjustment of prasugrel is required.</p> <p>Elvitegravir plasma concentrations are expected to be lower with antacids, medicinal products or oral supplements</p>

	<p>lactose stated in Section 2 of the SmPC and make minor editorial changes throughout the PI.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				<p>containing polyvalent cations, due to local complexation in the gastrointestinal tract and not to changes in gastric pH. It is recommended to separate Genvoya and administration of antacids, medicinal products or oral supplements containing polyvalent cations by at least 4 hours.</p>
IG/1399	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		
IB/0073/G	<p>This was an application for a group of variations.</p> <p>B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation</p> <p>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)</p>	30/03/2021	13/05/2022	SmPC	
IG/1304	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	02/12/2020	n/a		
IA/0071/G	This was an application for a group of variations.	21/10/2020	n/a		

	<p>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</p> <p>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</p>				
R/0069	Renewal of the marketing authorisation.	23/07/2020	17/09/2020	SmPC, Annex II, Labelling and PL	<p>Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Genvoya in the approved indications remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.</p> <p>The MAH also took the opportunity to update sections 4.3 and 4.5 of the SmPC to add the use of the lipid-modifying agent lomitapide as a contraindication, in order to ensure consistency with other cobicistat containing medicinal products.</p>
PSUSA/10449 /201911	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir alafenamide	11/06/2020	n/a		PRAC Recommendation - maintenance
WS/1746	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	06/02/2020	n/a		

	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data				
WS/1698/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation</p> <p>B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation</p>	23/01/2020	n/a		
PSUSA/10449 /201811	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir alafenamide	29/05/2019	25/07/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s) for PSUSA/10449/201811.
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	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	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

	<p>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.</p> <p>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.</p> <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				<p>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.</p> <p>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.</p>
IG/1090	B.I.b.1.d - Change in the specification parameters	29/05/2019	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)				
IAIN/0063	B.II.f.1.a.1 - Stability of FP - Reduction of the shelf life of the finished product - As packaged for sale	29/05/2019	25/07/2019	SmPC	
WS/1566	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	02/05/2019	25/07/2019	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/1086	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)	25/04/2019	n/a		

WS/1401	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.2, 4.4, 4.6 of the SmPC of Stribild, Tybost and Genvoya and section 5.2 of the SmPC of Genvoya and Stribild based on pharmacokinetics data in pregnancy from IMPAACT study P1026s (ClinicalTrials.gov ID NCT00042289); this is an ongoing, nonrandomized, open-label, parallel-group, multi-centre phase 4 prospective study of antiretroviral (ARV) pharmacokinetics (PK) and safety in HIV-1 infected pregnant women that includes an arm for EVG/COBI.</p> <p>The Package Leaflet is updated accordingly.</p> <p>In addition, the Worksharing applicant (WSA) took the opportunity to bring the PI in line with the latest QRD template version 10.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	28/02/2019	28/03/2019	SmPC and PL	<p>The results from a prospective study (IMPAACT P1026s) showed that treatment with cobicistat and elvitegravir-containing regimens during pregnancy results in lower elvitegravir and cobicistat exposures. Cobicistat levels decrease and may not provide sufficient boosting. The substantial reduction in elvitegravir and darunavir exposure may result in virological failure and an increased risk of mother-to-child transmission of HIV infection. Based on this, the product information for Genvoya, Stribild and Tybost have been updated to recommend that therapy with these therapies should not be initiated during pregnancy, and women who become pregnant during therapy should be switched to an alternative regimen.</p>
IB/0058	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	09/01/2019	n/a		
IG/1009	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting	18/12/2018	n/a		

	material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
WS/1466/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p> <p>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</p>	29/11/2018	n/a		
PSUSA/10449 /201805	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir alafenamide	29/11/2018	n/a		PRAC Recommendation - maintenance
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	23/11/2018	n/a		

	an obsolete parameter)				
IB/0056	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)	06/11/2018	28/03/2019	SmPC	
IG/0918	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	12/10/2018	n/a		
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/0919	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	26/09/2018	n/a		
IG/0983	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/09/2018	28/03/2019	SmPC	
PSUSA/10449 /201711	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir alafenamide	31/05/2018	26/07/2018		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s) for PSUSA/10449/201711.
II/0046	Update of sections 4.8 and 5.1 of the SmPC for Genvoya in order to amend the safety and pharmacodynamic information based on the final results from study Study GS-US-292-1515, listed as a category 3 study in the RMP; this is a Phase 2/3, open-label study to evaluate the safety and efficacy of E/C/F/TAF in HIV-1 infected virologically suppressed adolescents. The MAH also took the opportunity to make administrative updates to Section 4.5 and 5.1 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/06/2018	28/03/2019	SmPC	
WS/1322	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 4.3 and 4.5 of the SmPC for	28/06/2018	28/03/2019	SmPC, Labelling and PL	

	<p>Genvoya, Tybost and Stribild based on data on Drug-drug Interaction between cobicistat containing products and Direct Oral Anticoagulants (DOACs), whereby co-administration of apixaban, rivaroxaban and edoxaban is not recommended, and co-administration with dabigatran etexilate is contraindicated.</p> <p>The Patient Leaflet (PIL) has been updated for all three products as a consequence.</p> <p>The Worksharing MAH has taken this opportunity to introduce some minor administrative amendments throughout the product information, including Annex III, for all three products respectively. Minor linguistic amendments were also made to the following product information:</p> <ul style="list-style-type: none"> - Genvoya: CS, DA, DE, FI, HR, HU, IS, NO, PT and RO languages - Tybost: DA, ES and HU languages - Stribild: DA, DE, ES, FI, FR, IS, LV, MT, NO and RO languages. <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				
T/0045	Transfer of Marketing Authorisation	25/04/2018	07/06/2018	SmPC, Labelling and PL	

WS/1310	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	22/03/2018	07/06/2018	SmPC	
IG/0912/G	<p>This was an application for a group of variations.</p> <p>B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to</p>	20/03/2018	n/a		

	<p>10-fold</p> <p>B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold</p>				
WS/1305	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p>	18/01/2018	n/a		
WS/1234/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>Update of sections 4.4 and 4.5 of the SmPC based on data from Pharmacology Studies GS-US-216-1008 and GS-US-216-4032. Study GS-US-216-1008 is a Phase 1, randomized, fixed-sequence, open-label, single and multiple-dose, multiple-cohort, single-centre study that evaluated the drug interaction potential between darunavir (DRV)+COBI, atazanavir (ATV)+COBI, or Genvoya and the 3 hydroxy-3-methylglutaryl-coenzyme A (HMG CoA) reductase inhibitors rosuvastatin and/or atorvastatin. Study GS-US-216-4032 is an open-label, single-centre, multiple-cohort, fixed sequence, Phase 1 study that evaluated the effect of DRV+COBI or</p>	18/01/2018	07/06/2018	SmPC and PL	

	<p>ATV+COBI on the pharmacokinetic (PK) of a representative hormonal contraceptive medication, drospirenone/ethinyl estradiol.</p> <p>The Package Leaflet is updated accordingly. An administrative update in Section 4.3 of the SmPCs was also made.</p> <p>In addition, the Worksharing applicant (WSA) took the opportunity to make administrative changes to the PI of all three products and update the list of local representatives for Estonia, Latvia and Lithuania for Tybost and Stribild. Minor linguistic amendments were made to the Product Information.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				
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		
II/0026	Extension of Indication for Genvoya to include children aged from 6 years and with body weight at least 25kg for whom alternative regimens are unsuitable due to toxicities, infected with human	09/11/2017	08/12/2017	SmPC and PL	

	<p>immunodeficiency virus-1 (HIV-1) without any known mutations associated with resistance to the integrase inhibitor class, emtricitabine or tenofovir.</p> <p>As a consequence, sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on the analysis of the paediatric study GS-US-292-0106 (Cohort 2) "A Phase 2/3, Open-Label Study of the Pharmacokinetics, Safety, and Antiviral Activity of the Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide (E/C/F/TAF) Single Tablet Regimen (STR) in HIV-1 Infected Antiretroviral Treatment Naive Adolescents and Virologically Suppressed Children". In addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0. The Package Leaflet and the Risk Management Plan (v. 3.2) are updated in accordance.</p> <p>The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP on variation to the terms of the marketing authorisation.</p> <p>C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one</p>				
PSUSA/10449 /201705	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir alafenamide	30/11/2017	n/a		PRAC Recommendation - maintenance

IG/0861	B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	17/11/2017	n/a		
WS/1205	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>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).</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	14/09/2017	08/12/2017	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.
IG/0833/G	<p>This was an application for a group of variations.</p> <p>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</p>	08/09/2017	n/a		

	<p>manufacturer of a novel excipient</p> <p>B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -</p> <p>Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place</p>				
IG/0799	<p>B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -</p> <p>Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place</p>	14/07/2017	n/a		
WS/1136	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>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</p>	06/07/2017	08/12/2017	SmPC and PL	<p>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).</p> <p>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 cells/mm³. Ninety two percent (66/72 patients) had HBV DNA < 29 IU/mL using missing = failure analysis at Week</p>

	<p>Leaflet.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				<p>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 \geq 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.</p> <p>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 mono-infection.</p>
PSUSA/10449 /201611	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir alafenamide	09/06/2017	n/a		PRAC Recommendation - maintenance
IA/0032	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	10/05/2017	n/a		
WS/1152	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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</p>	05/05/2017	08/12/2017	SmPC and PL	<p>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</p>

	<p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				<p>moderate renal impairment (estimated glomerular filtration rate by Cockcroft Gault method [eGFR_{CG}]: 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.</p>
WS/1133/G	<p>This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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.</p> <p>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</p>	21/04/2017	08/12/2017	SmPC and PL	<p>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).</p> <p>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/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF; Complera), Dolutegravir (DTG; Tivicay) or 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</p>

<p>accordingly.</p> <p>Administrative update of section 4.8 of the SmPC for Viread, Atripla, Eviplera and Stribild.</p> <p>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/Rilpivirine/Tenofovir Disoproxil Fumarate (FTC/ RPV/TDF; Complera), Dolutegravir (DTG; Tivicay) o Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate (EVG/COBI/FTC/TAF) in Healthy Subjects.</p> <p>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.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>				<p>orGenvoya is warranted upon co-administration, and that Atripla should not be co-administered with sofosbuvir/velpatasvir.</p> <p>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.</p>
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	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/1010	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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".</p> <p>In addition, the Worksharing applicant (WSA) took the opportunity to update section 4.2 of the SmPC for Descovy.</p> <p>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.</p> <p>The requested worksharing procedure proposed amendments to the Summary of Product Characteristics.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	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.

IB/0028	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	03/02/2017	n/a		
WS/1027	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	02/02/2017	n/a		
WS/1093	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	26/01/2017	24/03/2017	SmPC, Annex II, Labelling and PL	
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-naïve 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,	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

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

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 μ mol/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	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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".</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	15/12/2016	16/02/2017	SmPC	<p>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).</p> <p>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.</p> <p>The recommendation concerning their co-administration with Odefsey is that no dose adjustment is required.</p> <p>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.</p> <p>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.</p>
PSUSA/10449 /201605	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir alafenamide	01/12/2016	n/a		PRAC Recommendation - maintenance
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	28/11/2016	n/a		

	batch control/testing takes place				
WS/1021	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation</p>	17/11/2016	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 intermediate used in the manufacture of the AS or manufacturer of a novel excipient	21/10/2016	n/a		
IA/0020/G	<p>This was an application for a group of variations.</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p>	15/09/2016	n/a		

	<p>the finished or intermediate product - Minor change in the manufacturing process</p> <p>B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process</p>				
WS/0978	<p>This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.</p> <p>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".</p> <p>The Package Leaflet and Labelling are updated accordingly.</p> <p>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 (EMA/H/C/xxxx/WS/0792) and to bring the PI for Genvoya and Descovy in line with the latest QRD template version 10.</p>	15/09/2016	16/02/2017	SmPC, Labelling and PL	<p>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 [eGFR_{CG}]: 30-69 mL/min) received emtricitabine and tenofovir alafenamide in combination with elvitegravir and cobicistat as a fixed-dose combination tablet.</p> <p>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.</p> <p>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</p>

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				(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/0014	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	04/08/2016	16/02/2017	SmPC and PL	
IB/0013/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	21/06/2016	n/a		

II/0011	<p>Update of SmPC sections 4.8 and 5.1 in order to include efficacy and safety data in antiretroviral naïve adolescents (Cohort 1) evaluated through 48 weeks in Study GS-US-292-0106. In addition, the MAH took the opportunity to make editorial changes in section 4.5 of the SmPC and to update the contact details of the local representatives in Czech Republic and Slovakia in the Package Leaflet.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	19/05/2016	16/02/2017	SmPC and PL	The 48-week adolescent data provided as part of this application are in line with the 24-week results already reflected in the SmPC.
IG/0677	<p>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</p>	25/04/2016	n/a		
IB/0006	<p>C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation</p>	22/02/2016	16/02/2017	SmPC and PL	
II/0001	<p>Update of sections 4.2, 4.8 and 5.1 of the SmPC with additional efficacy and safety interim data from studies GS-US-292-0104 and GS-US-292-0111 through 96 weeks of treatment.</p> <p>C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data</p>	11/02/2016	16/02/2017	SmPC	

IA/0010	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	10/02/2016	n/a		
IA/0009	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	08/02/2016	n/a		
IA/0008	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	08/02/2016	n/a		
IA/0007	B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method	28/01/2016	n/a		
IA/0005	A.7 - Administrative change - Deletion of manufacturing sites	28/01/2016	n/a		
IB/0004/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.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	06/01/2016	n/a		

	<p>batch control/testing takes place</p> <p>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</p> <p>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</p> <p>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</p>				
IB/0003	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	17/12/2015	n/a		
IA/0002	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	10/12/2015	n/a		