Stribild

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
WS/2320	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update Annex II and the RMP for Truvada and Stribild to version 19.0 and 15.0 to remove of the	12/01/2023		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).

	paediatric additional Risk Minimisation Measures (aRMMs) for HIV indication. In addition, the MAH took the opportunity to introduce changes to the PI. 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				
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	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 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	02/09/2021	15/09/2022	SmPC and PL	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. 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.

	introduced throughout the Product Information of all three products. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
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		
PSUSA/10082 /202008	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir disoproxil	25/03/2021	19/05/2021		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10082/202008.
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		
IG/1243	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder	25/05/2020	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				
II/0111/G	This was an application for a group of variations. - C.I.4 (Type II): Update of Section 4.5 of the SmPC to include data on the drug-drug interaction between Stribild and the thienopyridine anti-platelet drugs clopidogrel and prasugrel, based on a MAH cumulative safety review. The Package Leaflet is updated accordingly. - C.I.4 (Type II): Update of Section 4.5 of the SmPC to include data on the drug-drug interaction between Stribild and medicinal products or oral supplements containing polyvalent cations, based on a MAH cumulative safety review. The Package Leaflet is updated accordingly. - C.I.3.z (Type IBz): Update of Sections 4.5 and 4.8 of the SmPC to implement information related to the interaction with didanosine, and Section 4.8 of the SmPC to implement new wording regarding lactic acidosis, in line with the PRAC recommendation from EMEA/H/C/PSUSA/00002892/201903. 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	14/05/2020	19/05/2021	SmPC, Annex II and PL	

	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				
IG/1236	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	04/05/2020	n/a		
PSUSA/10082 /201908	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir disoproxil	12/03/2020	n/a		PRAC Recommendation - maintenance
WS/1698/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.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	23/01/2020	n/a		
IG/1090	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting	29/05/2019	n/a		

	material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
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	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4, 4.6 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. The Package Leaflet is updated accordingly. In addition, the Worksharing applicant (WSA) took the opportunity to bring the PI in line with the latest QRD template version 10.	28/02/2019	08/04/2019	SmPC and PL	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.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10082 /201808	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir disoproxil	14/03/2019	n/a		PRAC Recommendation - maintenance
WS/1492	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	13/12/2018	08/04/2019	SmPC, Labelling and PL	
IB/0103	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/12/2018	08/04/2019	Annex II	
II/0097	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/12/2018	n/a		
WS/1466/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or	29/11/2018	n/a		

	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				
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		
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/1447	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	08/04/2019	SmPC	
IG/0974	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)	07/09/2018	n/a		
IB/0095	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	19/07/2018	n/a		
WS/1351	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 and 4.5 of the SmPC for Viread, Truvada and Stribild and Section 4.5 of the SmPC for Eviplera in order to add the results from study Study GS-US-367-1657, listed as a category 3 study in the RMP; this is a Phase 1 Multiple Dose Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between Sofosbuvir/Velpatasvir/Voxilaprevir Fixed-Dose Combination and HIV Antiretroviral in Healthy	19/07/2018	08/04/2019	SmPC and PL	Results from Study GS-US-367-1657 showed that co administration of tenofovir disoproxil with sofosbuvir/velpatasvir/voxilaprevir and darunavir/ritonavir increases plasma concentrations of tenofovir and may lead to adverse reactions related to tenofovir disoproxil. The combination of tenofovir disoproxil containing products (Viread, Truvada, Eviplera, Stribild) and sofosbuvir/velpatasvir/voxilaprevir should be used with caution and frequently renally monitored.

	Subjects. The corresponding section 2 of the Package Leaflet for Viread, Truvada and Stribild has been updated. In addition, the Worksharing applicant (WSA) took the opportunity to implement minor linguistic amendments (MLAs) to the following translations: -Viread: CZ, DA, DE, ES, FI, FR, HR, HU, IS, LV, MT, NO, PT, SK, SL, SV -Truvada: CZ, DE, ES, FR, MT, NL, PT -Eviplera: DE, MT, NO -Stribild: CZ, DA, DE, ES, ET, FI, FR, HU, IT, MT, NO, PL, SK, SV. Furthermore, the WSA took the opportunity to align the text related to 'pregnancy outcomes' in Section 4.6 of the SmPC for Truvada, Stribild and Viread with the currently approved text in the Eviplera SmPC and to replace 'tenofovir disoproxil fumarate' with 'tenofovir disoproxil' throughout the Product Information for all the products concerned. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
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	08/04/2019	SmPC, Labelling and PL	

	Genvoya, Tybost and Stribild based on data on Drug-drug Interaction between cobicistat containing products and Direct Oral Anticoagulants (DOACs), whereby co-admistration of apixaban, rivaroxaban and edoxaban is not recommended, and co-administration with dabigatran etexilate is contraindicated. The Patient Leaflet (PIL) has been updated for all three products as a consequence. 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: - 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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0087	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/06/2018	n/a		

T/0093	Transfer of Marketing Authorisation	25/04/2018	04/06/2018	SmPC, Labelling and PL	
PSUSA/10082 /201708	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir disoproxil	22/03/2018	22/05/2018	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10082/201708.
R/0086	Renewal of the marketing authorisation.	22/02/2018	19/04/2018	SmPC, Labelling and PL	
IG/0912/G	This was an application for a group of variations. B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold	20/03/2018	n/a		
WS/1234/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. 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-	18/01/2018	19/04/2018	SmPC and PL	

	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 ATV+COBI on the pharmacokinetic (PK) of a representative hormonal contraceptive medication, drospirenone/ethinyl estradiol. The Package Leaflet is updated accordingly. An administrative update in Section 4.3 of the SmPCs was also made. 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. 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				
IG/0845	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	18/12/2017	n/a		

	of the AS				
II/0079	Extension of Indication to include the treatment of HIV 1 infection in adolescents aged 12 to <18 years weighing ≥ 35 kg without known mutations associated with resistance to any of the three antiretroviral agents in Stribild, and who have experienced toxicities which preclude the use of other regimens that do not contain tenofovir disoproxil fumarate (TDF); as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated based on pharmacokinetics, safety and efficacy data through 48 weeks of treatment with Stribild in Study GS-US-236-0112. The Package Leaflet, Annex II and Risk Management Plan (v.12.1) are updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor linguistic amendments. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	14/09/2017	19/10/2017	SmPC, Annex II and PL	
II/0083	Update of sections 4.5 of the Stribild SmPC in order to reflect that no drug-drug interaction data was identified between its components elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide and sertraline, from Study GS-US-292-1316; this is a Phase 1, open-label, fixed sequence study evaluating	14/09/2017	19/10/2017	SmPC	Results from the drug interaction study GS0US029201216 showed that no clinically significant drug interactions have been either observed or are expected between the components of Stribild (elvitegravir, cobicistat, emtricitabine, tenofovir alafenamide) and sertraline.

	the pharmacokinetics and drug interaction potential between elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide single-table regimen and sertraline in healthy subjects. In addition, the Marketing authorisation holder (MAH) took the opportunity make administrative amendments to section 4.8 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/0833/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.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	08/09/2017	n/a		
IG/0800	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	18/07/2017	n/a		

	batch control/testing takes place				
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/1086	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from Study GS-US-236-0140 listed as a category 3 study in the Risk Management Plan. This is a randomized, open-label, phase IV study evaluating the renal effect of Elvitegravir/ Cobicistat/ Emtricitabine/Tenofovir DF or other Tenofovir DF-containing Regimens (Ritonavir-boosted Atazanavir plus Emtricitabine /Tenofovir DF or Efavirenz /Emtricitabine/Tenofovir DF) compared to Ritonavir-boosted Atazanavir plus Abacavir/ Lamivudine in Antiretroviral Treatment-naïve HIV-1 Infected Adults with estimated glomerular filtration rate (eGFR) ≥70 mL/min. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/05/2017	n/a		The marketing authorisation holder presented the results of study GS-US-236-0140 which was conducted to provide information on renal function and markers of renal tubular function to address the safety concern of renal toxicity associated with tenofovir/disoproxil fumarate (TDF).The primary objective was to evaluate the effect of Stribild and other TDF-containing regimens on renal function, as assessed by markers of glomerular filtration rate (GFR) in HIV-infected treatment-naïve adults with estimated GFR (eGFR) calculated using the Cockcroft-Gault equation (eGFRCG) ≥ 70 mL/min. The results demonstrated that TDF-containing regimens administered as STB, TVD plus ATV/r, or ATR do not affect renal function as demonstrated by no effect in aGFR for up to 24 weeks in HIV-infected subjects. The results from Study GS-US-236-0140 also demonstrated that COBI does not affect the actual glomerular filtration rate and only affects the estimated glomerular filtration rate due to inhibition of MATE1 transporter-mediated secretion of creatinine in the proximal tubules. Given these effects, the decreases in mean values seen for estimated glomerular filtration rates calculated using the Cockcroft-Gault equation or the modification of diet in renal disease

					equation for COBI- and RTV-containing regimens were not considered clinically meaningful. In addition, there were no clinically relevant changes in markers of renal tubular functions (serum and urine creatinine, urine albumin, urine protein, urine β2-microglubulin, and urine RBP) for any of the treatment groups. Overall, the pharmacokinetic results were consistent with historical data for the respective treatments. All 4 study treatments were generally well tolerated and the safety profiles were as expected for these well characterized regimens, with no new safety findings reported. Based on these results no change to the product information was warranted.
WS/1113	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	11/05/2017	n/a		
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	21/04/2017	19/10/2017	SmPC and PL	The Marketing Authorisation Holder has submitted the results from Study GS-US-342-1167 and Study GS-US-342-1326 to update the Product Information for tenofovir disoproxil fumarate (TDF)-containing products (Viread, Truvada, Atripla, Eviplera and Stribild) and tenofovir alafenamide (TAF)-containing products (Genvoya, Descovy, Odefsey). Study GS-US-342-1167 is a Phase I Study to Evaluate the Pharmacokinetic Drug-Drug Interactions between Sofosbuvir/GS-5815 Fixed Dose Combination (FDC) Tablets

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

	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				
PSUSA/10082 /201608	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir disoproxil	09/03/2017	n/a		PRAC Recommendation - maintenance
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	26/01/2017	19/10/2017	SmPC, Annex II, Labelling and PL	

	Veterinary Medicinal Products - Other variation				
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		
WS/1021	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	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		
IG/0726	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	19/09/2016	n/a		
WS/0963	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	15/09/2016	06/02/2017	SmPC, Labelling and PL	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IB/0068	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/08/2016	n/a		
IG/0677	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	25/04/2016	n/a		
IG/0671	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	14/04/2016	n/a		
WS/0837	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final clinical study report (CSR) for Study GS-US-236-0118 (phase 3 open-label safety study of cobicistat-containing highly active antiretroviral regimens in HIV-1 infected patients with mild to moderate renal impairment) to fulfil a post authorisation MEA (additional pharmacovigilance activity, category 3). The MAH updated section 4.8 of the Summary of Product Characteristics with additional data on week 96 of study clinical study	01/04/2016	06/02/2017	SmPC and PL	The MAH submitted the final clinical study report (CSR) for Study GS-US-236-0118 (phase 3 open-label safety study of cobicistat-containing highly active antiretroviral regimens in HIV-1 infected patients with mild to moderate renal impairment) to fulfil a post authorisation MEA (additional pharmacovigilance activity, category 3). The main focus of this was on providing an evaluation of the effect of cobicistat on the renal parameters for a sample of 106 subjects exposed to cobicistat containing therapies over this period. The worksharing procedure leads to amendments of Tybost PI.

	(GS-US-236-0118). In addition the MAH took the opportunity to update details of some local representatives in the Package leaflet and correct minor linguistic amendments in Section 4.4 of the Swedish SmPC for Tybost. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0054	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	06/02/2017	SmPC, Annex II and PL	
WS/0792	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 4.4 of the SmPC in order to revise the HIV class label wording on mitochondrial dysfunction following the review of existing data on mitochondrial toxicity including the Mitochondrial Toxicity in Children (MITOC) Study. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	06/02/2017	SmPC and PL	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, that 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.
IB/0063/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	31/03/2016	n/a		
IA/0065	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	29/03/2016	n/a		
PSUSA/10082 /201508	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir disoproxil	17/03/2016	n/a		PRAC Recommendation - maintenance
II/0062	Update of section 4.5 of the SmPC, upon request by the CHMP/PRAC following the assessment of PSUSA/00010082/201502, with carbamazepine drug-drug interaction data from Study GS-US-216-0137. Further, section 5.1 of the SmPC has been updated to include further information regarding primary and secondary mutations based on in vitro data. In addition, the MAH took the opportunity to	25/02/2016	06/02/2017	SmPC, Labelling and PL	Co administration of carbamazepine, a potent CYP3A inducer, may significantly decrease cobicistat and elvitegravir plasma concentrations, which may result in loss of therapeutic effect and development of resistance. Primary mutations for raltegravir/elvitegravir do not affect the in vitro susceptibility of dolutegravir as single mutations, and the additional presence of secondary mutations (except Q148) also does not result in relevant

	implement minor editorial changes in the labelling and the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				fold changes in experiments with site directed mutants.
IG/0651	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	28/01/2016	n/a		
WS/0884	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	28/01/2016	06/02/2017	SmPC and PL	
II/0056/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/12/2015	n/a		
WS/0731	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	17/12/2015	24/02/2016	SmPC	

	Submission of the final clinical study report for Viread study GS-US-104-0423 "A Phase 4 Cross-Sectional Study of Bone Mineral Density in HIV-1 Infected Subjects" in fulfilment of a post-authorisation measure (PAM) for Viread, Truvada, Eviplera, Stribild and Atripla (category 3 additional pharmacovigilance activity for Viread, Truvada, Eviplera and Stribild, and category 4 for Atripla). An updated RMP (version 18.0 for Viread, 9.0 for Truvada, 13.0 for Atripla, 9.0 for Eviplera and 6.0 for Stribild) is agreed accordingly. Following the review and assessment of the data provided, section 4.4 of the SmPC was updated to add a warning regarding the more pronounced decreases in Bone Mineral Density seen in patients treated with TDF as part of boosted PI therapy. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IG/0616	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	03/11/2015	n/a		
IG/0622	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	30/10/2015	n/a		
IG/0613	B.I.d.1.c - Stability of AS - Change in the re-test	14/10/2015	n/a		

	period/storage period or storage conditions - Change to an approved stability protocol				
PSUSA/10082 /201502	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir disoproxil	10/09/2015	n/a		PRAC Recommendation - maintenance
IG/0600	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	18/08/2015	n/a		
IG/0599	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	12/08/2015	n/a		
IG/0595	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	04/08/2015	n/a		
IB/0050	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/07/2015	n/a		
IG/0583	A.7 - Administrative change - Deletion of manufacturing sites	23/07/2015	n/a		
IG/0572	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/06/2015	24/02/2016	SmPC and PL	

WS/0726/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.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.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 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 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	21/05/2015	n/a		
IG/0553	A.4 - Administrative change - Change in the name	07/05/2015	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				
WS/0719	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	23/04/2015	n/a		
PSUSA/10082 /201408	Periodic Safety Update EU Single assessment - cobicistat / elvitegravir / emtricitabine / tenofovir disoproxil	12/03/2015	n/a		PRAC Recommendation - maintenance
IB/0042/G	This was an application for a group of variations. To change the due date for study GU-US-236-0102 from Q1 to Q3 2015 in the RMP. The MAH also updated the milestone for provision of the reports on the Antiretroviral Pregnancy registry to include it in the PSUR submission as requested by the CHMP. C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority	08/03/2015	n/a		

	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IG/0521	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	26/02/2015	24/02/2016	Annex II and PL	
II/0039	Submission of the final study report of GS-US-183-1004 "A Phase 1, Multiple-Dose Study to Evaluate the Pharmacokinetics of Cobicistat-Boosted Elvitegravir in Subjects with Decreased UGT1A1 Activity" in fulfilling Stribild Post-Authorisation Measure (PAM) MEA 001 (a Category 3 additional pharmacovigilance activity in the Stribild Risk Management Plan [RMP]). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		
II/0036/G	This was an application for a group of variations. 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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	18/12/2014	n/a		

	authorisation, including the RMP - Other variation C.I.11.a - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of wording agreed by the competent authority				
IG/0479	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	17/09/2014	n/a		
PSUV/0029	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
IG/0469	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	07/08/2014	n/a		
WS/0586	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. WSA for Atripla, Truvada, Stribild, Viread and Eviplera to update sections 4.4 and 4.8 of the SmPC for all tenofovir disoproxil fumarate (TDF)-containing products to revise the renal monitoring recommendations and to implement additional renal safety information. The Package Leaflet was updated accordingly and the key messages for the annex II for Viread and Atripla were updated to reflect this information as appropriate. The MAH submitted this variation in fulfilment of a post-autorisation measure	24/07/2014	09/09/2014	SmPC, Annex II and PL	In fulfilment of a CHMP request for Viread pertaining to the reversibility of TDF associated renal tubulopathy, the MAH has submitted a worksharing variation to implementing renal safety information in the SmPC of all the TDF-containing products. The main messages on renal safety are the following: to differentiate the monitoring depending on the presence of renal risk factors (reinforced monitoring) or not (standard monitoring); to consider interruption of treatment with tenofovir disoproxil fumarate in case of progressive decline of renal function when no other cause has been identified; to reflect the impact of the NSAIDs and boosted PIs in renal function and to inform prescribers that in some patients, renal function did not completely resolve despite tenofovir disoproxil fumarate

	for Viread on the reversibility of TDF associated renal tubulopathy. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				discontinuation.
WS/0567	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final study report for Study PC-183-2030 to investigate the effect of elvitegravir on human gut flora to address a recommendation C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/07/2014	n/a		Results of study PC-183-2030 show that elvitegravir, at concentrations of up to 8 µg/mL, does not possess anti-bacterial activity against the range of organisms studied.
WS/0575	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 4.4 of the SmPC in order to update the safety information on the risk of renal injury in patients with risk factors for renal dysfunction after co-administration of non-steroidal anti-inflamatory drugs (NSAIDs) with tenofovir, following a cumulative review requested by PRAC. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to bring	24/07/2014	09/09/2014	SmPC, Labelling and PL	Available data from spontaneous cases and the literature suggest that the co-administration of non-steroidal anti-inflammatory drugs (NSAIDs) with tenofovir may expose patients to a higher risk of renal injury, especially if they present additional risk factors for renal impairment. In this worksharing procedure the MAH has updated section 4.4 of the SmPC and section 2 of the PL for Viread, Truvada, Atripla, Eviplera and Stribild to include a specific warning in patients with risk factors for renal dysfunction, following a cumulative review requested by PRAC.

	the PI of Truvada in line with the latest QRD template version 9. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IG/0447	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	04/07/2014	n/a		
IG/0448	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	02/07/2014	n/a		
II/0025	Update of sections 4.8 and 5.1 of the SmPC with interim (48 week) safety, efficacy and resistance data from three antiretroviral regimen switch studies of virologically-suppressed patients. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/05/2014	09/09/2014	SmPC	The MAH presented results at week 48 for three studies GS-US-236-0115, GS-US-236-0121 and GS-US-236-0123 in which virologically suppressed, HIV-1 infected adult patients were switched from protease inhibitor (PI)-, non-nucleoside reverse transcriptase inhibitor (NNRTI)-, and INSTI (raltegravir)-based regimens, respectively to Stribild. The results of the three studies show that subjects already virologically supressed on their regimen remained supressed on switching to Stribild. Subjects that stayed on their baseline regimen also remained virogically supressed. The efficacy of switching to Stribild was non-inferior to the efficacy observed in patients who stayed on their baseline regimen. The emergence of virogical failure at week 48 was low and similar in both groups. No treatment-emergent HIV-1 drug

					resistance developed in any treatment group. No new or significant safety concerns were identified during the conduct of the three studies.
PSUV/0018	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
IG/0422	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	28/03/2014	n/a		
IB/0024	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)	27/03/2014	09/09/2014	SmPC	
WS/0530	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 4.4 "Special warnings and precautions for use" of the SmPC for Atripla, Emtriva, Eviplera, Stribild, Truvada, Viread and Vitekta to revise the wording regarding the risk of sexual transmission of HIV infection following CHMP request adopted in December 2013. The PL has been updated accordingly. Furthermore, the MAH took the opportunity of this worksharing to update the PL with the details of the local representatives for Croatia and to introduce the Croatian language annexes for Emtriva and to update the bottle label to include the EDQM short standard term for the pharmaceutical form for Stribild.	20/03/2014	09/09/2014	SmPC, Labelling and PL	During recent years conclusive evidence has been collected which shows that the risk for HIV patients, who are well treated, to sexually transmit HIV to their partner is exceedingly low. A position statement on the use of antiretroviral therapy to reduce HIV transmission was published by the British HIV Association (BHIVA) in January 2013. As a consequence, the recommendations for post-exposure prophylaxis have also been changed in recently updated HIV treatment guidelines. For example, the 2013 BHIVA guideline does not generally recommend post-exposure prophylaxis (PEP) after exposure from a patient with well treated HIV. Based on these data, the wording on the risk of transmission for HIV products was revised to reflect the current scientific knowledge. While effective suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				transmission should be taken in accordance with national guidelines.
WS/0484	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Worksharing procedure to update of section 4.5 of the SmPC of Stribild, Tybost and Vitekta based on a phase 1 study evaluating the drug interaction potential between telaprevir (TVR) and elvitegravir/cobicistat/emtricitabine/tenofovir disoproxil fumarate single tablet regimen and between telaprevir and ritonavir-boosted atazanavir plus elvitegravir. . This study was conducted in fulfilment of MEA009 for Tybost. The PL is updated accordingly as relevant. Furthermore the MAH took the opportunity to revise section 6.1 of the SmPC list of excipients, to update the designation of the excipients. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	09/09/2014	SmPC and PL	Study GS-US-236-0135, is a Phase I study in healthy subjects that evaluated the drug-drug interaction potential of the HCV protease inhibitor telaprevir with the fixed dose combination tablet Stribild (elvitegravir/cobicistat/emtricitabine/tenofovir DF) and with Vitekta 85mg (elvitegravir) and atazanavir boosted by ritonavir. The study results did not indicate clinically significant interactions between telaprevir and Stribild nor between telaprevir and elvitegravir (with atazanavir/ritonavir). Section 4.5 of the SmPCs (and corresponding sections of the PLs) were updated to state that no dose adjustments are required when Stribild or Tybost are administered with telaprevir, nor when Vitekta is administered with ritonavir-boosted atazanavir plus telaprevir. The most frequently reported adverse events reported in the study were in line with the safety profiles of the drugs administered and no new safety concerns were identified.
WS/0488/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.	20/02/2014	n/a		

	This was an application for a group of variations. To add an alternative site responsible for the manufacture of a starting material used in the synthesis of the elvitegravir active substance. To add an alternative site responsible for the manufacture of a starting material used in the synthesis of the elvitegravir active substance. 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.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
II/0019	Update of sections 4.4, 4.8 and 5.1 of the SmPC based on 144 weeks data from the pivotal studies GS-US-236-0102 and GS-US-236-0103. The MAH took the opportunity of this variation to update the PL to position 'depression' in the uncommon side effects list in line with the correct order of decreasing seriousness as per the SmPC section 4.8. Additionally the MAH proposed minor linguistic amendments to the Croatian language Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	20/02/2014	09/09/2014	SmPC and PL	144 weeks data from the pivotal studies GS-US-236-0102 and GS-US-236-0103 showed that after 144 weeks of treatment the viral suppression was maintained. The 144 weeks data on renal and bone effects were consistent with the known safety profile of Stribild.

	data				
WS/0483	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Worksharing application consisting of the submission of the results for study PC-236-2013 which assessed the effect of cobicistat, elvitegravir, emtricitabine on the in vitro cytotoxicity of tenofovir in 293T human embryonic kidney cells transiently expressing OAT1 and MRP4. This study was performed in fulfilment of post authorisation measures for Stribild and Tybost. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/01/2014	n/a		In fulfilment of post authorisation measures, study PC-236-2013 was conducted to assess the effect of the components of Stribild (emtricitabine, elvitegravir and cobicistat) / Tybost (cobicistat) on the in vitro cytotoxicity of tenofovir in HEK293T cells transiently expressing OAT1 and MRP4. These data indicate that the components of Stribild / Tybost are not likely to directly affect the toxicity of tenofovir in renal cells and tissues expressing renal transporters relevant for its active tubular secretion. No update of the product information for Stribild / Tybost is needed in the view of these data.
WS/0451/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. Group of 5 type IB and 2 type IA variations: - I.B.a.1.z) to introduce an additional manufacturing, packaging, and batch release testing site for the cobicistat active substance. - I.B.a.1.z) to introduce an additional site of manufacturing of an intermediate of cobicistat. - I.B.a.1.z) to introduce an additional site of manufacturing of an intermediate of cobicistat.	18/12/2013	n/a		

	- I.B.a.1.z) to introduce an additional starting material supplier for cobicistat. - I.B.a.1.z) to introduce an additional starting material supplier for cobicistat. - A.4) to correct the name and address of a starting material supplier. - A.4) to correct the name and address of a starting material supplier. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or				

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
WS/0398	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To introduce a minor change to the manufacturing process of tenofovir disoproxil fumarate (TDF) active substance. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	18/12/2013	n/a		
IA/0017	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	13/12/2013	n/a		
IG/0378	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	29/11/2013	n/a		
IG/0368	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/11/2013	n/a		
WS/0422	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	24/10/2013	n/a		

	This is a type IB variation application following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008, to introduce an alternative manufacturer and release testing site of the active substance emtricitabine. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IA/0013	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	22/10/2013	n/a		
IAIN/0009	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	02/10/2013	n/a		
II/0006	Update of SmPC sections 4.4, 4.8 and 5.1 with interim 96 weeks data from extension of the two pivotal phase III studies. The Package Leaflet has been updated accordingly. In addition, the SmPC, Annex II and Package leaflet have been brought in line with the latest QRD template version, minor editorial changes have been made in the SmPC, details of the local representative for Croatia have been included in the PL and corrections have been made in Finnish and Swedish translations of the PI. C.I.4 - Variations related to significant modifications	19/09/2013	09/09/2014	SmPC, Annex II and PL	Interim week 96 results from the two pivotal phase III studies have been provided and assessed. The results did not reveal any important efficacy or safety differences from previously assessed week 48 results. Main results at week 96 regarding virologic outcomes, CD4 cell counts and resistance analyses have been included in the SmPC. The frequency groups of adverse reactions and data regarding adverse renal and bone effects have also been updated.

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IAIN/0005	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/07/2013	n/a		
IB/0003	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	12/07/2013	n/a		
IB/0001/G	This was an application for a group of variations. B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the	09/07/2013	n/a		

	manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions				
IB/0004	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	26/06/2013	n/a		
IA/0002	A.7 - Administrative change - Deletion of manufacturing sites	14/06/2013	n/a		