Tybost

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0064	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/02/2023		SmPC, Labelling and PL	
IG/1502	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	04/04/2022	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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		
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/09/2021	21/09/2022	PL	
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 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	02/09/2021	21/09/2022	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.
IG/1431	A.4 - Administrative change - Change in the name	25/08/2021	n/a		

	and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
PSUSA/10081 /202008	Periodic Safety Update EU Single assessment - cobicistat	11/03/2021	n/a		PRAC Recommendation - maintenance
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		
PSUSA/10081 /201908	Periodic Safety Update EU Single assessment - cobicistat	26/03/2020	20/05/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10081/201908.
II/0054	Update of sections 4.4 and 4.5 of the SmPC in order to add information regarding drug-drug interactions between cobicistat -containing products and thienopyridines and potential for lower exposures of active metabolites of drugs that rely on CYP3A for transformation of prodrug to active metabolite. The proposed addition is based on a cumulative safety review conducted by MAH and related to the Pharmacovigilance Risk Assessment Committee recommendation dated June 2019 with regards to the interaction of clopidogrel with boosted antiviral HIV therapy leading to insufficient inhibition of platelet aggregation. The section 2 of the Package Leaflet is updated accordingly.	14/05/2020	10/05/2021	SmPC and PL	The marketing authorisation holder presented results from a cumulative safety review following the Pharmacovigilance Risk Assessment Committee recommendation dated June 2019 with regards to the interaction of clopidogrel with boosted antiviral HIV therapy leading to insufficient inhibition of platelet aggregation. Based on this, the product information has been updated to highlight the drug-drug interactions between cobicistat-containing products and thienopyridines and potential for lower exposures of active metabolites of drugs that rely on CYP3A for transformation of prodrug to active metabolite. For more information, please refer to the Summary of Product Characteristics.

	In addition, the MAH took also the opportunity to amend of the amount of sunset yellow FCF aluminium lake (E110) per tablet in section 2 of the SmPC following the suggestion done by EMA Labelling group during the renewal application (EMEA/H/C/002572/R/0041). Moreover, the sodium excipient wording is added in accordance with the "Excipients in the labelling and package leaflet of medicinal products for human use" (SANTE-2017-11668). Finally, the PI is brought in line with the latest QRD template. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/1247	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	08/05/2020	n/a		
II/0051	Extension of Indication to modify the approved therapeutic indication for Tybost to include the adolescent population aged 12 years old and older weighing at least 35kg when Tybost is used in combination with ATV and at least 40 kg when it is used in combination with Darunavir. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2 of the SmPC and sections 1,2,3 of the Product leaflet have been updated accordingly. An updated RMP version 5 was agreed during the procedure.	30/01/2020	09/03/2020	SmPC and PL	Please refer to Scientific Discussion 'Tybost-H-C-002572-II-51

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
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/1125	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	25/06/2019	n/a		
IG/1090	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)	29/05/2019	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.	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

	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. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				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.
PSUSA/10081 /201808	Periodic Safety Update EU Single assessment - cobicistat	14/03/2019	n/a		PRAC Recommendation - maintenance
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		
IAIN/0047	C.I.11.z - Introduction of, or change(s) to, the	09/10/2018	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
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		
R/0041	Renewal of the marketing authorisation.	31/05/2018	26/07/2018	SmPC, Labelling and PL	
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 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	28/06/2018	08/04/2019	SmPC, Labelling and PL	

	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				
T/0043	Transfer of Marketing Authorisation	25/04/2018	04/06/2018	SmPC, Labelling and PL	
PSUSA/10081 /201708	Periodic Safety Update EU Single assessment - cobicistat	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/10081/201708.
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-centre study that evaluated the drug interaction potential between darunavir (DRV)+COBI, atazanavir	18/01/2018	22/05/2018	SmPC and PL	

	(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/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	08/09/2017	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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				
IA/0037	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	23/05/2017	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.	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

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				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		
II/0036	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	05/05/2017	n/a		

PSUSA/10081 /201608	Periodic Safety Update EU Single assessment - cobicistat	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 Veterinary Medicinal Products - Other variation	26/01/2017	17/03/2017	SmPC, Annex II, Labelling and PL	
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		
II/0029	Submission of the final Clinical Study Report of study GS-US-216-0130 in order to fulfil a post-authorisation measure (MEA 002). C.I.13 - Other variations not specifically covered	28/07/2016	n/a		

	elsewhere in this Annex which involve the submission of studies to the competent authority				
II/0009	Submission of a final study report on the physiologically based/pharmacokinetic (PBPK) simulations of the effect of potent cytochrome P450 3A4 (CYP3A4) inhibitors on cobicistat (COBI) exposure to fulfil a Tybost post authorisation measure (MEA 014) and in order to provide further information on drug-drug interactions with COBI. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/04/2016	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		
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	01/04/2016	17/03/2017	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

	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 (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				amendments of Tybost PI.
PSUSA/10081 /201508	Periodic Safety Update EU Single assessment - cobicistat	17/03/2016	n/a		PRAC Recommendation - maintenance
IG/0624	A.7 - Administrative change - Deletion of manufacturing sites	11/01/2016	n/a		
II/0023	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/11/2015	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		
PSUSA/10081 /201502	Periodic Safety Update EU Single assessment - cobicistat	10/09/2015	n/a		PRAC Recommendation - maintenance
IG/0599	B.I.c.2.b - Change in the specification parameters	12/08/2015	n/a		

	and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method				
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/0020	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		
IB/0018/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.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	29/06/2015	n/a		
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	21/05/2015	n/a		

	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				
IB/0016	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	05/05/2015	11/02/2016	SmPC	
WS/0719	This was an application for a variation following a	23/04/2015	n/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				
II/0012/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	23/04/2015	11/02/2016	SmPC	Section 4.5 of the SmPC has been updated to reflect the contraindication of co-administration of Tybost with carbamazepine.
PSUSA/10081 /201408	Periodic Safety Update EU Single assessment - cobicistat	12/03/2015	n/a		PRAC Recommendation - maintenance
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	11/02/2016	Annex II and PL	
II/0006	Update of sections 4.8 and 5.1 of the SmPC with safety and efficacy 144 week data from study GS-US-216-0114. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/10/2014	10/02/2015	SmPC	The 144 week efficacy and safety data from study GS-US-216-0114 were in line with previously reported 48-week efficacy and 48- and 96-week safety data from the same study. No new safety concerns were identified in the extended follow-up period.

PSUV/0007	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		
II/0004	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	10/02/2015	SmPC	
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		
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		
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	20/02/2014	10/02/2015	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

	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				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/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	18/12/2013	n/a		

	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. - 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				