Eviplera

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
PSUSA/9142/ 202308	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir disoproxil	25/04/2024	17/06/2024	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9142/202308.
WS/2629/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No	04/04/2024	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).

	1234/2008. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IG/1581/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.III.2.b - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Change to comply with an update of the relevant monograph of the Ph. Eur. or national pharmacopoeia of a Member State	16/12/2022	n/a		
IB/0111	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/12/2022	29/11/2023	SmPC 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		
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	08/11/2021	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
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/9142/ 202008	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir disoproxil	22/04/2021	17/06/2021		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9142/202008.
IB/0105	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/06/2020	n/a		
IG/1243	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	25/05/2020	n/a		
IG/1247	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	08/05/2020	n/a		
IG/1236	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or	04/05/2020	n/a		

	manufacturer of a novel excipient				
WS/1718	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.6 of the Eviplera and Odefsey SmPCs in order to reflect rilpivirine data from the Antiretroviral Pregnancy Registry (APR) Interim Report issued in December 2019. The Eviplera Package Leaflet is updated in accordance. Furthermore, section 4.6 of the SmPC was updated to harmonise the text for breast-feeding with the already agreed text for rilpivirine, sections 4.4, 4.5 and 4.8 of the SmPC regarding the drug-drug interaction with didanosine and section 4.8 of the SmPC was updated regarding lactic acidosis, as agreed by the PRAC in the Viread procedure EMEA/H/C/PSUSA/00002892/201903. Section 4.5 was also updated to remove the reference to simeprevir. In addition, the Worksharing applicant (WSA) took the opportunity to bring the PI in line with the latest QRD template version 10.1, make minor editorial changes and update the PI in line with the Annex to the European Commission guideline on `Excipients in the labelling and package leaflet of medicinal products for human use' (EMA/CHMP/302620/2017 Rev.1) regarding sodium content, for both products. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	17/04/2020	12/06/2020	SmPC, Annex II and PL	There are no adequate and well controlled studies of Eviplera/Odefsey or their components in pregnant women. A moderate amount of data on pregnant women (between 300-1,000 pregnancy outcomes) indicate no malformative or foeto/neonatal toxicity of rilpivirine (see sections 4.4, 5.1 and 5.2). Lower exposures of rilpivirine were observed during pregnancy; therefore viral load should be monitored closely. A large amount of data on pregnant women (more than 1,000 pregnancy outcomes) indicate no malformative nor foetal/neonatal toxicity associated with emtricitabine and tenofovir disoproxil. The use of Eviplera/Odefsey may be considered during pregnancy, if necessary. Because of both the potential for HIV transmission and the potential for adverse reactions in breastfed infants, women should be instructed not to breast feed if they are receiving Eviplera/Odefsey. Cases of lactic acidosis have been reported with tenofovir disoproxil alone or in combination with other antiretrovirals. Patients with predisposing factors such as patients with decompensated liver disease, or patients receiving concomitant medications known to induce lactic acidosis are at increased risk of experiencing severe lactic acidosis during tenofovir disoproxil treatment, including fatal outcomes.

	data				
II/0100	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/12/2019	n/a		
WS/1627	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.9 of the Eviplera and Odefsey SmPCs in order to remove the recommendation to use oral activated charcoal in the event of an overdose of rilpivirine and replace it with a general guidance to contact poison control. In addition the MAH has taken the opportunity to update the lactose wording in Section 4.4 of the SmPC and Section 2 of the PL of Eviplera, according to the annex to the EC guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use', as well as update Section 5.1 of the Eviplera SmPC to reflect the full waiver for the Eviplera PIP. The MAH has also taken the opportunity to introduce minor administrative updates in the product information for both for Eviplera and Odefsey. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/06/2019	12/06/2020	SmPC and PL	Section 4.9 of the Eviplera and Odefsey SmPCs have been updated to remove the mention of administration of activated charcoal to aid in the removal of unabsorbed rilpivirine hydrochloride, replaced by advice that further management of rilpivirine overdose should be as clinically indicated or as recommended by the national poisons centre, where available.
II/0098	C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	17/01/2019	n/a		

	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				
WS/1466/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	29/11/2018	n/a		
IG/1001	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	23/11/2018	n/a		
IG/0995	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2018	01/07/2019	SmPC	

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		
WS/1424	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	13/09/2018	n/a		
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		
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	19/07/2018	01/07/2019	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

	Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between Sofosbuvir/Velpatasvir/Voxilaprevir Fixed-Dose Combination and HIV Antiretroviral in Healthy 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				caution and frequently renally monitored.
T/0091	Transfer of Marketing Authorisation	25/04/2018	28/05/2018	SmPC, Labelling and	

				PL	
PSUSA/9142/ 201708	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir disoproxil	08/03/2018	n/a		PRAC Recommendation - maintenance
IG/0845	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	18/12/2017	n/a		
WS/1251	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.2, 4.4 , 4.6, 5.1 and 5.2 of the Eviplera and Odefsey SmPCs with data from Study TMC114HIV3015, a Category 4 additional pharmacovigilance activity in the Risk Management Plan for both the Eviplera and Odefsey. This is a single-arm, open-label study to assess the pharmacokinetics of Darunavir and Ritonavir, Darunavir and Cobicistat, Etravirine, and Rilpivirine in HIV-1 infected pregnant women results for the Rilpivirine arm. The Package Leaflet is updated accordingly. In addition, the Worksharing Applicant (WSA) has taken the opportunity to introduce some minor administrative amendments and to implement some minor linguistic amendments (MLAs) to the translations of the product information annexes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	19/10/2017	15/12/2017	SmPC, Labelling and PL	Rilpivirine (one of the components of Odefsey) in combination with a background regimen was evaluated in Study TMC114HIV3015 in 19 pregnant women during the 2nd and 3rd trimesters, and postpartum. The pharmacokinetic data demonstrate that total exposure (AUC) to rilpivirine as a part of an antiretroviral regimen was approximately 30% lower during pregnancy compared with postpartum (6-12 weeks). The virologic response was generally preserved throughout the study: of the 12 patients that completed the study, 10 patients were suppressed at the end of the study; in the other 2 patients an increase in viral load was observed only postpartum, for at least 1 patient due to suspected suboptimal adherence. No mother to child transmission occurred in all 10 infants born to the mothers who completed the trial and for whom the HIV status was available. Rilpivirine was well tolerated during pregnancy and postpartum. There were no new safety findings compared with the known safety profile of rilpivirine in HIV 1 infected adults. In the Phase 3 studies (C209 and C215), lower rilpivirine exposure, similar to that seen during pregnancy, has been associated with an increased risk of virological failure, therefore viral load

	data				should be monitored closely. Alternatively, switching to another antiretroviral regimen could be considered.
IAIN/0088/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	28/11/2017	n/a		
II/0082	Update of section 4.5 of the SmPC with Drug-Drug Interaction information for Eviplera based on the results from Study TMC435-TiDP16-C114; this is a Phase I, 2-panel, open-label, randomized, cross-over trial in healthy subjects to investigate the pharmacokinetic interaction between TMC435 and antiretroviral agents, TMC278 and tenofovir disoproxil fumarate (TDF), at steady-state. In addition, the drug-drug interaction information for telaprevir (also an HCV NS3/4A inhibitor) is removed from the Eviplera prescribing information due to the withdrawal of the telaprevir marketing authorisation in the EU. In addition, the Marketing authorisation holder took the opportunity to introduce minor administrative changes in the SmPC and to update the list of local representatives in the Package Leaflet for Estonia, Latvia and Lithuania. Minor linguistic amendments (MLAs) have been implemented to the translations of the product	14/09/2017	15/12/2017	SmPC and PL	The results from the study TMC435-TiDP16-C114 showed that coadministration of Simeprevir with Rilpivirine or Tenofovir disoproxil fumarate did not lead to a clinically relevant pharmacokinetic interaction and no new safety findings were observed compared to the known adverse reactions associated with either product. No dose adjustment is therefore required regarding the coadministration of Simeprevir with Eviplera.

	information annexes: CS, DE, ES, FR, IS, IT, NL, NO, PT, SE and SK. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
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 batch control/testing takes place	18/07/2017	n/a		
IG/0799	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	14/07/2017	n/a		
IG/0818	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	16/06/2017	n/a		
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	21/04/2017	15/12/2017	SmPC and PL	The Marketing Authorisation Holder has submitted the results from Study GS-US-342-1167 and Study GS-US-342-1326 to update the Product Information for tenofovir disoproxil fumarate (TDF)-containing products (Viread, Truvada, Atripla, Eviplera and Stribild) and tenofovir alafenamide (TAF)-containing products (Genvoya, Descovy, Odefsey).

	products (Viread, Truvada, Atripla, Stribild) which includes the results from Study GS-US-342-1167 and Study GS-US-342-1326. The Package Leaflets and Risk Management Plans for Viread (v. 22), Truvada (v.14), Atripla (v.16) and Stribild (v.11.1) have been updated accordingly. Update of section 4.5 for the tenofovir alafenamide (TAF)-containing products (Genvoya, Descovy, Odefsey) and for Eviplera, which include the results from Study GS-US-342-1167. The Risk Management Plan for Eviplera (v.13) has been updated accordingly. Administrative update of section 4.8 of the SmPC for Viread, Atripla, Eviplera and Stribild. 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				Study GS-US-342-1167 is a Phase I Study to Evaluate the Pharmacokinetic Drug-Drug Interactions between Sofosbuvir/GS-5815 Fixed Dose Combination (FDC) Tablets and Antiretrovirals Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF; Atripla), Emtricitabine/Riplivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF; Complera), Dolutegravir (DTG; Tivicay) o Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate (EVG/COBI/FTC/TAF) in Healthy Subjects. The recommendation stemming from this study is that no dose adjustment of sofosbuvir/velpatasvir with Eviplera orGenvoya is warranted upon co-administration, and that Atripla should not be co-administered with sofosbuvir/velpatasvir. Study GS-US-342-1326, 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.

	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF), Ritonavir-boosted Darunavir (DRV/r) plus Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF), Ritonavir-boosted Atazanavir (ATV/r) plus FTC/TDF, Ritonavir/boosted Lopinavir (LPV/r) plus FTC/TDF or Raltegravir plus FTC/TDF. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/9142/ 201608	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir disoproxil	09/03/2017	n/a		PRAC Recommendation - maintenance
IG/0745	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	28/11/2016	n/a		
IG/0725	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or 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	19/09/2016	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				
IA/0076	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	24/08/2016	n/a		
R/0074	Renewal of the marketing authorisation.	26/05/2016	22/07/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Eviplera in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
WS/0860/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. 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	26/05/2016	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/0829	This was an application for a variation following a worksharing procedure according to Article 20 of	01/04/2016	22/07/2016	SmPC, Annex II and PL	

	Commission Regulation (EC) No 1234/2008. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
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	22/07/2016	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.
PSUSA/9142/ 201508	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir disoproxil	17/03/2016	n/a		PRAC Recommendation - maintenance
IG/0651	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor	28/01/2016	n/a		

	changes to an approved test procedure				
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	31/03/2016	SmPC and PL	
IG/0624	A.7 - Administrative change - Deletion of manufacturing sites	11/01/2016	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. 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.	17/12/2015	31/03/2016	SmPC	

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IG/0613	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	14/10/2015	n/a		
II/0063/G	This was an application for a group of variations. Update of sections 4.4 and 4.8 of the SmPC in order to add safety information regarding severe skin reactions with systemic symptoms. The Package Leaflet and the RMP (V10.0) are updated accordingly. The RMP is also being updated to reflect study results from previous procedure EMEA/H/C/002312/II/0053, to align the RMP with that for the mono-component rilpivirine by deleting a safety concern (missing information regarding drug-drug interactions) and to amend the safety concern 'off label use' (potential risk) to reflect use for the product and not for the single component RPV. In addition, other minor amendments are made to the RMP. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	24/09/2015	31/03/2016	SmPC and PL	Cases of severe skin reactions with systemic symptoms have been reported during post marketing experience with Eviplera, including but not limited to rashes accompanied by fever, blisters, conjunctivitis, angioedema, elevated liver function tests, and/or eosinophilia. These symptoms resolved after Eviplera was discontinued. As soon as serious skin and/or mucosal reactions are observed, Eviplera must be discontinued and appropriate therapy should be initiated.

	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				
PSUSA/9142/ 201502	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir disoproxil	10/09/2015	n/a		PRAC Recommendation - maintenance
IA/0065/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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	21/08/2015	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		
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	31/03/2016	SmPC and PL	

IG/0553	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	07/05/2015	n/a		
IB/0057/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.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process 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	24/04/2015	n/a		
II/0053	Submission of the Clinical Study Report of the EVIPLERA Health Care Professional Survey which assessed the understanding and effectiveness of the current prescribing conditions in minimising the risk	23/04/2015	n/a		

	associated with taking the product without food and the risk of development of drug resistance. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0055	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	24/03/2015	n/a		
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	31/03/2016	Annex II and PL	
WS/0598/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. Worksharing including a group of variations: - type II variation to update of the RMP to reflect the fulfilment of a post-authorisation commitment; to add references to studies previously submitted and to add intermediate results for several studies. - type IB variation to update the deadline for the final submission of study 104-0423 in the RMP. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	26/02/2015	n/a		

	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 authorisation, including the RMP - Other variation				
PSUSA/9142/ 201408	Periodic Safety Update EU Single assessment - emtricitabine / rilpivirine / tenofovir disoproxil	12/02/2015	n/a		PRAC Recommendation - maintenance
WS/0596	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	25/09/2014	n/a		
WS/0573	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	25/09/2014	n/a		
WS/0564	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 phase 3 clinical study report	25/09/2014	n/a		The results from this extension phase tend to show that the median decrease in bone mineral density observed through the first 24-48 weeks of treatment seems to remain relatively stable over 13 years of treatment. As regards bone fractures, 8 events were reported during

	(Study GS-99-903) as a worksharing procedure to fulfil a Viread, Truvada and Eviplera Post-Authorisation Measure (PAM). This study was extended to evaluate the long-term efficacy, safety, and tolerability of treatment with tenofovir disoproxil fumarate, in particular to collect long-term exposure information on BMD and bone events. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				the study. All of them were trauma-related, not considered related to tenofovir or Truvada and were recovered. As regards the renal function, the median change in eGFRCG seems not clinically relevant (with no subjects experiencing eGFRCG below 50 mL/min) and glomerular function remained stable through study. No Fanconi syndrome or tubulopathy was reported. The only renal SAE reported was kidney pain which was not related to study drug. No new safety concern was raised from these final study results. No change to the SmPC of TDF-containing products is therefore necessary on the basis of these data.
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/0041	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
IB/0049	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)	03/09/2014	11/12/2014	SmPC	
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.	24/07/2014	11/12/2014	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-

	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 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				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 discontinuation.
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 the PI of Truvada in line with the latest QRD template version 9.	24/07/2014	11/12/2014	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.

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
II/0036	Submission of the final week 96 clinical study report (CSR) for study GS-US-264-0110,"A Phase 3B, Randomized, Open-label Study to Evaluate the Safety and Efficacy of a Single Tablet Regimen of Emtricitabine/Rilpivirine/Tenofovir Disoproxil Fumarate Compared With a Single Tablet Regimen of Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate in HIV-1 Infected, Antiretroviral Treatment-Naive Adults. 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		The week 96 data of study GS-US-264-0110 confirm the efficacy and safety profile of Eviplera and no update of the product information for Eviplera is needed in the view of these data.
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/0039	Update of section 5.1 of the SmPC with information regarding resistance and cross-resistance related to the substitution K70E (tenofovir resistance-associated) and the combination of substitutions L100I+K103N (rilpivirine resistance-associated). The MAH also took the opportunity to make minor editorial amendments to the SmPC and to the Package Leaflet.	26/06/2014	11/12/2014	SmPC and PL	The MAH presented evidence for gene mutations causing resistance against Eviplera treatment. One of these concerns the tenofovir disoproxil fumarate resistance-associated mutation K70E. Resistance against rilpivirine might be elicited by the L100I mutation in combination with the K103N mutation.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0035/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	31/03/2014	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/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	20/03/2014	11/12/2014	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

	Emtriva and to update the bottle label to include the EDQM short standard term for the pharmaceutical form for Stribild. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.
PSUV/0033	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
II/0030	Update of section 4.5 of the SmPC with information on interactions between rilpivirine and metformin according to the results of a drug interaction study performed to fulfil a Post-Authorization Measure. The package leaflet was revised accordingly. Based on an in vitro test section 4.5 of the SmPC was further updated with the information that rilpivirine is an in vitro inhibitor of the transporter MATE-2K with an IC50 of <2.7 nM and that the clinical implications of this finding are currently unknown. In addition the interactions section of the SmPC was further amended to better reflect information on rifapentine in the interactions table and for consistency a sentence was added to inform prescribers that rilpivirine should not be administered concomitantly with rilpivirine hydrochloride unless needed for dose adjustment with rifabutin. Furthermore the MAH took the opportunity of this variation to include administrative corrections to annex A and minor linguistic amendments were made to the German product information C.I.4 - Change(s) in the SPC, Labelling or PL due to	18/12/2013	11/12/2014	SmPC and PL	Rilpivirine has been shown to inhibit OCT2 in vitro. At the time of the study set up, no information on the effect of rilpivirine on MATE transporters was known. The current study was designed to assess the effect of steady-state rilpivirine on OCT2 in vivo, by evaluating its effect on the pharmacokinetics of the OCT2 substrate, metformin, in healthy adult subjects. The study showed that rilpivirine had no effect on the plasma pharmacokinetics of metformin and its urine clearance. An in vitro test showed that rilpivirine is an in vitro inhibitor of the transporter MATE-2K with an IC50 of <2.7 nM and that the clinical implications of this finding are currently unknown.

	new quality, preclinical, clinical or pharmacovigilance data				
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		
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		
II/0021	Extension of Indication to to adults without known mutations associated with resistance to the non-nucleoside reverse transcriptase inhibitor (NNRTI) class, tenofovir or emtricitabine (from the previous 'antiretroviral treatment-naïve') and with a viral load ≤ 100,000 HIV-1 RNA copies/ml. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/10/2013	29/11/2013	SmPC and PL	Please refer to the assessment report number EMEA/H/C/002312/II/0021.

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. 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	24/10/2013	n/a		
II/0027	To update section 4.2, 4.3 and 4.5 of the SmPC regarding rilpivirine-rifabutin interaction after the completion of the study TMC278IFD1003, with the finding that under rifabutin treatment rilpivirine can be used concomitantly (previously contraindicated) if an additional dose of 25 mg rilpivirine is taken. The package leaflet was updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 9.0 In addition the list of representatives in the leaflet was updated to add Croatia. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	19/09/2013	29/11/2013	SmPC and PL	The interaction study TMC278IFD1003, which was requested at the time of the Marketing Authorisation, showed that after administration rifabutin 300 mg q.d. and 25 mg q.d. rilpivirine, the AUC, Cmax and Cmin for rilprivirine decreased by 42, 31 and 48%, respectively while an increase in the rilpivirine dose to 50 mg q.d. lead to an increase of rilpivirine AUC and Cmax of about 16 and 42%, while Cmin decreased 7%. The observed differences, compared to a 25 mg q.d. dose of rilpivirine, were considered safe and efficacious and it was considered that a rilpivirine dose of 50 mg q.d could compensate for the inducing effect of rifabutin. The CHMP therefore agreed that the contraindication for coadministration of Eviplera with rifabutin could be replaced

	clinical, clinical or pharmacovigilance data				with a warning in SmPC section 4.4 and instructions in SmPC sections 4.2 and 4.5 stating that when Eviplera is co-administered with rifabutin, an additional 25 mg tablet of rilpivirine per day is recommended to be taken concomitantly with Eviplera, for the duration of the rifabutin co-administration.
WS/0391	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 4.8 of the SmPC in order to update the safety information regarding autoimmune disorders in relation to Immune Reactivation Syndrome, following a class labelling for antiretrovirals as requested by the CHMP. The Package Leaflet was updated accordingly. In addition, the WSA took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, Annex II is being brought in line with the latest QRD template version and minor editorial changes are implemented in the SmPC. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	30/05/2013	21/06/2013	SmPC, Annex II and PL	Upon review of safety data and literature on immune disorders in association with antiretrovirals for the treatment of HIV, the CHMP considered that there is sufficient evidence to conclude that immune reconstitution syndrome (IRS) after antiretroviral therapy may be associated with autoimmune disease/disorders even if the number of case reports is limited. Therefore, the CHMP had requested the inclusion of information on immune disorders under immune reconstitution as a class labelling for all antiretrovirals for the treatment of HIV.
IG/0294	A.7 - Administrative change - Deletion of manufacturing sites	03/04/2013	n/a		

IG/0290	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/04/2013	n/a		
II/0020	Update of section 4.5 of the SmPC with results of a drug-drug interaction study between rilpivirine and digoxin (study TMC278IFD1001). Section 4.5 of the SmPC was also updated to remove reference to the interaction with 'troleandomycin' as it is no longer marketed in the EU. The Package Leaflet was updated accordingly. The MAH also corrected an editorial mistake in the Package Leaflet of the Finnish Annexes. Furthermore, Annex II was brought in line with the latest QRD template version 8.3. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/02/2013	21/06/2013	SmPC, Annex II and PL	Rilpivirine has P-glycoprotein (P-gp) inhibitory properties in vitro with an apparent half maximum inhibitory concentration (IC50) value of 3.4 µg/ml. While rilpivirine plasma concentrations in healthy volunteers and in HIV-1 infected patients are below this level, theoretically the intestinal concentration of rilpivirine after administration of a 25 mg oral dose could be up to 100 µg/ml. Therefore rilpivirine could potentially affect the pharmacokinetics of P-gp substrates. The results from study TMC278IFD1001 demonstrated that the pharmacokinetics of the P-gp substrate digoxin is not affected by rilpivirine, administered at the recommended 25 mg daily dose. This was further substantiated by urinary excretion data. However, the CHMP noted that digoxin is not very sensitive to inhibition of intestinal P-gp, thus it cannot be concluded that there is no effect of rilpivirine on more sensitive substrates of intestinal P-gp, such as dabigatran etexilate. This information was included in section 4.5 of the SmPC, and the reference to troleandomycin was deleted as this product is no longer marketed in the EU.
IA/0022/G	This was an application for a group of variations. 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	30/01/2013	n/a		

	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 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				
II/0017	Update of sections 4.2 and section 5.2 of the SmPC following results of clinical study GS-US-264-0112 "A Phase 1 Study to Determine the Effect of Food on the Pharmacokinetics of	17/01/2013	21/06/2013	SmPC and PL	The food interaction study GS-US-264-0112 showed that rilpivirine and tenofovir exposure are increased after intake of a standard meal or a light meal. Comparing with fasted conditions, statistically significant

	Emtricitabine/Rilpivirine/Tenofovir DF Single Tablet Regimen". Minor editorial corrections are also included. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				increases were found in rilpivirine with a standard meal in AUC0-t and Cmax by 19 and 26%, and with a light meal only in Cmax by 34%. For tenofovir with a standard/light meal this resulted in a statistically significant increase in AUC0-t, AUC0-inf and Cmax by 41/31, 38/28 and 32/12%, respectively. In addition, for emtricitabine no clinically significant effect on exposure was observed. These results are in line with those obtained from the single agent rilpivirine tablet, although less pronounced, and for tenofovir and emtricitabine from Viread and Emtriva, respectively. As different meal type definitions exist across studies, the caloric content of the standard and light meals of the present study has been included in the updated product information.
II/0015	Update of section 5.1 of the SmPC in order to include Y188L as a rilpivirine resistance-associated mutation (RAM). In addition, the MAH took the opportunity to implement linguistic corrections to the German Product Information. Following CHMP request annex II of the product information was updated according to the QRD template version 8, revision 2. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	13/12/2012	21/06/2013	SmPC and Annex II	The association of decreased susceptibility to Rilpivirine due to baseline RAM Y188L has been confirmed in analysis of data from a database of clinical specimens and site-directed mutagenesis studies and spontaneous individual case report. Section 5.1 of the SmPC is updated accordingly.
IA/0019/G	This was an application for a group of variations. 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	06/12/2012	n/a		

	oral dosage form or oral solutions B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits				
IG/0234	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	06/12/2012	n/a		
II/0014	Update of section 4.5 of the SmPC on interactions between rilpivirine and telaprevir. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/11/2012	21/06/2013	SmPC	Rilpivirine is a substrate of CYP3A, therefore plasma concentrations of rilpivirine could be increased when coadministered with telaprevir. This is confirmed in the currently submitted phase I study in healthy volunteers. Including the results of all subjects, the data showed that rilpivirine AUC, Cmax and Cmin increased 78, 49 and 93%, respectively due to co-administration of telaprevir 750 mg thrice daily. However, rilpivirine did not affect the plasma concentrations of telaprevir. Although plasma concentrations of rilpivirine increased, it is agreed that no dose adjustment is required.
II/0012	Update of section 4.5 of the SmPC on interaction with raltegravir. This Type II variation is submitted to fullfil the following post-authorisation measure: MEA 002. The MAH took opportunity to add the date of first authorisation in the SmPC and the Marketing Authorisation number in both SmPC and Labelling. This variation also proposes to make minor linguistic amendments to the Portuguese language annexes. C.I.4 - Variations related to significant modifications	20/09/2012	24/10/2012	SmPC and Labelling	Raltegravir is eliminated mainly by metabolism via a uridine glucuronyl-transferase (UGT) 1A1-mediated pathway (main [inactive] metabolite: raltegravir glucuronide). Raltegravir has a low propensity for causing drug interactions with substrates of CYP enzymes (such as rilpivirine) as it is not a substrate, an inhibitor, or an inducer of CYP enzymes. Rilpivirine is a substrate of CYP3A and is unlikely to affect metabolic enzymes (including UGT) to a clinically relevant extent. No interaction is expected. This is confirmed in the currently submitted phase I study, based on data obtained in 23 subjects.

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
II/0006	The MAH proposed the update of sections 4.1, 4.4, 4.8 and 5.1 of the SmPC to reflect the 96 weeks results of the pivotal studies C209 and C215. The Package Leaflet was updated accordingly. The MAH took the opportunity to update section 6 of the PL to mention that each bottle contains a silica gel desiccant. The requested variation proposed amendments to the SmPC and Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	24/10/2012	SmPC and PL	Results of pivotal studies C209 and C215 confirmed the non-inferior virologic efficacy of RPV 25 mg once daily over 96 week in the approved indication. Similar results were observed for the FTC/TDF backbone which is the background regimen in the fixed dose combination. Week 96 data confirm the safety of the product. The benefit risk of the product remains positive.
IG/0203	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	03/08/2012	n/a		
IB/0011	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	11/07/2012	n/a		
IB/0010	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	11/07/2012	n/a		

WS/0245	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Addition of a new manufacturing and quality control testing site for the active substance. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	21/06/2012	21/06/2012		
WS/0244	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Minor change in the manufacturing process of the active substance tenofovir disoproxil fumarate. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/05/2012	24/05/2012		
IAIN/0008/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	16/04/2012	n/a		

IG/0166	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	13/04/2012	n/a		
IAIN/0003/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	02/03/2012	n/a		
IB/0001	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	01/03/2012	n/a		
IB/0002	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	10/01/2012	n/a		