Atripla

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
WS/1509	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of updated RMPs version 18.0 for Atripla and version 16.0 for Truvada, in order to: 1) implement Revision 2 of the EU-RMP template and amend the safety concerns accordingly, 2) remove the additional risk minimisation measures for tenofovir	14/03/2019		Annex II	The Annex IID "Conditions or restrictions with regard to the safe and effective use of the medicinal product" of Atripla and Truvada was amended to remove the HIV renal educational brochure (including the creatinine clearance slide ruler) for adults, in line with a previous CHMP decision for tenofovir disoproxil-containing products. In addition, the Annex IIIB (Package Leaflet) of Truvada was revised to amend the recommendation pertaining to pregnancy in line with the SmPC recommendation, to remove the following statement

[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).

	disoproxil fumarate in the form of education materials regarding renal toxicity and bone events, with the resulting amendment of Annex II of the product information, 3) add clinical data from study GS-US-104-0352 (A Phase III, Randomized, Open-Label Study Comparing the Safety and Efficacy of Switching Stavudine or Zidovudine to Tenofovir Disoproxil Fumarate Versus Continuing Stavudine or Zidovudine in Virologically Suppressed HIV-Infected Children Taking Highly Active Antiretroviral Therapy), 4) revise the due dates for two category 3 studies for Truvada, GS-US-276-0103 (A Prospective, Observational Study of Individuals Who Seroconvert While Taking Truvada for Pre Exposure Prophylaxis (PrEP)) and GS-EU-276-4027 (A Cross-Sectional Post Authorization Safety Study to Assess Healthcare Provider's Level of Awareness of Risk Minimisation Materials for Truvada for Pre Exposure Prophylaxis in the European Union), 5) change the Marketing Authorisation Holder's (MAH) name from Gilead Sciences International Ltd. to Gilead Sciences Ireland UC., 6) update the milestones for the Truvada study GS-US-276-0104 (Seroconversions, Resistance, Adverse Events and Drug Adherence among Subjects taking Truvada for PrEP: A Nested Case Control study) in the Truvada EU-RMP and 7) correct a discrepancy in Annex IIIB of the Truvada PI regarding the recommendation pertaining to pregnancy, by aligning the PL wording with that of the SmPC. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing				from Section 2 - What you need to know before you take Truvada: "If you are a woman who could get pregnant during treatment with Truvada, you must use an effective method of contraception to avoid becoming pregnant."

	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				
PSUSA/1201/ 201807	Periodic Safety Update EU Single assessment - efavirenz / emtricitabine / tenofovir	14/02/2019	n/a		PRAC Recommendation - maintenance
IA/0141	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/02/2019	n/a		
N/0140	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	05/02/2019		PL	
IA/0139	A.7 - Administrative change - Deletion of manufacturing sites	14/12/2018	n/a		
WS/1466/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or 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 -	29/11/2018	n/a		

	Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
IG/1001	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	23/11/2018	n/a		
II/0130	Update of sections 4.3 and 4.5 of the SmPC in order to include drug-drug interaction data between efavirenz and elbasvir/grazoprevir based on a review of the antiviral product Zepatier. The Marketing authorisation holder has taken the opportunity to introduce changes to the sodium wording in Section 4.4 of the SmPC and to align the text in Section 4.6 (Fertility, pregnancy and lactation) for Atripla with the currently approved wording in the Eviplera SmPC. The Package Leaflet has been updated accordingly. In addition, the MAH has also taken the opportunity to implement some minor linguistic amendments (MLAs) to the translations of the product information annexes for the following languages: DE, FI, FR, IT, NL and NO. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/09/2018	22/11/2018	SmPC and PL	Based on a review of drug-drug interactions with efavirenz, co administration of Atripla with elbasvir/grazoprevir is contraindicated due to the expected significant decreases in plasma concentrations of elbasvir and grazoprevir. This effect is due to induction of CYP3A4 or P gp by efavirenz and may result in loss of therapeutic effect of elbasvir/grazoprevir.
WS/1447	This was an application for a variation following a worksharing procedure according to Article 20 of	04/10/2018	n/a		

	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				
IG/0985	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/09/2018		SmPC	
IG/0974	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	07/09/2018	n/a		
N/0131	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	25/07/2018	22/11/2018	PL	
II/0129	Update of sections 4.4 and 4.5 of the Atripla SmPC in order to add a warning that co administration of Atripla and sofosbuvir/velpatasvir/voxilaprevir is not recommended, and reflect the corresponding drug-drug interaction data based on the final results from study GS-US-342-1167, listed as category 3 study in the RMP: 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;	17/05/2018	22/11/2018	SmPC, Labelling and PL	The Marketing Authorisation Holder has submitted the results of Study GS-US-342-1167, a phase I pharmacokinetic drug-drug interaction study. The results suggest that co administration of Atripla and sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir should not be recommended since plasma concentrations of velpatasvir and voxilaprevir are expected to decrease following co administration with efavirenz leading to reduced therapeutic effect of sofosbuvir/velpatasvir or sofosbuvir/velpatasvir/voxilaprevir.

	Tivicay) or elvitegravir/cobicistat/emtricitabine/tenofovir alafenamide fumarate (EVG/COBI/FTC/TAF) in healthy subjects. Section 2 of the Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder took the opportunity to bring the product information in line with the latest QRD template version 10, make minor editorial amendments to sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1, 5.2 and 5.3 and minor linguistic amendments to the following languages: BG, CS, ET, HU, LT, LV, RO, SK. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
II/0127/G	This was an application for a group of variations. Update of sections 4.3, 4.4, 4.5 and 5.1 of the SmPC to include the final report for Study AI266959; this is an interventional study to determine the concentration-electrocardiographic effects of efavirenz in healthy subjects enriched for Cyp2b6 Polymorphism, to fulfill the legally binding measure (LEG) requested by the PRAC following to the conclusion of the PSUR (EMA/PRAC/679906/2016) for Sustiva. Update of sections 4.4 and 4.8 of the Atripla SmPC to add catatonia as a Psychiatric symptom following an assessment of catatonia cases reported in the literature and via the United States (US) Food and	08/02/2018	23/03/2018	SmPC and PL	

	Drug Administration Adverse Event Reporting System (FAERS). Removal of Telaprevir from section 4.5 pf the SmPC as it is no longer authorised in the EU. Submission of an updated RMP v.17 to remove malignant neoplasms as a potential risk, in line with GVP Module V, and approved by PRAC following the conclusion of the latest annual report on malignancy events (MEA 039.6). The MAH took the opportunity to implement minor editorial changes in the Product Information and minor linguistic amendments to the following languages: DA, DE, ES, FI, FR, HR, HU, IS, MT, NO, PT and SV. An update to Section 4.6 Fertility, pregnancy and lactation, whereby two paragraphs of text providing information on the possibility of neural tube defects in pregnancy with efavirenz, and results from the Antiretroviral Pregnancy Registry (APR) in 2013 had been previously omitted, was made for the following languages: BG, CS, ET, HU, LV, LT, RO, SK, and SL. 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 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				

IA/0128	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	12/02/2018	n/a		
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		
II/0125/G	This was an application for a group of variations. B.I.a.2.b (Type II) - To add route 8 as alternative synthesis route for efavirenz active substance B.I.a.1.f (Type IA) - To add Siegfried Evionnaz SA, Route du Simplon 1, 36, 1902 Evionnaz, Switzerland as stability QC testing site for efavirenz active substance B.I.a.1.f (Type IA) - To add Solvias AG, Romerpark 2, 4303 Kaiseraugst, Switzerland as QC testing site for efavirenz active substance B.I.a.3.b (Type IA) - To reduce the batch size compared to previous active substance synthetic routes to align with current equipment and capacity at the new facility, and support current market demand. The Icelandic and the Norwegian CHMP members agree with the above-mentioned recommendation of the CHMP on variation to the terms of the marketing authorisation. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS -	26/10/2017	n/a		

	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.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.3.b - Change in batch size (including batch size ranges) of AS or intermediate - Downscaling down to 10-fold				
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		
IA/0122/G	This was an application for a group of variations. B.II.c.2.a - Change in test procedure for an excipient -	09/06/2017	n/a		

	Minor changes to an approved test procedure B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure				
WS/1133/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Updates of sections 4.4 and 4.5 of the SmPC for the tenofovir disoproxil fumarate (TDF)-containing products (Viread, Truvada, Atripla, Stribild) which includes the results from Study GS-US-342-1167 and Study GS-US-342-1326. The Package Leaflets and Risk Management Plans for Viread (v. 22), Truvada (v.14), Atripla (v.16) and Stribild (v.11.1) have been updated accordingly. Update of section 4.5 for the tenofovir alafenamide (TAF)-containing products (Genvoya, Descovy, Odefsey) and for Eviplera, which include the results from Study GS-US-342-1167. The Risk Management Plan for Eviplera (v.13) has been updated accordingly. Administrative update of section 4.8 of the SmPC for Viread, Atripla, Eviplera and Stribild. 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	21/04/2017	23/03/2018	SmPC and PL	The Marketing Authorisation Holder has submitted the results from Study GS-US-342-1167 and Study GS-US-342-1326 to update the Product Information for tenofovir disoproxil fumarate (TDF)-containing products (Viread, Truvada, Atripla, Eviplera and Stribild) and tenofovir alafenamide (TAF)-containing products (Genvoya, Descovy, Odefsey). Study GS-US-342-1167 is a Phase I Study to Evaluate the Pharmacokinetic Drug-Drug Interactions between Sofosbuvir/GS-5815 Fixed Dose Combination (FDC) Tablets and Antiretrovirals Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF; Atripla), Emtricitabine/Riplivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF; Complera), Dolutegravir (DTG; Tivicay) o Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate (EVG/COBI/FTC/TAF) in Healthy Subjects. The recommendation stemming from this study is that no dose adjustment of sofosbuvir/velpatasvir with Eviplera orGenvoya is warranted upon co-administration, and that Atripla should not be co-administered with sofosbuvir/velpatasvir. Study GS-US-342-1326, 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

	Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate (EVG/COBI/FTC/TAF) in Healthy Subjects. Study GS-US-342-1326, a Phase I Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between Sofosbuvir/GS-5816 (SOF/GS-5816) Fixed-Dose Combination (FDC) Tablet and HIV Antiretroviral Regimens Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF), Ritonavir-boosted Darunavir (DRV/r) plus Emtricitabine/Tenofovir Disoproxil Fumarate (FTC/TDF), Ritonavir-boosted Atazanavir (ATV/r) plus FTC/TDF, Ritonavir/boosted Lopinavir (LPV/r) plus FTC/TDF or Raltegravir plus FTC/TDF. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				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.
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	21/10/2016	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				
IG/0726	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	19/09/2016	n/a		
WS/0963	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/09/2016	16/12/2016	SmPC, Labelling and PL	
IA/0116	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	03/08/2016	n/a		
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	26/05/2016	n/a		

	authorisation, including the RMP - Other variation				
IA/0115/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 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	25/05/2016	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 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	01/04/2016	16/12/2016	SmPC, Annex II and PL	
WS/0792	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC in order to revise	01/04/2016	16/12/2016	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;

	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				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/1201/ 201507	Periodic Safety Update EU Single assessment - efavirenz / emtricitabine / tenofovir	11/02/2016	n/a		PRAC Recommendation - maintenance
IG/0651	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	28/01/2016	n/a		
WS/0884	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/01/2016	16/12/2016	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. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/12/2015	16/12/2016	SmPC	
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		
IAIN/0106	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	04/08/2015	n/a		

	location				
IG/0583	A.7 - Administrative change - Deletion of manufacturing sites	23/07/2015	n/a		
II/0100	Update of the section 4.5 of the SmPC in order to introduce information that co-administration of simeprevir with efavirenz (one of the components of Atripla) is not recommended. The Package Leaflet is updated accordingly. Additionally, minor editorial changes have been introduced throughout the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	14/12/2015	SmPC and PL	The MAH presented in this variation drug interaction data on concomitant administration of efavirenz, tenofovir and emtricitabine with simeprevir (Olysio). Concomitant administration of simeprevir with efavirenz resulted in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by efavirenz, which may result in reduction of therapeutic effect of simeprevir. Concomitant administration of simeprevir and tenofovir DF led to minor changes in drug exposures that are not considered clinically relevant. No drug interaction data are available for concomitant administration of emtricitabine and simeprevir. However, based on the differential ADME profiles and the lack of in vitro interactions with CYPs and transporters, the theoretical risk of a drug-drug interaction between the emtricitabine component of Atripla and simeprevir is considered highly unlikely. Due to the observed interaction with efavirenz co-administration of simeprevir (Olysio) with Atripla is not recommended.
IG/0572	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/06/2015	14/12/2015	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		

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	14/12/2015	Annex II and PL	
WS/0650	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 5.1 of the SmPC to include reference to the tenofovir resistance-associated substitution K70E. In addition, the product information has been updated to reflect the right expression of pack sizes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	18/12/2014	14/12/2015	SmPC, Labelling and PL	The MAH has provided literature references to support the proposal to include information regarding the K70E mutation resulting in reduced tenofovir disoproxil fumarate (TDF) susceptibility in section 5.1 of the SmPC of Atripla, Truvada and Viread as follows: "In addition, a K70E substitution in HIV-1 RT has been selected by tenofovir and results in low-level reduced susceptibility to abacavir, emtricitabine, lamivudine and tenofovir."
IA/0098	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	20/11/2014	n/a		
II/0088	Addition of an alternative manufacturing process for the synthesis of the active substance B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	23/10/2014	n/a		

WS/0599	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		
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		
IA/0094/G	This was an application for a group of variations. 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 A.7 - Administrative change - Deletion of manufacturing sites	08/08/2014	n/a		
IAIN/0095	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	07/08/2014	n/a		
WS/0586	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. WSA for Atripla, Truvada, Stribild, Viread and Eviplera	24/07/2014	22/01/2015	SmPC, Annex II and PL	In fulfilment of a CHMP request for Viread pertaining to the reversibility of TDF associated renal tubulopathy, the MAH has submitted a worksharing variation to implementing renal safety information in the SmPC of all the TDF-containing products. The main messages on renal safety are the

	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				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. C.I.z - Changes (Safety/Efficacy) of Human and	24/07/2014	22/01/2015	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.

	Veterinary Medicinal Products - Other variation				
IAIN/0092	Introduction of an agreed wording (section 4.6 of the SmPC) regarding the number of pregnancies and Neutral Tube Defects (NTD) for efavirenz after the PRAC assessment and following implementation of the same wording in the SmPC for Sustiva. C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority	16/07/2014	22/01/2015	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		
II/0084	Update of section 4.5 of the SmPC concerning information on false positive results in screening tests for cannabinoid metabolites in line with the changes for the efavirenz component adopted by the CHMP on 23 January 2014 (Sustiva/Stocrin EMEA/H/C/XXXX/WS/434). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/05/2014	22/01/2015	SmPC	A literature review indicated that efavirenz may interfere with the results of a number of commercially available tests used for routine screening of cannabinoid use, and not just one test as had been previously included in the SmPC. Section 4.5 of the SmPC was updated with a more general statement (mention of specific assays was removed) and with a recommendation for confirmation of positive screening tests by a more specific method, such as GC/MS. This update in line with the changes for the efavirenz (EFV) component, which were previously approved by the CHMP for Sustiva/Stocrin (efavirenz)

IAIN/0085	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	31/03/2014	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 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	20/03/2014	22/01/2015	SmPC, Labelling and PL	During recent years conclusive evidence has been collected which shows that the risk for HIV patients, who are well treated, to sexually transmit HIV to their partner is exceedingly low. A position statement on the use of antiretroviral therapy to reduce HIV transmission was published by the British HIV Association (BHIVA) in January 2013. As a consequence, the recommendations for post-exposure prophylaxis have also been changed in recently updated HIV treatment guidelines. For example, the 2013 BHIVA guideline does not generally recommend post-exposure prophylaxis (PEP) after exposure from a patient with well treated HIV. Based on these data, the wording on the risk of transmission for HIV products was revised to reflect the current scientific knowledge. While effective suppression with antiretroviral therapy has been proven to substantially reduce the risk of sexual transmission, a residual risk cannot be excluded. Precautions to prevent transmission should be taken in accordance with national guidelines.
II/0081	Update of section 4.6 of the SmPC with information on the excretion of efavirenz (EFV) into human breast milk in line with the changes approved for the efavirenz single product. Furthermore, the MAH took the opportunity of this variations to include minor changes for consistency.	20/02/2014	22/01/2015	SmPC and PL	A published study analysing the levels of efavirenz in plasma and breast milk of 13 breast-feeding mothers and in the plasma of their non-antiretroviral-treated infants. Results from this study demonstrated that efavirenz passes easily into human milk, with a strong correlation between the levels in maternal plasma and breast milk, as well as between the

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				levels in milk and plasma levels in breast-feeding infants. There is insufficient information on the effects of efavirenz in newborns/infants. Importantly, HIV-infected mothers should not breast-feed under any circumstances to avoid HIV transmission to the infant.
II/0080	Update of section 4.5 of the SmPC on interactions with artemether/lumefantrine in line with the changes approved for the efavirenz single product. The PL was updated accordingly. Moreover the MAH took the opportunity of this variation to implement minor linguistic amendments in the Swedish PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	22/01/2015	SmPC and PL	In a drug-drug interaction study in healthy volunteers coadministration of efavirenz with the antimalarial artemisinin-based combination therapy artemether/lumefantrine resulted in reduced exposure (AUC) to artemether, its metabolite dihydroartemisinin, and lumefantrine. Since reduced drug concentrations may result in decreased antimalarial efficacy, caution is recommended when Atripla (triple combination regimen containing efavirenz) and artemether/ lumefantrine are coadministered.
IB/0082/G	This was an application for a group of variations. B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue 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	03/02/2014	n/a		
II/0077	The MAH has submitted an updated RMP version 12 to	23/01/2014	n/a		

	to reflect the most recent discussions on the potential safety concerns; to add the required study ACTG5224 in the pharmacovigilance plan; to include the results of several completed studies; to include the interim results of ongoing studies; to present the summary data of cumulative review of the reversibility of renal tubulopathy associated with tenofovir DF; to update the RMP format to the latest regulatory requirements; and to align the Atripla RMP to the RMPs of other products containing the components of Atripla. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
II/0075	Update of section 4.5 of the SmPC with information on the drug-drug interaction with the HCV protease inhibitors boceprevir and telaprevir and with additional information on the interaction with rifabutin. The PL is updated accordingly. In addition, the PI is being brought in line with the latest QRD template version 9. The PL further is updated to include minor amendments for clarity. The MAH also took this opportunity to implement a minor linguistic correction in the DE annexes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/01/2014	22/01/2015	SmPC and PL	This procedure aimed to update section 4.5 of the SmPC to include information on the interaction of efavirenz with the HCV NS3 protease inhibitors telaprevir and boceprevir and to complement information on the interaction with rifabutin. The drug-drug interaction information on concomitant use of efavirenz with either boceprevir or telaprevir was updated consistently with their respective SmPCs. Additionally, the SmPC was updated to inform prescribers that the recommended dose adjustments for rifabutin when coadministered with efavirenz have not been clinically evaluated. These updates for atripla (fixed-dose combination of efavirenz , emtricitabine and tenofovir disoproxil fumarate) are in line with the approved SmPC for efavirenz

					(Sustiva/Stocrin).
IB/0079	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/01/2014	22/01/2015	SmPC and PL	
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		
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	24/10/2013	n/a		

	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				
IAIN/0074	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	02/10/2013	n/a		
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,	30/05/2013	13/06/2013	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.

	or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				
IG/0288	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	05/04/2013	n/a		
IG/0294	A.7 - Administrative change - Deletion of manufacturing sites	03/04/2013	n/a		
II/0067	Update of sections 4.2, 4.4, 4.5 and 5.2 of the SmPC on mechanism of interactions and in particular on interactions with darunavir, bupropion, rifampicin, atovaquone/proguanil and acenocoumarol and with respect to metabolic enzymes . Section 4.8 is also updated to add hypertriglyceridaemia, hypercholesterolaemia, elevated aspartate aminotransferase, elevated alanine aminotransferase and elevated gamma-glutamyltransferase. The Package Leaflet is updated accordingly. In addition the MAH took the opportunity of this variation to correct minor linguistic error to the French version of the PL. 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	13/06/2013	SmPC and PL	
II/0066	The MAH proposed the update of sections 4.2 and 5.2 of the SmPC on tenofovir exposure when taken on an empty stomach and the update of section 5.1 of the	13/12/2012	13/06/2013	SmPC and Annex II	Sections 4.2 and 5.2 of the SmPC were updated on level of tenofovir exposure when taken on an empty stomach. It is anticipated that tenofovir exposure (AUC) will be

	SmPC to include data from the extension phase of Study GS-01-934. This submission addresses CHMP request during the Renewal (EMEA/H/C/000797/R/0062). In addition the MAH took the opportunity of this variation to implement new Annex II statements as per the latest QRD template. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				approximately 30% lower following administration of Atripla on an empty stomach as compared to the individual component tenofovir disoproxil fumarate when taken with food. Compared to fasted administration, dosing of tenofovir disoproxil fumarate and emtricitabine in combination with either a high fat meal or a light meal increased the mean AUC of tenofovir by 43.6% and 40.5%, and Cmax by 16% and 13.5%. Section 5.1 was updated to reflect the final results of the study GS-01-934 including details on resistance data. Data are available from 286 patients who switched to Atripla: 160 had previously received efavirenz, emtricitabine and tenofovir disoproxil fumarate, and 126 had previously received Combivir and efavirenz. High rates of virologic suppression were maintained by subjects from both initial treatment groups who then received Atripla in the open label extended phase of the study. After 96 weeks of Atripla treatment, HIV 1 RNA plasma concentrations remained < 50 copies/ml in 82% of patients and < 400 copies/ml in 85% of patients. The CHMP endorsed the implementation of these changes and agreed that, overall, these changes do not affect the positive benefit-risk balance of therapy with the fixed dose combination tablet Atripla in HIV infected patients.
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		
IB/0065	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	06/11/2012	13/06/2013	SmPC	

R/0062	Renewal of the marketing authorisation.	19/07/2012	17/09/2012	SmPC, Annex II, Labelling and PL	
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		
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		
IA/0063	C.I.9.h - Changes to an existing pharmacovigilance	13/04/2012	n/a		

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
IB/0057	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	19/01/2012	n/a		
IB/0058	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	04/01/2012	n/a		
IB/0059	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	16/12/2011	n/a		
II/0050	Update of section 4.6 of the Summary of Product Characteristics (SmPC) on efavirenz to be in line with Sustiva (efavirenz). In addition, the MAH took the opportunity to make a minor correction on section 4.4 of the SmPC and to make linguistic corrections to the Polish version C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/10/2011	22/11/2011	SmPC	The Antiretroviral Pregnancy Registry (APR) has received, as of July 2010 prospective reports of 718 pregnancies with first-trimester exposure to efavirenz-containing regimens, resulting in 604 live births. One child was reported to have a neural tube defect, and the frequency and pattern of other birth defects were similar to those seen in children exposed to non efavirenz containing regimens, as well as those in HIV negative controls. The incidence of neural tube defects in the general population ranges from 0.5 1 case per 1,000 live births. In retrospective reports, there have been six cases of findings consistent with neural tube defects including meningomyelocele, all in mothers exposed to efavirenz containing regimens in the first trimester. A causal relationship of these events to the use of efavirenz has not been established and the total number of pregnant women

					exposed to efavirenz-containing regimens is unknown. As neural tube defects occur within the first 4 weeks of foetal development (at which time neural tubes are sealed), this potential risk would concern women exposed to efavirenz during the first trimester of pregnancy. The SmPC was updated to reflect these data and the restriction for women with childbearing potential for Atripla was revised as follows: Atripla should not be used during pregnancy, unless the clinical condition of the woman requires such treatment with efavirenz/emtricitabine/tenofovir disoproxil fumarate. Women of childbearing potential should undergo pregnancy testing before initiation of Atripla. Prescribers are referred to section 5.3 to relevant preclinical safety data.
IA/0051/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	26/10/2011	n/a		
IA/0052/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites 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	20/10/2011	n/a	Annex II and PL	

	place B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.II.b.3.a - Change in the manufacturing process of the finished product - Minor change in the manufacturing process of an immediate release solid oral dosage form or oral solutions				
IB/0048/G	This was an application for a group of variations. B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	08/09/2011	n/a		
WS/0115	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the Product information (PI) in line with the SmPC Guideline, revision 2, September 2009 and the current QRD template version 7.3.1. The MAH took this opportunity to harmonize the PI across the products Viread, Emtriva, Truvada and Atripla. Following CHMP request, section 4.6 "fertility, pregnancy and lactation" of the SmPC was updated	23/06/2011	19/08/2011	SmPC, Annex II, Labelling and PL	The MAH took this opportunity to harmonize the PI across the products Viread (tenofovir disoproxil fumarate), Emtriva (emtricitabine), Truvada (emtricitabine and tenofovir disoproxil fumarate) and Atripla (efavirenz, emtricitabine and tenofovir disoproxil fumarate). Following CHMP request section 4.6 of the SmPC on fertility, pregnancy and lactation was revised. A moderate amount of data mainly from the Antiretroviral Pregnancy Registry on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformations or foetal / neonatal toxicity associated with tenofovir disoproxil fumarate nor with emtricitabine.

	according to the Guideline on Risk Assessment of Medicinal Products on Human Reproduction and Lactation: From Data to Labelling (EMEA/CHMP/203927/2005). In addition a number of minor linguistic amendments were implemented. Furthermore the contact details of the local representatives in the PL were updated. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IA/0049	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	05/07/2011	n/a		
WS/0114	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To extend the retest period of the active substance from 24 months to 36 months. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	23/06/2011	23/06/2011		
IA/0047/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 supplier of the	31/05/2011	n/a		

	AS, starting material, reagent or intermediate used in the manufacture of the AS 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.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				
IB/0046/G	This was an application for a group of variations. C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation 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 C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the	10/05/2011	n/a	Annex II	To update the Detailed Description of the Pharmacovigilance System (DDPS) to version 5.0, dated 16 March 2011 and: - a change in the deputy of the Qualified Person for Pharmacovigilance (QPPV); - a change in the safety database; - a change in the major contractual arrangements. - administrative changes not impacting the operation of the pharmacovigilance system. Annex II.B has also been updated with the latest wording as per the October and November 2010 CHMP procedural announcement. Furthermore minor linguistic corrections were made to the LV annexes.

	back-up procedure of the QPPV				
II/0044	Update of the section 4.8 of the SmPC according to the SmPC Guideline (September 2009) Rev. 2 following CHMP request from the procedure II/29. The MAH took the opportunity of this variation to further update sections 4.2, 4.3, 4.4, 4.5 and 5.2 based on the SmPC Guideline and to align with the Product Information from the individual products including information related to hepatic failure. PL was update accordingly. Annex II was revised with editorial changes. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/11/2010	20/12/2010	SmPC, Annex II and PL	Update of the section 4.8 of the SmPC according to the SmPC Guideline (September 2009) Rev. 2 following CHMP request both as regards structure as well as regards the estimation of frequency for each adverse drug reaction to be in line with the SmPC of the individual products. The MAH took the opportunity of this variation to further update sections 4.2, 4.3, 4.4, 4.5 and 5.2 based on the SmPC Guideline and to align with the Product Information from the individual products including information related to hepatic failure.
WS/0048	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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/10/2010	21/10/2010		
WS/0047	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.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/10/2010	21/10/2010		

II/0029	Update of sections 4.2, 4.4, 4.5, 4.6 and 4.8 of the SmPC to align the information with the efavirenz product information and to include tenofovir related safety information in accordance with the Company Core Data Sheet (CCDS) version 3 for Atripla. The PL was updated in accordance. In addition, the MAH took this opportunity to update contact details of local representatives in the PL. Update of Summary of Product Characteristics and Package Leaflet	18/03/2010	10/05/2010	SmPC and PL	The Product Information of Atripla was updated to reflect recent updates of the efavirenz interaction information, as well as any available new information on interactions with emtricitabine and tenofovir DF. Aiming at the harmonisation of the wording with the efavirenz product information the dose adjustment to 800 mg/day (i.e. additional 200 mg/day) of efavirenz when Atripla is co-administered with rifampicin has been amended to reflect that this dose adjustment may be considered rather than recommended. Also, a statement was included in section 4.4 of the Atripla SmPC on closer monitoring of renal function in patients who have previously experienced renal events while receiving adefovir dipivoxil, similar to that already included in the Viread (tenofovir DF) and Truvada (emtricitabine/tenofovir DF) SmPCs. During the review of cases of possible allergic reaction, a total of 14 reports that involved angioedema or possible symptoms of angioedema were identified in which there was some evidence of a potential causal association with tenofovir DF- or emtricitabine-containing products. As a causal relationship could not be excluded, this adverse side effect was added to the Atripla SmPC as well.
IB/0041	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	16/04/2010	n/a	SmPC, Annex II, Labelling and PL	
IB/0042	To change in-process controls during the manufacture of the finished product. B.II.b.5.z - Change to in-process tests or limits applied	12/04/2010	n/a		

	during the manufacture of the finished product - Other variation				
IA/0040	To introduce minor changes to the manufacturing parameters of the finished product. 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	23/02/2010	n/a		
IB/0039	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	14/01/2010	n/a		
IA/0038	IA_01_Change in the name and/or address of the marketing authorisation holder	28/08/2009	n/a	SmPC, Labelling and PL	
IB/0034	IB_10_Minor change in the manufacturing process of the active substance	18/08/2009	n/a		
IA/0037	IA_09_Deletion of manufacturing site	12/08/2009	n/a		
IA/0036	IA_09_Deletion of manufacturing site	12/08/2009	n/a		
IA/0035	IA_09_Deletion of manufacturing site	09/06/2009	n/a		
IA/0032	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	28/05/2009	n/a		
IA/0033	IA_05_Change in the name and/or address of a manufacturer of the finished product	27/05/2009	n/a		

IB/0031	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	23/04/2009	n/a		
IA/0030	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	27/03/2009	n/a		
IB/0027	IB_17_b_Change in the storage conditions for the active substance	25/03/2009	n/a		
IB/0026	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	25/03/2009	n/a	SmPC	
IA/0028	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	17/03/2009	n/a		
II/0019	Update sections 4.1, 4.4, 4.8, 5.1 and 5.2 of the SPC to reflect the 48 week data results for study AI266073 comparing the efficacy and safety of the single regimen of Atripla with an unmodified HAART regimen in HIV-1 infected virologic suppressed patients. Update of Summary of Product Characteristics	20/11/2008	22/12/2008	SmPC	The 48 week data from study AI266073, an open label study comparing the single tablet regimen Atripla to unmodified HAART in HIV 1 infected subjects who have achieved stable virologic suppression (< 200 copies/ml on two consecutive measurements for at least 3 months) on their current HAART regimen, confirmed the non inferiority of Atripla. However, the relevance of a conclusion on the overall population is somewhat disputable and confidence is deemed necessary that this conclusion is valid for both, the PI and NNRTI stratum. In this field, a signal is raised that patients switching from prior PI-containing antiretroviral regimens to Atripla may do worse than patients staying on their regimen. These patients should therefore be carefully monitored for rises in viral load and, since the safety profile of efavirenz

					differs from that of PIs for adverse events. A warning in this regards has being included in SPC. The safety results from this study do not allow a reliable conclusion however; the available data appears to be in accordance with the known safety profile of the individual compounds of Atripla.
IA/0025	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	17/12/2008	n/a	Annex II and PL	
II/0024	Update of sections 4.4, 4.5 and 4.8 of the SPC with safety related information following the update of the Company Core Safety Information (CCSI). The PL was updated accordingly. Annex IIB was amended to reflect the current version of the RMP and to remove PSUR requirements which were fulifilled. The contact details of the local representative in Austria have been updated in the PL and minor linguistic amendments were made in some EU languages version of the annexes, as relevant. Update of Summary of Product Characteristics and Package Leaflet	23/10/2008	26/11/2008	SmPC, Annex II and PL	The Atripla SPC has been updated in line with the CCSI version 2, dated 29 February 2008. Therefore, section 4.4 and 4.5 of the SPC and section 2 of the PL now warns for the non concomitant administration of Atripla with adefovir dipivoxil (Hepsera) due to possible risk of renal toxicity. The information on HIV/HBV co-infected patients was updated to add a recommendation not to discontinue Atripla in patients with cirrhosis or advanced liver disease since post-treatment exacerbation of hepatitis may lead to hepatic decompensation. Sections 4.4 and section 3 of the PL are updated accordingly. Sections 4.4 and section 2 of the PL are updated to state that bone abnormalities associated with proximal renal tubulopathy may infrequently contribute to fractures. Section 4.8 and section 4 of the PL were updated to include: cerebellar coordination and balance disturbances, hypokalaemia, hepatic steatosis, rhabdomyolysis, and muscular weakness as adverse reactions to Atripla treatment. It is also explained that rhabdomyolysis, osteomalacia, hypokalaemia, muscular weakness, myopathy, and hypophosphatemia may occur as a consequence of proximal renal tubulopathy associated with tenofovir DF treatment.

IB/0023	IB_33_Minor change in the manufacture of the finished product	10/09/2008	n/a		
IB/0021	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	10/09/2008	n/a		
II/0018	Change(s) to the manufacturing process for the active substance	26/06/2008	16/07/2008		
IA/0022	IA_32_a_Change in batch size of the finished product - up to 10-fold	09/07/2008	n/a		
II/0008	Update of section 4.5 of the SPC and section 2 of the PL with interaction with tacrolimus (study GS-US-174-0105) and of sections 4.8 and 5.1 of the SPC with HIV-1 patients co-infected with HBV or HCV and resistance data from the 144 week analysis of study GS-01-934. These amendments align the Product Information for Atripla with its individual components, as agreed at the time of the initial Marketing Authorisation. In addition, minor linguistic changes were made in some of the EU version languages of the Annexes. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	18/06/2008	SmPC and PL	The lack of interaction observed between tacrolimus and the fixed-dose combination emtricitabine/tenofovir DF and the decreased exposure of tacrolimus levels expected when in co-administration with efavirenz are now reflected in the SPC of Atripla. Tacrolimus doses may require adjustment. Tacrolimus levels should be closely monitored at least two weeks of starting or stopping treatment with Atripla. The PL has been updated accordingly. The 144 week resistance analysis of study GS-01-934 (a randomised, open-label, parallel, active-controlled study designed to assess non-inferiority of tenofovir DF + emtricitabine + efavirenz relative to lamivudine/zidovudine + efavirenz in the treatment of HIV-1 infected antiretroviral naïve patients) showed that mutations associated with resistance to efavirenz (predominantly K103N) or with resistance to emtricitabine or lamivudine (M184V/I) occurred less often in the emtricitabine + tenofovir DF group than in the lamivudine/zidovudine group. No subject developed the K65R mutation that can be selected by tenofovir. The SPC information on co-infected HIV-1/HBV (n=13) and

					HIV-1/HCV (n=26) patients included in study GS-01-934 was updated with data from the 144 week analysis.
II/0003	Update of the Detailed Description of the Pharmacovigilance System (DDPS) and the EU Risk Management Plan (RMP) to reflect the MAH change of name. The DDPS format is also updated in line with Volume 9 of the Notice to Applicants. Update of DDPS (Pharmacovigilance)	24/04/2008	18/06/2008	Annex II	The pharmacovigilance system and the EU risk management plan agreed at the time of the initial Marketing Authorisation for Atripla have been updated to reflect the MAH change of the name. Furthermore, the detailed description of the pharmacovigilance system has been updated to the format required by Volume 9 of the Notice to Applicants.
IB/0020	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	23/05/2008	23/05/2008	SmPC, Labelling and PL	
IA/0017	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	10/04/2008	n/a		
IA/0016	IA_09_Deletion of manufacturing site	10/04/2008	n/a		
IA/0015	IA_09_Deletion of manufacturing site	10/04/2008	n/a		
IA/0014	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	10/04/2008	n/a		
IA/0013	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	10/04/2008	n/a		
IA/0012	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	10/04/2008	n/a		

IA/0011	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	10/04/2008	n/a		
IA/0010	IA_09_Deletion of manufacturing site	10/04/2008	n/a		
IA/0009	IA_05_Change in the name and/or address of a manufacturer of the finished product	10/04/2008	n/a		
N/0002	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/02/2008	n/a	PL	
IA/0004	IA_09_Deletion of manufacturing site	14/02/2008	n/a	Annex II and PL	
IA/0001	IA_01_Change in the name and/or address of the marketing authorisation holder	14/02/2008	n/a	SmPC, Labelling and PL	
IA/0007	IA_09_Deletion of manufacturing site	08/02/2008	n/a		
IA/0006	IA_09_Deletion of manufacturing site	08/02/2008	n/a		
IA/0005	IA_09_Deletion of manufacturing site	08/02/2008	n/a		