Truvada

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
IAIN/0171	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	07/05/2021		SmPC and PL	
IB/0170	C.I.11.z - Introduction of, or change(s) to, the	06/05/2021	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).

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/1210/202004	Periodic Safety Update EU Single assessment - emtricitabine / tenofovir disoproxil	12/11/2020	07/01/2021	SmPC, Annex II and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1210/202004.
IB/0168	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Other variation	02/09/2020	07/01/2021	SmPC	
WS/1774	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	18/06/2020	07/01/2021	Annex II, Labelling and PL	
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	04/05/2020	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
IAIN/0162	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	14/02/2020	07/01/2021	SmPC, Labelling and PL	
II/0161	Submission of the final clinical study report for the non-interventional study GS-US-276-0103, 'A Prospective, Observational Study of Individuals Who Seroconvert While Taking Truvada for Pre-Exposure Prophylaxis (PrEP)', listed as a Category 3 study in the Truvada RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/11/2019	n/a		
PSUSA/1210/ 201904	Periodic Safety Update EU Single assessment - emtricitabine / tenofovir disoproxil	31/10/2019	n/a		PRAC Recommendation - maintenance
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	14/03/2019	19/07/2019	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

	the additional risk minimisation measures for tenofovir 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.				with the SmPC recommendation, to remove the following statement 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."

	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/0159	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/02/2019	n/a		
WS/1492	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/12/2018	19/07/2019	SmPC, Labelling and PL	
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	29/11/2018	n/a		

	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
IG/1001	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	23/11/2018	n/a		
PSUSA/1210/201804	Periodic Safety Update EU Single assessment - emtricitabine / tenofovir disoproxil	31/10/2018	n/a		PRAC Recommendation - maintenance
IAIN/0156	B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	26/10/2018	n/a		
WS/1447	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	04/10/2018	n/a		
IG/0985	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	28/09/2018	19/07/2019	SmPC	
IG/0974	B.I.b.1.d - Change in the specification parameters	07/09/2018	n/a		

	and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
IA/0151	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	01/08/2018	n/a		
II/0147	Submission of final results from study Study ATN-113 (CO-US-164-0455), listed as a category 3 study in the RMP; this is a Project PrEPare - An open label demonstration project and phase II safety study of pre-exposure prophylaxis use among 15 to 17 year old men who have sex with men (YMSM) in the United States. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/07/2018	n/a		
WS/1351	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Sections 4.4 and 4.5 of the SmPC for Viread, Truvada and Stribild and Section 4.5 of the SmPC for Eviplera in order to add the results from study Study GS-US-367-1657, listed as a category 3 study in the RMP; this is a Phase 1 Multiple Dose Study to Evaluate the Pharmacokinetic Drug-Drug	19/07/2018	19/07/2019	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 caution and frequently renally monitored.

	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				
T/0148	Transfer of Marketing Authorisation	25/04/2018	04/06/2018	SmPC, Labelling and	

				PL	
WS/1326	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from study GS-EU-104-0433, listed as a category 3 study in the RMP. This is an observational, drug utilisation study (DUS) of Viread in children and adolescents with HIV-1 infection, in fulfilment of a post-authorisation measure (PAM) for Viread (MEA 46) and Truvada (MEA 276). C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/05/2018	n/a		Study GS-EU-104-0433 was requested to collect information on the effectiveness of risk minimization measures for paediatric patients, i.e. the current recommendations stated in the Summary of Product Characteristics (SmPC) as regards the need of renal function monitoring and the educational brochures distributed to Healthcare providers (HCP) specialized in the management of HIV-1 infected paediatric patients. The final results of this DUS in HIV-1 infected children show a low adherence to the renal monitoring recommendations. The dissemination of a new educational brochure to physicians of paediatric HIV-infected patients would be of limited impact, following the recent redistribution of paediatric educational brochures at the end of 2017 for the extension of Truvada indication in HIV-1 infected adolescents. Furthermore, it is anticipated that the use of Tenofovir Disoproxil Fumarate (TDF) as part of antiretroviral regimens in children and adolescent will ultimately be replaced by tenofovir alafenamide (TAF)-containing regimens for which a lesser impact on bone and renal function is expected. Furthermore, the results of this DUS suggest that there were minimal renal or bone safety adverse events across all evaluated laboratory measures observed with the Viread/TDF-Fixed Dose Combinations treatment groups and patients generally recovered within a few weeks of the adverse event; reflecting that population of HIV infected children and adolescents is kept under close scrutiny by

					paediatricians with frequent visits in clinical practice.
II/0135	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	14/12/2017	05/02/2018	SmPC and PL	
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		
PSUSA/1210/ 201704	Periodic Safety Update EU Single assessment - emtricitabine / tenofovir disoproxil	26/10/2017	n/a		PRAC Recommendation - maintenance
II/0138/G	This was an application for a group of variations. Submission of the final report from studies GS-US-276-0101 and GS-US-276-0105, listed as a category 3 studies in the Risk Management Plan. GS-US-276-0101 is a prospective, observational study of pregnancy outcomes among women exposed to Truvada for pre-exposure prophylaxis nested in the antiretroviral pregnancy registry. GS-US-276-0105 is a prospective, observational, drug utilization study of subjects taking Truvada for pre-exposure prophylaxis in the USA. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/09/2017	n/a		Results from study (GS-US-276-0101) to identify missing information safety in pregnancy showed that there were no statistically significant differences in adverse pregnancy outcomes of abortion and birth defects between the pre-exposure prophylaxis group and the treatment group. The current SmPC wording adequately describes recommendations for use of Truvada in pregnancy. Results from study GS-US-276-0105 to identify risks of HIV-1 acquisition including infection resulting from non-adherence and development of resistance in patients with unrecognised or acute infection showed that the majority of users (67.8%) were >80% adherent to the pre-exposure prophylaxis regimen and overall seroconversion rate was low (less than 1% annually). The current SmPC wording sufficiently describes the warnings and precautions associated with adherence to preexposure prophylaxis of HIV-1 infection and the risk of resistance.

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/0140/G	This was an application for a group of variations. B.II.c.2.a - Change in test procedure for an excipient - 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	09/06/2017	n/a		
N/0139	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/06/2017	05/02/2018	PL	
WS/1134	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.5 of the SmPC for Viread and Truvada with interactions between emtricitabine, tenofovir disoproxil fumarate, ledipasvir, sofosbuvir and dolutegavir based on new clinical pharmacology	21/04/2017	05/02/2018	SmPC	Results from the study GS-US-337-1501 showed that an increase (approximately 65%) in the systemic exposure of tenofovir (TFV; the metabolite of TDF) was observed following coadministration of Harvoni and FTC/TDF+DTG, compared with FTC/TDF+DTG alone. The overall tenofovir exposures observed in this study were in the range of those observed when TDF is administered as part of a boosted regimen notably. No clinically significant drug interactions

	data from study GS-US-377-1501. This is a Phase 1, open-label, multiple-dose study that evaluated the pharmacokinetic drug-drug interaction potential between Harvoni (ledipasvir [LDV]/sofosbuvir [SOF]) and FTC/TDF+dolutegravir (DTG). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				were observed between emtricitabine or dolutegravir and Harvoni. Accordingly, Truvada and Viread can be coadministered with Harvoni without dose adjustment but with close monitoring of renal function as the increased exposure of tenofovir could potentiate adverse reactions associated with tenofovir disoproxil fumarate, including renal disorders. Renal function should be closely monitored.
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.	21/04/2017	05/02/2018	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-342-1167 is a Phase I Study to Evaluate the Pharmacokinetic Drug-Drug Interactions between Sofosbuvir/GS-5815 Fixed Dose Combination (FDC) Tablets and Antiretrovirals Efavirenz/Emtricitabine/Tenofovir Disoproxil Fumarate (EFV/FTC/TDF; Atripla), Emtricitabine/Riplivirine/Tenofovir Disoproxil Fumarate (FTC/RPV/TDF; Complera), Dolutegravir (DTG; Tivicay) o Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Alafenamide Fumarate (EVG/COBI/FTC/TAF) in Healthy Subjects. Study GS-US-342-1326, a Phase I Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between Sofosbuvir/GS-5816 (SOF/GS-5816) Fixed-Dose Combination (FDC) Tablet and HIV Antiretroviral Regimens Elvitegravir/Cobicistat/Emtricitabine/Tenofovir Disoproxil Fumarate (EVG/COBI/FTC/TDF), Ritonavir-boosted Darunavir (DRV/r) plus 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				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.

II/0131	Extension of Indication for Truvada in the treatment of human immunodeficiency virus, type 1 (HIV-1) infected adolescents, with nucleoside reverse transcriptase inhibitor (NRTI) resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated in order to include information on the target patient population, posology, warnings, interactions, undesirable effects and pharmacodynamics derived from three studies with emtricitabine (FTC-202, FTC-203 and FTC-211) and two studies with tenofovir disoproxil fumarate in paediatric populations (GS-US-104-0321 and GS-US-104-0352). The Package Leaflet and the Risk Management plan (RMP version 13.1) are updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	23/02/2017	24/03/2017	SmPC and PL	Please refer to the Scientific Discussion Truvada EMEA/H/C/000594/II/0131.
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		
PSUSA/1210/ 201604	Periodic Safety Update EU Single assessment - emtricitabine / tenofovir disoproxil	27/10/2016	n/a		PRAC Recommendation - maintenance

IG/0725	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	21/10/2016	n/a		
IG/0726	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	19/09/2016	n/a		
II/0126	Extension of the indication to add Pre-exposure prophylaxis (PrEP) in combination with safer sex practices to reduce the risk of sexually acquired HIV-1 in adults at high risk. As a consequence, sections 4.1, 4.2, 4.3, 4.4, 4.5, 4.7, 4.8, 4.9, 5.1, 5.2 and 5.3 of the SmPC are updated. The annex II is updated to include additional risk minimisation measures. Furthermore, the MAH performed minor linguistic amendments. The Package Leaflet is updated in accordance. In addition, the MAH took the opportunity of this variation to perform minor linguistic amendments in the translations of the product information for Truvada. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/07/2016	18/08/2016	SmPC and PL	Please refer to the scientific discussion 'Truvada EMEA/H/C/000594/II/0126'.

WS/0920	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final clinical study report (CSR) for the Stribild study GS-US-236-0103 in fulfilment of a post-authorisation measure (PAM) for Viread and Truvada. The provision of the final study report (Week 192) is an additional pharmacovigilance activity (category 3) in the Risk Management Plan associated with the important identified risk of bone events due to proximal renal tubulopathy /loss of bone mineral density. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	28/04/2016	n/a		
WS/0903/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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	28/04/2016	n/a		

	authorisation, including the RMP - Other variation				
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	18/08/2016	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 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	18/08/2016	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.
IA/0128	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	22/02/2016	n/a		
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	18/08/2016	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,	17/12/2015	11/02/2016	SmPC	

	Eviplera, Stribild and Atripla (category 3 additional pharmacovigilance activity for Viread, Truvada, Eviplera and Stribild, and category 4 for Atripla). An updated RMP (version 18.0 for Viread, 9.0 for Truvada, 13.0 for Atripla, 9.0 for Eviplera and 6.0 for Stribild) is agreed accordingly. Following the review and assessment of the data provided, section 4.4 of the SmPC was updated to add a warning regarding the more pronounced decreases in Bone Mineral Density seen in patients treated with TDF as part of boosted PI therapy. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IG/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		
PSUSA/1210/ 201504	Periodic Safety Update EU Single assessment - emtricitabine / tenofovir disoproxil	08/10/2015	n/a		PRAC Recommendation - maintenance
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	11/02/2016	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		
IG/0521	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	26/02/2015	11/02/2016	Annex II and PL	
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 authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH	26/02/2015	n/a		

	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				
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	10/03/2015	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."
PSUV/0108	Periodic Safety Update	04/12/2014	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	25/09/2014	n/a		

	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				
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 (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	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 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		
IG/0469	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	07/08/2014	n/a		

WS/0586	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. WSA for Atripla, Truvada, Stribild, Viread and Eviplera to update sections 4.4 and 4.8 of the SmPC for all tenofovir disoproxil fumarate (TDF)-containing products to revise the renal monitoring recommendations and to implement additional renal safety information. The Package Leaflet was updated accordingly and the key messages for the annex II for Viread and Atripla were updated to reflect this information as appropriate. The MAH submitted this variation in fulfilment of a post-autorisation measure 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	24/07/2014	10/03/2015	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 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	24/07/2014	10/03/2015	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. 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 Veterinary Medicinal Products - Other variation				cumulative review requested by PRAC.
IG/0448	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	02/07/2014	n/a		
IG/0422	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	28/03/2014	n/a		
IB/0097/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	28/03/2014	n/a		

	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				
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	10/03/2015	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.
N/0095	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/02/2014	10/03/2015	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 Commission Regulation (EC) No 1234/2008, to introduce an alternative manufacturer and release testing site of the active substance emtricitabine.	24/10/2013	n/a		

	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation				
IB/0090/G	This was an application for a group of variations. 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 currently approved batch size 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	29/07/2013	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.	30/05/2013	01/07/2013	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.

	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				
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		
IG/0290	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/04/2013	n/a		
N/0085	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/02/2013	01/07/2013	PL	
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		
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.	21/06/2012	21/06/2012		

	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				
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		
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		
IB/0070	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	09/11/2011	n/a		
IG/0114/G	This was an application for a group of variations. C.I.9.d - Changes to an existing pharmacovigilance	17/10/2011	n/a		

	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				
IB/0069/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)	30/08/2011	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 according to the Guideline on Risk Assessment of	23/06/2011	27/07/2011	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.

	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				
IG/0078	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	14/07/2011	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/0068	A.7 - Administrative change - Deletion of manufacturing sites	29/04/2011	n/a	Annex II and PL	
IA/0067	B.II.b.5.b - Change to in-process tests or limits	22/03/2011	n/a		

	applied during the manufacture of the finished product - Addition of a new tests and limits				
IG/0047/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.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.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	10/03/2011	n/a	Annex II	
II/0064	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/09/2010	26/11/2010	SmPC and PL	Update of section 4.5 of the SmPC, in line with Annex A of the HIV guideline and the SmPC Guideline in response to a commitment made during the Truvada renewal. This section was further updated to include the interaction of ritonavir boosted darunavir when co-administered with tenofovir disoproxil fumarate (tenofovir DF) and to align interactions within tenofovir DF containing products. The MAH took the opportunity of this variation to delete from section 4.4 of the SmPC reference to zalcitabine as it is no longer licensed in the European Union.
II/0063	Update of section 4.4 of the SmPC to add an additional warning about hepatic events as a	23/09/2010	26/11/2010	SmPC	In the 7th Truvada PSUR the MAH provided an updated cumulative review on immune reconstitution syndrome.

	manifestation of Immune Reconstitution Syndrome (IRS) in HIV infected patients co-infected with hepatitis B (HBV) as requested by the CHMP in October 2009 following evaluation of the PSUR covering the period 03 April 08 to 02 April 09. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				This review identified a total of 104 cases of IRS cumulative to 29th February 2008 for emtricitabine- and tenofovir DF-containing products. 18 cases were identified reporting hepatic disorders as the manifestation of IRS involved: one case with Emtriva, four with Truvada, eight with Viread, and five with Emtriva and Viread.). Based on this review the MAH submitted this variation to include a warning for HIV infected patients co-infected with hepatitis B virus. These patients may experience acute exacerbations of hepatitis associated with immune reactivation syndrome following the initiation of antiretroviral therapy.
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		
IA/0066	B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold	23/09/2010	n/a		

	compared to the currently approved batch size				
II/0054	Update of sections 4.4, 4.5 and 4.8 of the SmPC and sections 2 and 4 of the PL with safety related information following the update of the Company Core Data Sheet. In addition section 4.8 was fully revised according to the SmPC guideline and updated in regard of the adverse reaction's frequency aiming consistency throughout all tenofovir DF-containing products, as requested by the CHMP in October 2008. Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/07/2010	31/08/2010	SmPC, Labelling and PL	This type II variation added statements regarding non-concomitant use of adefovir dipivoxil and non-concomitant use of other medicinal products containing any of the components of Truvada: Viread (tenofovir DF), Emtriva (emtricitabine) and Atripla (tenofovir DF, emtricitabine, efavirenz). Section 4.8 was updated to include the new postmarketing events of 'angioedema' and 'exacerbations of hepatitis after discontinuation of treatment with Truvada in patients co-infected with HIV and hepatitis B'. This section was also updated according to the SmPC guideline and a full revision was performed to the reporting frequencies of adverse reactions in section 4.8 in order to be consistent throughout all tenofovir DF-containing products.
IA/0065	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	13/08/2010	n/a	Annex II	
R/0062	Renewal of the marketing authorisation.	19/11/2009	20/01/2010	SmPC, Annex II, Labelling and PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that the benefit risk balance of Truvada continues to be favourable. The CHMP recommended the renewal of the Marketing Authorisation for Truvada with

					unlimited validity.
IB/0059	IB_10_Minor change in the manufacturing process of the active substance	17/06/2009	n/a		
IA/0061	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	29/05/2009	n/a		
IA/0060	IA_09_Deletion of manufacturing site	29/05/2009	n/a		
IB/0058	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	15/05/2009	n/a	SmPC	
IB/0057	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	27/04/2009	n/a		
IA/0056	IA_05_Change in the name and/or address of a manufacturer of the finished product	07/04/2009	n/a		
IA/0055	IA_09_Deletion of manufacturing site	07/04/2009	n/a		
IB/0053	IB_33_Minor change in the manufacture of the finished product	07/01/2009	n/a		
IB/0052	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	07/01/2009	n/a		
II/0044	Update the dosing recommendations for renal impairment in sections 4.2, 4.4 and 5.2 of the SPC to reflect the results of a study conducted in HIV-1 infected renal impaired patients and changes made for tenofovir disoproxil fumarate's product	20/11/2008	22/12/2008	SmPC and PL	Limited available data from an open label study designed to evaluate the safety, tolerability, efficacy, and pharmacokinetics of tenofovir disoproxil fumarate in combination with emtricitabine for 48 weeks in treatment-naïve and treatment-experienced HIV 1 infected patients

	information as regards renal impairment. The contact details for the local representatives in Austria, Belgium, Cyprus, Denmark, Finland, Greece, Iceland, Luxembourg, Netherlands, Norway and Sweden were updated in section 6 of the PL. Futhermore, minor linguistic amendments were made to the German and Greek versions of the annexes, as relevant. Update of Summary of Product Characteristics and Package Leaflet				with different degrees of renal impairment is now reflected in section 4.2, 4.4 and 5.2 of the SPC. This study, which enrolled only 8 patients with varying degrees of renal impairment, supports the existing advice that no dose adjustment to the normal once daily dosing is required in patients with mild renal impairment. However, very careful consideration and benefit risk assessment is needed in all patients with Creatinine Clearance (CrCl) <60 ml/min. The limited data available indicate that in patients with borderline CrCl (close to 50 ml/min), current dosing recommendation of one tablet in every 24 h resulted in 2- to 4-fold increase in tenofovir exposure which was accompanied by decreased renal function and discontinuation due to adverse events.
IA/0051	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	21/10/2008	n/a		
IA/0050	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	22/09/2008	n/a		
II/0045	Update of sections 4.4 and 4.8 of the SPC and sections 2, 3 and 4 of the PL in accordance with the recent updates to the Company Core Safety Information (CCSI version 7, dated 20 December 2007) as regards renal, hepatic and bone safety information. In addition minor linguistic changes are made to the German version of the annexes in order to further improve clarity. Update of Summary of Product Characteristics and	24/07/2008	29/08/2008	SmPC and PL	Section 4.4 of the SPC and section 2 of the PL were updated to indicate that bone abnormalities associated with proximal renal tubulopathy may infrequently contribute to fractures. In section 4.4 of the SPC, the term Pneumocystis carinni pneumonia was replaced by Pneumocystis jiroveci pneumonia which is a more medically accepted term. Section 4.4 of the SPC and section 3 of the PL were updated regarding post-treatment exacerbation of hepatitis following discontinuation of therapy. This includes addition of a recommendation not to discontinue Truvada in patients with cirrhosis or advanced liver disease.

	Package Leaflet				Section 4.8 of the SPC and section 4 of the PL were updated to include hypokalaemia, hepatic steatosis, rhabdomyolysis, and muscular weakness and wording to indicate that osteomalacia may be manifested as bone pain and infrequently contribute to fractures. Explanatory text was added in section 4.8 to indicate that the adverse reactions of rhabdomyolysis, osteomalacia, hypokalaemia, muscular weakness, myopathy, and hypophosphatemia may occur as a consequence of proximal renal tubulopathy and that these events are not considered to be causally associated with tenofovir disoproxil fumarate (tenofovir DF) therapy in the absence of proximal renal tubulopathy.
IA/0049	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	08/08/2008	n/a		
IA/0048	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	08/08/2008	n/a		
IA/0047	IA_09_Deletion of manufacturing site	08/08/2008	n/a		
IB/0046	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	05/06/2008	05/06/2008	SmPC, Labelling and PL	
IA/0043	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	30/04/2008	n/a	Annex II and PL	
II/0036	Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	28/02/2008	SmPC and PL	The 144 week data show that a significantly higher proportion of subjects in the emtricitabine + tenofovir DF group (71%) compared with the lamivudine/zidovudine

	Update of sections 4.8 and 5.1 of the SPC with 144 week efficacy, safety and resistance data of study GS-01-934 in HIV-1 infected antiretroviral naïve patients comparing emtricitabine, tenofovir DF in combination with efavirenz versus with lamivudine/zidovudine and efavirenz. Minor linguistic changes were made in the German and Greek PL. Update of Summary of Product Characteristics and Package Leaflet				group (58%) achieved and maintained plasma HIV-1 RNA < 400 copies/ml. The corresponding percentages for HIV 1 RNA < 50 copies/ml were not statistically significantly different between the groups. The 144 week resistance analysis 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 group than in the lamivudine/zidovudine group. It is notable that no subject developed the K65R mutation that can be selected by tenofovir. In relation to co-infected HIV-1/HBV patients, no conclusions can be drawn regarding the potential efficacy of emtricitabine/tenofovir DF and its relative efficacy vs lamivudine in controlling HBV replication based on the limited number of co-infected patients in this study (n=13 with a mixture of HBeAg+ and HBeAg-). The long term safety data in antiretroviral naïve patients are reassuring as regards the safety profile of the combined use of emtricitabine + tenofovir DF. There appeared to be less nausea and anaemia with this regimen then with lamivudine/zidovudine. No new signal has emerged concerning any higher risk of fractures, skin hyperpigmentation and renal toxicity. Treatment was discontinued in 5% in the emtricitabine + tenofovir DF group due to treatment-emergent adverse events and 11% in the lamivudine/zidovudine group.

					Smaller increases in fasting serum triglycerides and total cholesterol levels occurred in the emtricitabine/tenofovir DF group compared with the lamivudine/zidovudine group. The emtricitabine/tenofovir group demonstrated a preferential effect on lipid metabolism and limb fat compared to lamivudine/zidovudine.
IA/0041	IA_05_Change in the name and/or address of a manufacturer of the finished product	27/02/2008	n/a		
II/0035	Update of Summary of Product Characteristics, Labelling and Package Leaflet Update of section 4.8 of the SPC to include "anaemia" to the list of adverse reactions and update of section 4.5 with information from the tacrolimus interaction study, as requested by the CHMP following the assessment of the 4th PSUR (covering the period from 3 August 2006 to 2 February 2007). Section 4 of the PL is amended accordingly. Furthermore minor linguistic changes were introduced to the Bulgarian, Czech, Danish, Estonian, French, German, Greek, Icelandic, Italian, Latvian, Polish, Romanian, Slovakian and Slovenian SPC, Labelling and PL, as relevant. Update of Summary of Product Characteristics, Labelling and Package Leaflet	15/11/2007	18/12/2007	SmPC, Labelling and PL	Data from a cumulative review of anaemia cases in adult patients on treatment with emtricitabine as well as data from clinical trials suggested that emtricitabine can cause anaemia, in between 0.5 and 1.0% of patients. Based on these findings, "anaemia" was included in the Emtriva product information as an uncommon adverse reaction to emtricitabine treatment in adult patients, in a variation approved in August 2007. For consistency, "anaemia" is now also being added in the Truvada product information as an uncommon adverse reaction. In addition, results from a pharmacokinetic study did not show any clinically relevant drug-drug interactions between Truvada and tacrolimus. This information has been included in the SPC.
IA/0040	IA_05_Change in the name and/or address of a manufacturer of the finished product	07/11/2007	n/a		

IA/0039	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	18/10/2007	n/a		
IA/0038	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	18/10/2007	n/a		
IA/0037	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	18/10/2007	n/a		
II/0034	Quality changes	20/09/2007	26/09/2007		
IA/0033	The Marketing Authorisation Holder applied to up-date the ATC code for Truvada from J05AF30 to J05AR03 IA_06_a_Change in ATC code: Medicinal products for human use	06/06/2007	n/a	SmPC	
II/0030	Update of sections 4.2 and 4.4 of the SPC with a warning regarding the possible exacerbation of hepatitis when the treatment is discontinued. In addition, the warning in section 4.4 regarding co-administration with didanosine is updated with regards to CD4 cell counts. Section 2 of the PL is amended in accordance. Update of Summary of Product Characteristics and Package Leaflet	22/03/2007	24/04/2007	SmPC and PL	The risk of hepatitis reactivation after emtricitabine or tenofovir discontinuation and the possible severity of the reactivation are now reflected in the SPC of the fixed combination emtricitabine/tenofovir product -Truvada. A recommendation to closely monitor patients co-infected with HIV and HBV for evidence of exacerbation of hepatitis is also added to section 4.2 of the SPC. The warnings on the co-administration of tenofovir DF and didanosine have been amended to reflect the suppression of CD4 cell counts observed in patients who were taken both agents at the same time. Furthermore the whole paragraph of this warning has been reworded and reorganised in section 4.4. The PL was amended

					accordingly.
II/0029	Update of sections 4.2 and 4.4 of the SPC with renal safety information including updated dosing guidelines based on an analysis of relevant tenofovir disoproxil fumarate clinical studies. The MAH also took the opportunity to update the EMEA website address in the SPC and PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/03/2007	24/04/2007	SmPC, Annex II, Labelling and PL	Tenofovir exposure is increased in patients with renal impairment. A dosing interval adjustment is recommended for patients with moderate renal impairment (creatinine clearance 30-49 ml/min) and Truvada is not recommended in patients with severe renal impairment (creatinine clearance <30 ml/min) and in haemodialysis patients. However, concerning patients with mild renal impairment (creatinine clearance 50-80 ml/min), limited available data from three clinical studies have not indicated that the safety and efficacy profile of tenofovir disoproxil fumarate is different to the profile in patients with normal renal function. These limited data tend to support the existing advice that no dosing adjustment to the normal once daily dosing is required in patients with mild renal impairment. This information was reflected in section 4.2 of the SPC. Section 4.4 of the SPC was also updated with renal safety information concerning possible renal adverse events and the need to assess the potential benefit of tenofovir disoproxil fumarate therapy in patients with moderate renal impairment against the potential risk of renal toxicity.
IB/0032	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	17/04/2007	n/a	SmPC	
IA/0031	IA_01_Change in the name and/or address of the marketing authorisation holder	14/03/2007	n/a	SmPC, Labelling and PL	
II/0025	Update of section 4.5 SPC to reflect the results of a pharmacokinetic study investigating the potential	24/01/2007	01/03/2007	SmPC and PL	A pharmacokinetic study performed in 24 healthy subjects which during 10 days received tenofovir DF 300 mg in

	interactions between tenofovir and rifampicin. In addition, Section 4.5 is further updated in regard of the interactions between tenofovir DF and lopinavir/ritonavir and atazanavir/ritonavir, as agreed for Viread at the time of the renewal. Section 2 and section 4 of the PL are also amended accordingly to the CHMP requests. Update of Summary of Product Characteristics and Package Leaflet				combination with rifampicin 600 mg, once daily showed no clinically relevant interactions between these two drugs. Section 4.5 of the SPC reflects this information. This section was further update in regard to the interactions of tenofovir with lopinavir/ritonavir and with atazanavir/ritonavir in particular to stress the fact that higher concentrations of tenofovir could increase the potential for adverse reactions, including renal disorders. The PL was updated in section 2 and 4 in line with the above changes and with changes made to the Viread PL following the renewal.
II/0028	Quality changes	22/02/2007	26/02/2007		
II/0023	Quality changes	22/02/2007	26/02/2007		
II/0024	Update of sections 4.4 and 4.8 of the SPC and section 2 of the PL to implement the class labelling text on osteonecrosis, agreed by the CHMP in September 2006. Section 6 of the PL was updated with the local representatives in Bulgaria and Romania. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	12/01/2007	SmPC and PL	Cases of osteonecrosis (death of the bone tissue resulting from an insufficient blood supply) have been reported in HIV-infected patients since the end of the 80's. Although the cause of this disease could be due to multi factors (including the use of corticosteroids, alcohol consumption, severe immunosuppression, higher body mass index) it has occurred specially in patients with HIV advanced disease and/or in patients with long term use of combination antiretroviral therapy (CART). Further to the review of all available data the CHMP agreed that this information should now be included in the SPC and PL of all antiretroviral medicinal products. Patients should be warned to seek medical advice in case they experience joint stiffness, aches and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.

IB/0027	IB_33_Minor change in the manufacture of the finished product	20/12/2006	n/a		
IB/0026	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	20/12/2006	n/a		
II/0018	Update of section 4.8 of the SPC and section 4 of the PL to include "myopathy, osteomalacia (both in association with proximal renal tubulopathy)" and "acute interstitial nephririts" in light of the cumulative review of renal events for tenofovir. The MAH has also taken this opportunity to amend the SPC, Annex II, labelling and the PL in line with the latest EMEA QRD template and to introduce minor linguistic changes to some EU languages, as relevant. In addition, the list of local representatives in some EU Member States were updated in section 6 of the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	27/07/2006	28/08/2006	SmPC, Annex II, Labelling and PL	A review of the bone events in renal cases showed that 8 of the 12 cases with evidence for a positive tenofovir dechallenge included osteomalacia. In non-clinical studies tenofovir was already associated with osteomalacia in monkeys. Osteomalacia was recognised as an adverse reaction to tenofovir treatment but for which the frequency is currently not known. The muscle events in cases of possible fanconi syndrome were also reviewed: in 8 of the 15 cases describing muscle events, a positive dechallenge with clear improvement of the muscle symptoms was described. Myopathy is therefore an adverse reaction to tenofovir treatment for which the frequency is currently not known. A cumulative review of renal disorders lead to the inclusion of acute interstitial nephritis as an adverse reaction to tenofovir treatment. Section 4.8 of the SPC and section 4 of the PL were amended in accordance.
IB/0022	IB_10_Minor change in the manufacturing process of the active substance	11/08/2006	n/a		
IB/0021	IB_10_Minor change in the manufacturing process of the active substance	11/08/2006	n/a		
IA/0020	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	03/07/2006	n/a		

IA/0017	IA_09_Deletion of manufacturing site	30/05/2006	n/a		
IA/0016	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	30/05/2006	n/a		
II/0013	Update of section 4.8 of the SPC and section 4 of the PL, to reflect the results of 48-week data from three clinical studies evaluating emtricitabine in combination with other antiretroviral agents in HIV infected paediatric patients. Update of Summary of Product Characteristics and Package Leaflet	23/02/2006	29/03/2006	SmPC and PL	Safety results of three clinical studies conducted in HIV-1 infected children treated with emtricitabine in combination with other antiretroviral medicinal products showed that anemia and skin discolouration (increased pigmentation) occurred more frequently in children compared to adults. This information is currently reflected in the emtricitabine product information - Emtriva, approved for use in children older than 4 months. Although Truvada, the fixed combination product of emtricitabine and tenofovir disoproxil (as fumarate) is not approved for use in children, this safety information has been included in section 4.8 of the SPC and in section 4 of the PL for Truvada.
II/0011	Update of section 4.5 of the SPC in view of the results from two pharmacokinetic drug interaction studies between tenofovir DF and saquinavir (unboosted and ritonavir boosted) and nelfinavir respectively. Update of Summary of Product Characteristics	26/01/2006	28/02/2006	SmPC	Two pharmacokinetic studies performed in healthy volunteers investigating potential interactions between tenofovir DF and saquinavir (unboosted and ritonavir boosted) and nelfinavir, respectively showed no clinically relevant interactions. However, while for the concomitant use of tenofovir DF and nelfinavir no effect was observed for saquinavir (boosted regimen) an increased exposure was observed when tenofovir DF is co-administrated. This increase is considered no to be clinically relevant and the SPC has been amended in section 4.5 to reflect these results.
IA/0015	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	13/01/2006	n/a		

II/0010	Update of section 5.3 of the SPC to reflect the results of the one-month dog repeat dose toxicity study and the results of two in vitro genotoxicity studies as requested by the CHMP following the assessment of the in vitro final study reports. Update of Summary of Product Characteristics	17/11/2005	23/12/2005	SmPC	The 4 week repeat dose toxicity study in dogs investigating whether the combination treatment (emtricitabine/tenofovir DF) could enhance the renal toxicity observed with tenofovir DF alone revealed that the presence of emtricitabine did not enhance the toxicity of tenofovir DF. No exacerbation of the toxicological effects was found compared to the separate components. The mutagenicity of emtricitabine was previously found to be negative in a range of mutagenicity tests whilst tenofovir DF was positive in a number of in vitro genotoxicity assays. The two in vitro studies performed with combination emtricitabine/tenofovir DF which were assessed by the CHMP in June 2005 showed that Truvada displays mutagenicity in a mammalian mutagenesis assay comparable to that observed with tenofovir DF alone. Section 5.3 of the SPC has been updated to reflect these findings.
IB/0012	IB_10_Minor change in the manufacturing process of the active substance	21/12/2005	n/a		
IA/0014	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	16/12/2005	n/a		
II/0003	Update section 5.1 of the SPC to reflect the 48 week efficacy, safety and resistance data from a clinical study in antiretroviral naïve, HIV-1 infected patients comparing Truvada plus efavirenz versus Combivir plus efavirenz Update of Summary of Product Characteristics	13/10/2005	16/11/2005	SmPC	This is an ongoing, open-label, randomized, active-controlled study comparing the efficacy and safety of tenofovir DF + emtricitabine + efavirenz and lamivudine/zidovudine + efavirenz in HIV-1 infected antiretroviral naïve patients. This is the 48 week follow-up of the pivotal GS-01-934 study supportive of the initial Marketing Authorisation for Truvada.

					The efficacy results showed superior antiviral activity of the tenofovir DF + emtricitabine arm compared with the lamivudine/zidovudine arm. No new or novel mutation associated with phenotypic resistance to either emtricitabine or tenofovir has developed. Section 5.1 was updated to reflect these results. The 48 week safety data are reassuring in terms of the safety profile of the combined use of tenofovir DF + emtricitabine. No new information has emerged concerning skin pigmentation or bone and renal toxicity and the existing warnings in the SPC remain sufficient.
II/0005	Update of sections 4.4, 4.5 and 4.8 of SPC and corresponding sections of PL further to CHMP request and additional safety data related to post-marketing experience of the individual components of Truvada, to ensure consistency. Minor linguistic changes were made in the SPC, Labelling or PL for some of the EU languages, as relevant. Update of Summary of Product Characteristics, Labelling and Package Leaflet	15/09/2005	25/10/2005	SmPC, Labelling and PL	Further to the initial Marketing Authorisation of Truvada the safety information of the individual components (emtricitabine - Emtriva and tenofovir disoproxil fumarate - Viread) has been updated in view of post-marketing experience. The Truvada safety information is being updated in line with those changes. Sections 4.4 and 4.5 of the SPC include recommendations and warnings regarding co-administration of tenofovir and didanosine. Wording regarding laboratory markers of proximal tubulopathy has been incorporated into section 4.4. Nephritis and nephrogenic diabetes insipidus were included in the undesirable effects section as an outcome of the review of cumulative cases reported for Viread. Further amendments in terms of system organ class, frequency and adverse drug reactions were made in view of the harmonization of the safety information with Emtriva and Viread. The PL was updated in accordance.
IB/0009	IB_33_Minor change in the manufacture of the finished product	11/10/2005	n/a		

IB/0007	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	15/09/2005	n/a		
IA/0008	IA_32_b_Change in batch size of the finished product - downscaling down to 10-fold	24/08/2005	n/a		
IB/0004	IB_10_Minor change in the manufacturing process of the active substance	03/08/2005	n/a		
II/0002	Quality changes	23/06/2005	28/06/2005		
IA/0001	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	06/04/2005	n/a		