Viread

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
PSUSA/2892/ 202303	Periodic Safety Update EU Single assessment - tenofovir disoproxil	14/12/2023	16/02/2024		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2892/202303.
IA/0209/G	This was an application for a group of variations.	13/02/2023	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).

	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				
IB/0208	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/12/2022	31/05/2023	SmPC and PL	
IG/1570/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	08/11/2022	n/a		
II/0204	Update of the section 5.1 of the Viread SmPC based on the final study report for study GS-US-174-0144, listed as category 3 study in the RMP for Viread. This is a randomized, double-blind evaluation of the antiviral efficacy, safety and tolerability of Tenofovir disoproxil fumarate. This application fulfils the Article 46 requirement to provide the final (Week 192) study results. The risk minimisation measures for the paediatric population are being removed from the Risk Management Plan (RMP) and Annex II of the PI. The RMP version 26 has been submitted. The MAH also took the opportunity to implement minor linguistic amendments throughout the PI. In addition, the expression of lactose content in Annex I for the tablets was changed, to refer to lactose base (not as monohydrate), in line with current practice.	24/02/2022	31/05/2023	SmPC and Annex II	

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IG/1456	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	08/11/2021	n/a		
N/0203	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/04/2021	31/05/2023	PL	
PSUSA/2892/ 202003	Periodic Safety Update EU Single assessment - tenofovir disoproxil	12/11/2020	14/01/2021	SmPC, Annex II, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2892/202003.
IB/0201	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/11/2020	n/a		
IA/0202/G	This was an application for a group of variations. 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) 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)	22/10/2020	n/a		

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	14/01/2021	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		
PSUSA/2892/ 201903	Periodic Safety Update EU Single assessment - tenofovir disoproxil	14/11/2019	16/01/2020	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2892/201903.
II/0191	Extension of Indication based on results from interim Week 48 clinical study report (CSR) for Study GS-US-174-0144; a 'Randomized, Double-Blind Evaluation of the Antiviral Efficacy, Safety and Tolerability of Tenofovir Disoproxil Fumarate Versus Placebo in Pediatric Patients with Chronic Hepatitis B Infection', resulting in the following changes: 1) Viread 123 mg, 163 mg and 204 mg film coated tablets: new chronic hepatitis B (CHB) indication to include treatment of CHB in paediatric patients aged 6 to < 12 years, update of Sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 of the SmPC. 2) Viread 245 mg film-coated tablets, update of Sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC.	28/02/2019	08/04/2019	SmPC and PL	Please refer to the Scientific Discussion – Viread-191.

	3) Viread granules 33 mg/g: extension of the existing CHB indication to include treatment of CHB in paediatric patients aged 2 to < 12 years, update of Sections 4.1, 4.2, 4.4, 5.1 and 5.2 of the SmPC. The Package Leaflet has been updated accordingly for all formulations. In addition, a discrepancy in the PI regarding the recommendation pertaining to pregnancy was corrected, by aligning the PL wording with that of the SmPC. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0196	Submission of the final abbreviated clinical study report from the post-authorisation safety study (PASS) GS-EU-174-1403, a pharmacoepidemiology study to define the long-term safety profile of tenofovir disoproxil fumarate (TDF) and describe the management of TDF-associated renal and bone toxicity in Chronic Hepatitis B (CHB)-infected adolescents aged 12 to <18 years in Europe, listed in the Viread RMP as a category 3 study. This submission fulfils this additional pharmacovigilance activity and fulfils the post-authorisation measures MEA 255.1, MEA 255.2 and MEA 265.8. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/01/2019	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	08/04/2019	SmPC, Labelling and PL	
PSUSA/2892/ 201803	Periodic Safety Update EU Single assessment - tenofovir disoproxil	31/10/2018	n/a		PRAC Recommendation - maintenance
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	08/04/2019	SmPC	
IG/0974	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	07/09/2018	n/a		
II/0190	Update of the RMP to version 23.0 to remove the additional risk minimization activities (healthcare professional educational program) for the identified	06/09/2018	08/04/2019	Annex II	

	risk of renal toxicity for HIV and HBV adult patients. The RMP was also updated in accordance with the revised guidance in the Guideline on good pharmacovigilance practices Module V. Annex II.D is also updated accordingly to remove the adult HIV and HBV renal educational brochure information. 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/0188	Submission of the final report from study GS-EU-174-0224 listed as a category 3 study in the RMP. This is a cross-sectional drug utilisation study in children and adolescents with Chronic Hepatitis B to assess whether physicians prescribing Viread to paediatric patients with Chronic Hepatitis B in the EU were following the relevant recommendations in the Viread SmPC and educational brochures. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/09/2018	n/a		
II/0186	Submission of the final report from study GS-EU-174-1846, listed as a category 3 study in the RMP, in fulfilment of MEA 273. This is a 'multicenter, non-interventional, retrospective, matched cohort study	06/09/2018	n/a		

	of patients monoinfected with chronic hepatitis B and with moderate or severe renal impairment treated with Viread or Baraclude'. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
T/0187	Transfer of Marketing Authorisation	25/04/2018	23/07/2018	SmPC, Labelling and PL	
WS/1351	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Sections 4.4 and 4.5 of the SmPC for Viread, Truvada and Stribild and Section 4.5 of the SmPC for Eviplera in order to add the results from study Study GS-US-367-1657, listed as a category 3 study in the RMP; this is a Phase 1 Multiple Dose Study to Evaluate the Pharmacokinetic Drug-Drug Interaction Potential between Sofosbuvir/Velpatasvir/Voxilaprevir Fixed-Dose Combination and HIV Antiretroviral in Healthy 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	19/07/2018	08/04/2019	SmPC and PL	Results from Study GS-US-367-1657 showed that co administration of tenofovir disoproxil with sofosbuvir/velpatasvir/voxilaprevir and darunavir/ritonavir increases plasma concentrations of tenofovir and may lead to adverse reactions related to tenofovir disoproxil. The combination of tenofovir disoproxil containing products (Viread, Truvada, Eviplera, Stribild) and sofosbuvir/velpatasvir/voxilaprevir should be used with caution and frequently renally monitored.

	amendments (MLAs) to the following translations: -Viread: CZ, DA, DE, ES, FI, FR, HR, HU, IS, LV, MT, NO, PT, SK, SL, SV -Truvada: CZ, DE, ES, FR, MT, NL, PT -Eviplera: DE, MT, NO -Stribild: CZ, DA, DE, ES, ET, FI, FR, HU, IT, MT, NO, PL, SK, SV. Furthermore, the WSA took the opportunity to align the text related to 'pregnancy outcomes' in Section 4.6 of the SmPC for Truvada, Stribild and Viread with the currently approved text in the Eviplera SmPC and to replace 'tenofovir disoproxil fumarate' with 'tenofovir disoproxil' throughout the Product Information for all the products concerned. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
WS/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).	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

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				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.
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/2892/ 201703	Periodic Safety Update EU Single assessment - tenofovir disoproxil	26/10/2017	n/a		PRAC Recommendation - maintenance
II/0182	Submission of the final report from Study GX-US-174-0172, listed as a category 3 study in the Risk Management Plan. This is a 5-year observational (non-interventional) renal safety registry conducted to provide further safety data in HBV-infected	01/09/2017	n/a		The Marketing Authorisation Holder has submitted the results of a 5-year observational (non-interventional) renal safety registry conducted to provide further safety data in HBV-infected patients with decompensated liver disease (Study GX-US-174-0172). The very limited number of

	patients with decompensated liver disease. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				patients who completed the registry preclude to draw formal interpretation and conclusions on the efficacy and safety data derived from this study. There is no particular concern identified on the basis of the few data obtained in this registry.
IA/0181	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	28/07/2017	n/a		
IG/0800	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	18/07/2017	n/a		
N/0178	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/06/2017	23/04/2018	PL	
IA/0177/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		
IA/0176	B.II.c.2.a - Change in test procedure for an excipient - Minor changes to an approved test procedure	09/06/2017	n/a		
WS/1134	This was an application for a variation following a	21/04/2017	23/04/2018	SmPC	Results from the study GS-US-337-1501 showed that an

	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 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				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 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	21/04/2017	23/04/2018	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

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

	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				
II/0173	Submission of final long-term safety and efficacy data (480 weeks) from two completed Phase 3 studies in chronic hepatitis B e antigen negative (HBeAg−) patients (study GS-US-174-0102) and e antigen positive (HBeAg+) patients (Study GS-US-174-0103). GS-US-174-0102 - a randomized, double-blind, controlled evaluation of tenofovir disoproxil fumarate versus adefovir dipivoxil for the treatment of presumed pre-core mutant chronic hepatitis B. GS-US-174-0103 - a randomized, double-blind, controlled evaluation of tenofovir disoproxil fumarate versus adefovir dipivoxil for the treatment of HBeAg positive chronic hepatitis B. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/03/2017	n/a		The two studies consisted of 48 weeks of double blind therapy with Viread 300 mg or Hepsera 10 mg once daily, followed by open label treatment with Viread until week 480. Data through week 384 (Year 8) have been previously submitted and assessed (EMEA/H/C/000419/II/0143). Those long-term data confirmed the potency and high genetic barrier of the drug even though mitigated by a limited hepatitis B surface antigen (HBs) seroconversion rate and have been reflected in the SmPC. The current report remains limited as only a third of the patients remains in the study after Year 8. Virologic suppression was maintained in patients with available data through Week 480 and no mutations associated with resistance to tenofovir were detected in patients who received tenofovir/disoproxil fumarate for up to 480 weeks. The 480 week safety data in both pivotal studies GS-US-174-0102 and GS-US-174-0103 were consistent with the known safety profile of the drug, with renal and bone adverse events still representing the most commonly drug-related adverse reactions in TDF-treated patients. The CHMP concluded that these results do not warrant an update of the SmPC.

IB/0172	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)	01/12/2016	16/02/2017	SmPC	
PSUSA/2892/ 201603	Periodic Safety Update EU Single assessment - tenofovir disoproxil	27/10/2016	n/a		PRAC Recommendation - maintenance
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	16/02/2017	SmPC, Labelling and PL	
II/0168	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	16/02/2017	SmPC	
IA/0170	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	14/09/2016	n/a		
II/0166	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	04/08/2016	n/a		

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	28/04/2016	n/a		

	obligations and conditions of a marketing 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	16/02/2017	SmPC, Annex II and PL	
WS/0792	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 of the SmPC in order to revise the HIV class label wording on mitochondrial dysfunction following the review of existing data on mitochondrial toxicity including the Mitochondrial Toxicity in Children (MITOC) Study. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	16/02/2017	SmPC and PL	Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants exposed in utero and/or postnatally to nucleoside analogues; these have predominantly concerned treatment with regimens containing zidovudine. The main adverse reactions reported are haematological disorders (anaemia, neutropenia) and metabolic disorders (hyperlactatemia, hyperlipasemia). These events have often been transitory. Late onset neurological disorders have been reported rarely (hypertonia, convulsion, abnormal behaviour). Whether such neurological disorders are transient or permanent is currently unknown. These findings should be considered for any child exposed in utero to nucleos(t)ide analogues, that present with severe clinical findings of unknown etiology,

					particularly neurologic findings. These findings do not affect current national recommendations to use antiretroviral therapy in pregnant women to prevent vertical transmission of HIV.
II/0158	Update of SmPC sections 4.8 and 5.1 of affected strengths based on the final CSR (240 weeks) for Study GS-US-174-0121; a study evaluating the antiviral efficacy, safety and tolerability of tenofovir disoproxil fumarate (DF) monotherapy vs emtricitabine (FTC) plus tenofovir DF fixed-dose combination therapy in subjects with chronic hepatitis B who are resistant to lamivudine (LAM). The provision of the CSR fulfils the RMP commitment (category 1-3 pharmacovigilance activity) to provide the final report by Q3 2015. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	03/03/2016	16/02/2017	SmPC	After 240 weeks of treatment, 117 of 141 subjects (83%) randomised to tenofovir disoproxil fumarate had HBV DNA < 400 copies/ml, and 51 of 79 subjects (65%) had ALT normalisation. After 240 weeks of treatment with emtricitabine plus tenofovir disoproxil fumarate, 115 of 139 subjects (83%) had HBV DNA < 400 copies/ml, and 59 of 83 subjects (71%) had ALT normalisation. Among the HBeAg positive subjects randomised to tenofovir disoproxil fumarate, 16 of 65 subjects (25%) experienced HBeAg loss, and 8 of 65 subjects (12%) experienced anti HBe seroconversion through week 240. In the HBeAg positive subjects randomised to emtricitabine plus tenofovir disoproxil fumarate, 13 of 68 subjects (19%) experienced HBeAg loss, and 7 of 68 subjects (10%) experienced anti HBe seroconversion through week 240. Two subjects randomised to tenofovir disoproxil fumarate experienced HBsAg loss by Week 240, but not seroconversion to anti HBs. Five subjects randomised to emtricitabine plus tenofovir disoproxil fumarate experienced HBsAg loss, with 2 of these 5 subjects experiencing seroconversion to anti-HBs. In study GS US 174 0121, 141 patients with lamivudine resistance substitutions at baseline received tenofovir disoproxil fumarate for up to 240 weeks. Cumulatively, there were 4 patients who experienced a viremic episode (HBV DNA>400 copies/ml) at their last timepoint on TDF. Among them, sequence data from paired baseline and on

					treatment HBV isolates were available for 2 of 4 patients. No amino acid substitutions associated with resistance to tenofovir disoproxil fumarate were identified in these isolates.
IA/0164	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	26/02/2016	SmPC and PL	
II/0149	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	26/02/2016	SmPC	
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	17/12/2015	26/02/2016	SmPC	

	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				
II/0154/G	This was an application for a group of variations. 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 C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required C.I.11.z - Introduction of, or change(s) to, the	19/11/2015	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
PSUSA/2892/ 201503	Periodic Safety Update EU Single assessment - tenofovir disoproxil	06/11/2015	n/a		PRAC Recommendation - maintenance
IG/0616	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	03/11/2015	n/a		
IA/0156	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)	24/09/2015	n/a		
IG/0595	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	04/08/2015	n/a		
IG/0583	A.7 - Administrative change - Deletion of manufacturing sites	23/07/2015	n/a		
IG/0572	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/06/2015	26/02/2016	SmPC and PL	
IG/0553	A.4 - Administrative change - Change in the name	07/05/2015	n/a		

	and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient				
II/0143	Update of sections 4.8 and 5.1 of the SmPC of tenofovir 245mg tablets and 33 mg/g granules based on analysis of longer term safety and efficacy data (384 weeks) from studies GS-US-174-0102 and GS-US-174-0103 in HBeAg negative and HBeAg positive patients with chronic hepatitis B. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/04/2015	26/02/2016	SmPC	Information on the impact on renal function of Viread have been updated after analysis of long term data from Weeks 384 (Year 8) open-label safety, efficacy and virology pivotal phase III studies GS-US-174-102 and GS-US-174-0103 in HBeAg+ and HBeAg- patients. After an initial decline of approximately 4.9 ml/min (using Cockcroft Gault equation) or 3.9 ml/min/1.73 m2 (using modification of diet in renal disease [MDRD] equation) after the first 4 weeks of treatment, the rate of annual decline post-baseline of renal function reported in tenofovir disoproxil fumarate treated patients was 1.41 ml/min per year (using Cockcroft Gault equation) and 0.74 ml/min/1.73 m2 per year (using MDRD equation).
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	26/02/2016	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	26/02/2015	n/a		

	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 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				
IB/0145	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/01/2015	n/a		
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	19/03/2015	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."

PSUSA/2892/ 201403	Periodic Safety Update EU Single assessment - tenofovir disoproxil	06/11/2014	n/a		PRAC Recommendation - maintenance
II/0140	Submission of a study (included in the RMP) in order to collect information on the safety of tenofovir DF in HBV infected patients with decompensated liver disease, including patients with a CPT score >9. 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/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		
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/0469	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	07/08/2014	n/a		
WS/0586	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	24/07/2014	19/03/2015	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

	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				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 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	24/07/2014	19/03/2015	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.

	template version 9. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IG/0422	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	28/03/2014	n/a		
WS/0530	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.4 "Special warnings and precautions for use" of the SmPC for Atripla, Emtriva, Eviplera, Stribild, Truvada, Viread and Vitekta to revise the wording regarding the risk of sexual transmission of HIV infection following CHMP request adopted in December 2013. The PL has been updated accordingly. Furthermore, the MAH took the opportunity of this worksharing to update the PL with the details of the local representatives for Croatia and to introduce the Croatian language annexes for 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	19/03/2015	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.

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		
II/0123/G	This was an application for a group of variations. Update of sections 4.2, 4.4 and 5.2 of the SmPC for Viread 33 mg/g granules to allow daily dose adjustment using the granules formulation in adults with moderate and severe renal impairment, as an alternative to dose-interval adjustment using the Viread 245 mg film-coated tablets. The Package Leaflet was updated accordingly. This group submission includes a Type IB variation to update section 4.2 of the SmPC for 245 mg film coated tablets to reflect daily dose adjustment using the granules formulation in adults with moderate and severe renal impairment. The annex II was updated accordingly. Furthermore, the MAH took the opportunity of this variation to make a minor correction to section 5.2 of the SmPC. C.I.z - Changes (Safety/Efficacy) of Human and	19/09/2013	18/10/2013	SmPC, Annex II and PL	Dosing recommendations for TDF in adult patients with moderate or severe renal impairment, or patients with end-stage renal disease who are receiving haemodialysis, were implemented by prolonging the dosing interval of TDF 300-mg tablets. The availability of the TDF granules formulation allows for dose adjustment. As a consequence of the availability of this new formulation, the CHMP requested to provide additional PK simulations to evaluate the adequacy of daily dose adjustment in adult patients with moderate and severe renal impairment. Daily dosing of a lower dose could provide a narrower range of TFV exposures than those with dose interval adjustment. Pharmacokinetic modelling of single dose pharmacokinetic data in non HIV and non HBV infected adult subjects with varying degrees of renal impairment was used to determine dose adjustment recommendations for adult subjects with varying degrees of renal impairment. Based on these submitted data, recommendations for daily dose adjustments were introduced for patients with moderate and severe renal impairment as well as for patients with

	Veterinary Medicinal Products - Other variation C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				end stage of renal disease and haemodialysis patients.
II/0121	Update of sections 4.8 and 5.1 of the SmPC for 245 mg film-coated tablet formulation, in order to add longer term safety and efficacy data (week 288) from Study GS-US-174-0102 and Study GS-US-174-0103 in patients with compensated chronic hepatitis B. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/09/2013	18/10/2013	SmPC	In April 2008, EU marketing authorisation was first granted for Viread indicated in the treatment of chronic hepatitis B (CHB) in adults. Marketing authorisation of Viread for CHB was based primarily on data from 266 adult subjects with hepatitis B early antigen positive (HBeAg+) compensated CHB and 375 subjects with hepatitis B early antigen negative (HBeAg−) compensated CHB who enrolled in the similarly designed pivotal studies GS-US-174-0102 (HBeAg− subjects) and GS-US-174-0103 (HBeAg+ subjects). For both trials 0102 and 0103, week 288 longer term (open label) continuation data has become available. These data are now reflected in the Product Information. It is remarked that viral suppression, biochemical and serological responses were maintained with continued tenofovir disoproxil fumarate treatment. Also, the adverse reactions observed with continued treatment for 288 weeks were consistent with the known safety profile of tenofovir disoproxil fumarate. Nevertheless, a worrying trend has been detected towards a small but increasing proportion of TDF-treated patients experiencing mild to moderate decrease in creatinine clearance (Clcr) over the last two years of continuous treatment. The impact of the latter is under further assessment. It is concluded that the benefit-risk balance in the use of Viread in patients with compensated chronic hepatitis B remains unchanged.

II/0128	Update of sections 4.8 and 5.1 of the SmPC for 245 mg film-coated tablet and 33 mg/g granules formulations, in order to add safety and efficacy data from Study GS-US-174-0108, a phase 2, double-blind, randomized study comparing tenofovir disoproxil fumarate (TDF), emtricitabine (FTC) plus TDF, and entecavir (ETV) in the treatment of CHB in subjects with decompensated liver disease. In addition, the MAH took the opportunity to add agreed changes, proposed for SmPC Section 5.3 for all available formulations; and further to SmPC Section 3 and Annex IIIa Section 4, for the 123, 163, and 204 mg film-coated tablet formulations. Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 9. A series of minor linguistic amendments are also proposed (DA, ES, IS, SE, and SK language Annexes). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	18/10/2013	SmPC, Annex II, Labelling and PL	In April 2008, EU marketing authorisation was first granted for Viread indicated in the treatment of chronic hepatitis B (CHB) in adults. Licensing of Viread for CHB was based primarily on data from 266 adult subjects with hepatitis B early antigen positive (HBeAg+) compensated CHB and 375 subjects with hepatitis B early antigen negative (HBeAg−) compensated CHB who enrolled in the similarly designed pivotal studies GS-US-174-0102 (HBeAg− subjects) and GS-US-174-0103 (HBeAg+ subjects). The application for the CHB indication also included supportive safety data, blinded with regard to treatment assignment, from Study GS-US-174-0108, which is a double-blind, active-controlled study of tenofovir DF in subjects with CHB and decompensated liver disease. A total of 112 subjects have been treated in this study, and the planned primary analyses of safety and efficacy, based on the first 48 weeks of treatment with tenofovir DF, the fixed-dose combination of emtricitabine/tenofovir DF, or entecavir, were previously presented and assessed. On the basis of these study results, the MAH received an extension of the indication for Viread to include the treatment of patients with decompensated chronic hepatitis B. Since the original submission of the 48-weeks data, the week 168 final clinical study report for Study GS-US-174-0108 has become available. These data are now reflected in the Product Information. It is remarked that the study was not adequately powered to clearly demonstrate meaningful differences in efficacy parameters between groups. The benefit-risk balance in the use of Viread in patients with decompensated CHB remains unchanged.

WS/0391	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information regarding autoimmune disorders in relation to Immune Reactivation Syndrome, following a class labelling for antiretrovirals as requested by the CHMP. The Package Leaflet was updated accordingly. In addition, the WSA took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, Annex II is being brought in line with the latest QRD template version and minor editorial changes are implemented in the SmPC. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	30/05/2013	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.
N/0124	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/04/2013	01/07/2013	PL	
IG/0290	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/04/2013	n/a		
IAIN/0125	A.5.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release	27/03/2013	01/07/2013	Annex II and PL	

II/0120	Extension of the indication: Treatment of adults with lamivudine resistant chronic hepatitis B. As a consequence, sections 4.1, 4.8 and 5.1 of the SmPC were updated. Updates to Annex I and IIIa are proposed to reflect the fact that the EDQM short standard term 'tablet(s)' was introduced into the Viread packaging Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8. Also, the MAH took the opportunity of this variation to perform minor linguistic amendments for the CZ and DE annexes. A factual error in the Estonian SmPC is corrected. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/03/2013	29/04/2013	SmPC, Annex II and Labelling	See scientific discussion.
IG/0234	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	06/12/2012	n/a		
II/0119	Update of sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC in order to extend the therapeutic indication for the treatment of HIV 1 infected adolescents, with NRTI resistance or toxicities precluding the use of first line agents, aged 12 to < 18 years. The annex II, labelling and package leaflet are updated accordingly.	20/09/2012	22/11/2012	SmPC, Annex II, Labelling and PL	See scientific discussion.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0115	Update of sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order extend the indication for the treatment of chronic hepatitis B in adolescents 12 to < 18 years of age. The Package Leaflet and Labelling are updated accordingly. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/09/2012	22/11/2012	SmPC, Annex II, Labelling and PL	See scientific discussion.
X/0105/G	This was an application for a group of variations. Update of section 4.2 "Posology and method of administration" of the SmPC of Viread 245 film-coated tablets, to make reference to the availability of the oral granules formulation. Annex I_2.(c) Change or addition of a new strength/potency C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation Annex I_2.(d) Change or addition of a new pharmaceutical form	20/09/2012	22/11/2012	SmPC, Annex II, Labelling and PL	See scientific discussion.
WS/0245	This was an application for a variation following a worksharing procedure according to Article 20 of	21/06/2012	21/06/2012		

	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				
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		
II/0104	Update of sections 4.8 and 5.1 of the SmPC with longer term safety and efficacy data (240 weeks) from studies GS-US-174-0102 and GS-US-174-0103 on hepatitis B Virus in adults. Furthermore, The MAH took the opportunity of this variation to update section 9 of the SmPC with the date of the latest	15/12/2011	31/01/2012	SmPC	The long term data up to 240 weeks of the two pivotal studies GS-US-174-0102 and GS-US-174-0103 in HBeAg+ and HBeAg- patients with chronic Hepatatis B confirms the efficacy and good genetic barrier of the drug. In both studies, viral suppression was maintained through week 240 in patients who received tenofovir for 5 years with a

	renewal. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				rate of responders (HBV DNA < 400 copies/ml) reaching 83% in HbeAg- and 64% in HBeAg+ patients) and in those who switched to tenofovir after 48 weeks of adefovir reaching 84% in HbeAg- and 66% in HBeAg+ patients. However, this good virological response only translates into a slight increase in patients achieving HBeAg loss and seroconversion (around 38% and 30% had HBeg loss/seroconversion at week 240 respectively). Cumulatively, 8% of patients (all HBeAg+ patients) achieved HBsAg loss at week 240. No mutations associated with resistance to tenofovir were detected in patients who received tenofovir for up to 240 weeks. The adverse reactions observed with continued treatment for 240 weeks were consistent with the safety profile of tenofovir disoproxil fumarate.
R/0103	Renewal of the marketing authorisation.	20/10/2011	14/12/2011	SmPC, Annex II 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 profile of Viread continues to be favourable.
IG/0114/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	17/10/2011	n/a		

	the pharmacovigilance system				
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 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	23/06/2011	05/08/2011	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.
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	14/07/2011	n/a		

	the pharmacovigilance system				
II/0101	Update of section 4.8 of the SmPC to include Stevens-Johnson syndrome, following a CHMP request after assessment of PSUR 7. In addition, pneumonia and hypoglycaemia have been added as adverse drug reactions to bring the Product Information in line with the Company Core Safety Data Sheet. The PL was updated accordingly C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	13/07/2011	SmPC	Based on 7 spontaneously reported cases of Stevens Johnson Syndrome, the CHMP agreed to include the adverse events "Severe skin reactions, including Stevens - Johnson syndrome" in section 4.8 of the SmPC. An estimated frequency of Stevens-Johnson syndrome could not be determined for this adverse event since the identified reports include only spontaneous cases and true exposure data from these sources are limited. After a search of the MAH's database, the MAH further identified "Hypoglycaemia" and "Pneumonia" as additional adverse events to be included in section 4.8. Based on an evaluation of the incidences in the pivotal phase III studies the estimated frequencies of pneumonia (1.4%) and hypoglycaemia (1.2%) have been determined to fall within the CIOMS frequency category of Common
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/0102	A.7 - Administrative change - Deletion of manufacturing sites	29/04/2011	n/a	Annex II and	

				PL	
II/0098	Update of Summary of Product Characteristics (SmPC) and Annex II Update of sections 4.2, 4.4, 4.6, 4.8 5.1, 5.2 and 5.3 based on the 48-week results of a safety and efficacy study GS-US-104-0321 in treatment-experienced adolescents aged 12 to 18 years old. Annex II was updated to reflect the 6 month PSUR cycle and to be in line with QRD templates C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/02/2011	24/03/2011	SmPC and Annex II	For further information please refer to the scientific conclusion: Viread H-419-II-98-AR.
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	

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		
IB/0100	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)	18/10/2010	n/a	SmPC	
II/0097	Extension of indication to include the treatment of patients with decompensated liver disease. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	22/07/2010	06/09/2010	SmPC and Annex II	For further information please refer to the scientific conclusion: Viread H-419-II-97-AR.
II/0092	Update of section 4.8 of the SmPC and section 4 of the PL with safety related information following the update of the Company Core data Sheet (version 1, dated 11 December 2008). In addition section 4.8 is 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. Furthermore, the MAH took this opportunity to introduce minor amendments to the Czech, Danish, French, Greek, Hungarian, Latvian, Lithuanian, Polish, Portuguese and Slovakian version of the annexes, as relevant.	22/07/2010	06/09/2010	SmPC and PL	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 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. Following this review the frequency category of 'rare' was included for the ADRs: hepatitis, proximal renal tubulopathy (including Fanconi syndrome), acute tubular necrosis, nephrogenic diabetes insipidus. osteomalaia and nephritis.

	Update of Summary of Product Characteristics and Package Leaflet				
IA/0099	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	12/08/2010	n/a	Annex II	
II/0096	Update of sections 4.8 and 5.1 of the SmPC based on the long term results (144 weeks) from studies GS-US-174-0103 and GS-US-174-0102 in hepatitis B infected patients. In addition MAH took this opportunity to introduce minor linguistic amendments in some of the language versions. The PL was updated in accordance. Update of Summary of Product Characteristics and Package Leaflet	18/02/2010	09/04/2010	SmPC and PL	The long term safety data of the two pivotal clinical studies in HBeAg+ and HBeAg- patients underline both the efficacy and safety of tenofovir in its indication in the treatment of Hepatitis B. In both studies, viral suppression was maintained through week 144, reaching 87% in HBeAg- and 71% in HBeAg+ patients. Nevertheless, this good virological response only translated into a slight increase in patients achieving HBeAg loss and seroconversion (around 25 and 30% had HBeAg loss/seroconversion at week 144 respectively). Cumulatively, 8% of patients (all HBeAg+ patients) achieved HBsAg loss at week 144. No mutations associated with resistance to tenofovir were detected. The 144 week safety data from the two pivotal were in line with the known safety profile of the medicinal product and raised no new concerns.
IB/0094	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	17/07/2009	n/a	SmPC	
IB/0093	IB_10_Minor change in the manufacturing process of the active substance	16/06/2009	n/a		

IA/0095	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	29/05/2009	n/a		
II/0089	Update of section 5.1 or the SPC to reflect the 48 weeks data from study GS-US-174-0106, in hepatitis B infected patients receiving adefovir dipivoxil with persistent viral replication. Update of Summary of Product Characteristics	19/03/2009	22/04/2009	SmPC	Study -106 is an ongoing phase II, randomised, double-blind 168 week study, evaluating the efficacy, safety, and tolerability of tenofovir DF monotherapy versus the fixed-dose combination of emtricitabine /tenofovir DF in subjects being treated with adefovir dipivoxil (ADV) for chronic hepatitis B (CHB) and who had persistent viral replication after 24-96 weeks of treatment. The 48 week results presented do not allow a direct comparison between the both treatment groups beyond week 24 since the study design allowed patients with partial response to treatment to switch to open label emtricitabine /tenofovir DF. Therefore, the SPC is updated with the results at week 24 which further confirm that tenofovir DF is a potent drug in treatment experienced patients with active replication under adefovir dipivoxil therapy. Furthermore, resistance analysis at 1 year suggests that tenofovir DF has a high genetic barrier in treatment-experienced patients. The safety profile of tenofovir DF in this study was consistent with the safety profile described in pivotal studies in naïve patients.
II/0088	Update of section 4.8 and 5.1 of the SPC to reflect the 96 weeks data from studies GS-US-174-0103 and GS-US-174-0102 in hepatitis B infected patients. The PL has been revised in line with the results from readability focused testing. In addition the MAH took this opportunity to make minor linguistic amendments in some EU language version of the annexes, as relevant.	19/03/2009	22/04/2009	SmPC and PL	Studies GS-US-174-0102 and GS-US-174-0103 are two ongoing phase III, randomised studies in nucleoside/nucleotide naïve patients with HBeAg positive (-103) or negative (-102) chronic hepatitis B. These studies were similar in design, with first 48 weeks of double-blind therapy with tenofovir DF once daily or with adefovir dipivoxil once daily, followed by open-label treatment with tenofovir DF through week 384. The 48 weeks double-blind

	Update of Summary of Product Characteristics and Package Leaflet				phase of these studies supported the extension of the indication of Viread for the treatment of HBV. The 96 weeks data (48 weeks open label) now submitted, show the maintenance of viral suppression, biochemical and serological responses with continued tenofovir DF treatment through week 96 in both HBe Ag positive and negative patients. No mutations associated with viral failure have been detected for tenofovir DF. No new safety finding has been observed in this first year of open label phase particularly in regard to renal toxicity. These results are reflected in section 4.8 and 5.1 of the SPC. Furthermore the PL has been subject to a readability focused testing with the major change being the re-ordering of the information in subsection "Taking other medicines" to give greater priority to the information on the anti-HIV medicines.
IA/0091	IA_05_Change in the name and/or address of a manufacturer of the finished product	16/02/2009	n/a		
IA/0090	IA_09_Deletion of manufacturing site	16/02/2009	n/a		
IB/0087	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	08/01/2009	n/a		
IA/0086	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	21/10/2008	n/a		
N/0085	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/10/2008	n/a	PL	

IA/0084	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	19/09/2008	n/a		
IA/0083	IA_09_Deletion of manufacturing site	19/09/2008	n/a		
II/0082	Update of sections 4.4 and 4.8 of the SPC and sections 2 and 4 of the PL in accordance with the recent updates to the Company Core Safety Information (CCSI version 22, dated 20 December 2007) as regards renal, hepatic and bone safety information. In addition, minor linguistic amendments are made to the German language version of the annexes, as relevant. Update of Summary of Product Characteristics and Package Leaflet	24/07/2008	12/09/2008	SmPC and PL	A cumulative review identified 8 cases in which tenofovir DF-related proximal renal tubulopathy may have led to osteomalacia and fractures. Section 4.4 of the SPC and section 2 of the PL were therefore updated to indicate that bone abnormalities associated with proximal renal tubulopathy may infrequently contribute to fractures. Section 4.8 of the SPC and section 4 of the PL were updated to include hypokalaemia (as the review of this adverse event identified 19 key cases of Grade 3 or 4 hypokalaemia where there was evidence of an association with tenofovir DF therapy; all 19 cases involved intercurrent proximal renal tubulopathy). Section 4.8 of the SPC and section 4 of the PL were updated to include hypokalaemia (as the review of this adverse event identified 19 cases of Grade 3 or 4 with evidence of an association with tenofovir DF therapy). In addition, section 4.8 of the SPC and section 4 of the PL were updated to include hepatic steatosis (given that cases of hepatic steatosis have been observed in association with tenofovir DF therapy), rhabdomyolysis, and muscular weakness (as nine reports of unlisted muscle disorders occurring in the context of proximal tubulopathy were identified) 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.
IA/0081	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/0075	To extend the current therapeutic indication to include the treatment of chronic hepatitis B. Extension of Indication	19/03/2008	23/04/2008	SmPC and PL	For further information please refer to the scientific conclusions: Viread H-419-II-75-AR.
IB/0079	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	14/03/2008	14/03/2008	SmPC, Labelling and PL	
IA/0078	IA_05_Change in the name and/or address of a manufacturer of the finished product	27/02/2008	n/a		
IA/0077	IA_05_Change in the name and/or address of a manufacturer of the finished product	12/12/2007	n/a	Annex II and PL	
IA/0074	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	24/10/2007	n/a		
IA/0073	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	24/10/2007	n/a		
II/0068	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	22/03/2007	02/05/2007	SmPC and PL	In HIV/HBV co-infected patients, the withdrawal of current suppressive therapies to treat HBV infection may lead to post-treatment hepatic flares. Tenofovir is also active 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				vitro against HBV. Therefore post-treatment hepatic flares are a possible consequence of discontinuation of tenofovir DF therapy. This information as been included in section 4,4 of the SPC and reflected in section 4.2. 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/0067	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. Update of Summary of Product Characteristics and Package Leaflet	22/03/2007	02/05/2007	SmPC, Annex II, Labelling and PL	Tenofovir exposure is increased in patients with renal impairment and a dosing interval adjustment is recommended for these 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 support the existing advice that no dosing adjustment to the normal once daily dosing is required in patients with mild renal impairment. Dosing interval adjustment is however required in all patients with moderate or severe renal impairment (creatinine clearance <50 ml/min). 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 or severe renal impairment against the potential risk of renal toxicity.

IA/0072	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	17/04/2007	n/a		
IA/0071	IA_01_Change in the name and/or address of the marketing authorisation holder	14/03/2007	n/a	SmPC, Labelling and PL	
IB/0070	IB_33_Minor change in the manufacture of the finished product	07/03/2007	n/a		
IB/0069	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	07/03/2007	n/a		
II/0066	Update of section 4.5 of the SPC to reflect the results from a pharmacokinetic study investigating the potential interaction between tenofovir and rifampicin, as requested by the CHMP. Section 4.5 is further updated in regard of the interactions between tenofovir DF and lopinavir/ritonavir and atazanavir/ritonavir, as agreed 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	24/01/2007	28/02/2007	SmPC and PL	A pharmacokinetic study performed in 24 healthy subjects which during 10 days received tenofovir DF 300 mg in 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 is further updated 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 is updated in section 2 and 4 with changes requested at the time of the renewal. Among other changes the list of medicines, which may damage the kidneys now include the indication for which they are used. The undesirable effects listed in the PL are presented by frequency of occurrence and in a more patient friendly way. However, the PL will be revised in view of a more

					understandable wording by the patient.
II/0065	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. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	15/01/2007	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.
R/0061	Renewal of the marketing authorisation.	18/10/2006	08/01/2007	SmPC, Annex II, Labelling and PL	The quality, safety and efficacy of Viread continues to be adequately and sufficient demonstrate since the approval of this product. The benefit/risk profile of Viread in the treatment of the HIV-1 infected adults patients continues to be favourable. However, considering the safety profile of tenofovir (e.g. renal toxicity, bone events, particularly those related to renal events hepatic events) and the evolving therapeutic management of HIV infected patients there is the need for optimisation of therapies and to review its benefit/risk profile. Therefore, it was agreed that Viread should be further review within 5-years time. Moreover, the period safety update reports will be submitted yearly.

II/0059	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. Section 4.4 of the SPC and section 2 of the PL are updated to include the warning on the concomitant use of Viread with other medicinal products containing tenofovir disoproxil fumarate (Truvada). In addition, the list of local representatives in some EU Member States were updated in section 6 of the PL and minor linguistic changes were introduce in some EU languages versions, as relevant. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	01/09/2006	SmPC 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 but for which a frequency could not be yet determined. Section 4.8 of the SPC and section 4 of the PL were amended in accordance. The fact that Viread should not be taken with any other medicinal product containing tenofovir, particularly Truvada has been included in section 4.4 of the SPC and in section 2 of the PL.
IB/0064	IB_10_Minor change in the manufacturing process of the active substance	24/08/2006	n/a		
IB/0063	IB_10_Minor change in the manufacturing process of the active substance	24/08/2006	n/a		
IA/0062	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	13/07/2006	n/a		

II/0054	Update of section 4.5 of the SPC in view of the results from two pharmacokinetic interaction studies between tenofovir disoproxil fumarate and saquinavir (unboosted and ritonavir boosted) and nelfinavir respectively, as requested by the CHMP. Minor linguistic changes were introduced in the SPC and Package Leaflet of some EU languages versions, as relevant. Update of Summary of Product Characteristics and Package Leaflet	26/01/2006	28/02/2006	SmPC and PL	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/0058	IA_05_Change in the name and/or address of a manufacturer of the finished product	06/02/2006	n/a		
IA/0057	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	06/02/2006	n/a		
N/0056	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/01/2006	n/a	PL	
IA/0055	IA_09_Deletion of manufacturing site	13/01/2006	n/a		
II/0053	Update of section 4.4 "Special warnings and special precautions for use" of the Summary of Product characteristics (SPC) as requested by the CHMP following the assessment of a cumulative analysis of the measured renal parameters from the proximal tubulopathy reported cases. Section 4.8 "Undesirable effects" is amended in accordance with the cumulative review of nephrogenic diabetes insipidus	15/09/2005	25/10/2005	SmPC, Annex II, Labelling and PL	In order to define the most specific and predictive parameters for monitoring renal function and fulfilling a post-approval commitment a cumulative analysis has been submitted by the MAH. Further to the assessment of these data the CHMP requested, in May 2005, an update of section 4.4 of the SPC to include measurements of blood glucose, blood potassium and urine glucose concentrations as laboratory markers for renal toxicity.

	and nephritis submitted in parallel with the Viread 7th PSUR (01.11.04 - 30.04.05) on June 05, as requested by the CHMP. In addition, the MAH took this opportunity to introduce minor linguistic changes to the Czech, Danish, Dutch, Estonian, Finnish, Hungarian, Icelandic, Italian, Latvian, Lithuanian, Portuguese, Slovakian, Spanish and Swedish SPC, Annex II, Labelling and Package Leaflet, as relevant. Update of Summary of Product Characteristics, Labelling and Package Leaflet				Furthermore, "nephritis" and "nephrogenic diabetes insipidus" were included in the undesirable effects section of the SPC further to a cumulative safety review submitted, as a fulfilment of a follow-up measure, in parallel with the 7th Viread PSUR covering the period (01.11.04 - 30.04.05).
IB/0052	IB_10_Minor change in the manufacturing process of the active substance	22/07/2005	n/a		
S/0048	Annual re-assessment.	21/04/2005	08/07/2005	SmPC and Annex II	
IA/0051	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	05/07/2005	n/a		
IA/0050	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	27/04/2005	n/a		
N/0049	To update the contact details of the Local Representatives for Estonia, Latvia, Lithuania, Iceland and Cyprus in the Package Leaflet. In addition, the MAH took this opportunity to introduce minor corrections to the existing contact details and to be in line with the latest EMEA/QRD templates."	07/04/2005	n/a	PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
II/0044	Update of section 4.7 "Effects on ability to drive and use machines" and 4.8 "Undesirable effects" of the Summary of Product Characteristics and the relevant sections of the Package Leaflet in accordance with the safety-related changes to the Company Core Safety Information, reviewed in the 4th and 5th PSUR covering the period of 01.05.03 to 30.04.04 for Viread 245 mg film-coated tablets. In addition, the MAH applied for the update of section 4.4 "Special warning and special precautions for use" regarding the co-administration of tenofovir with didanosine, as proposed by the CHMP following the assessment of the 5th PSUR and further responses of the 4th PSUR. In addition, the MAH took this opportunity to update section 6.1 "List of excipients" of the Summary of Product Characteristics and relevant section of the Package Leaflet to add the correspondent "E" number. Moreover, Annex II is amended to be in accordance with the latest QRD template. Moreover, the French and Greek Summary of Product Characteristics and Package Leaflet are amended to correct some spelling mistakes. Update of Summary of Product Characteristics and	20/01/2005	07/03/2005	SmPC, Annex II and PL	As mentioned in the 4th (covering the period 01.05.03 - 31.10.03) and 5th (covering the period 01.11.03 - 30.04.04) PSURs, the Company Core Safety Information (CCSI) was updated based on a review of the safety data to reactions and to highlight the fact that the ability of patients to drive and operate machines may be affected as very commonly Viread causes dizziness. Section 4.8 has been updated to include the acute tubular necrosis, increased transaminases and hepatitis as adverse reactions to Viread and section 4.7 as regards dizziness. The PL was amended accordingly. Further to assessment of the 5th PSUR the CHMP concluded that the main safety concerns were the reactions reported with the association tenofovir-didanosine (pancreatitis and lactic acidosis, including rare fatal cases). Section 4.4 and 4.5 were updated not to recommend the co-administration of tenofovir and didanosine and to specify the careful monitoring for efficacy and didanosine related adverse reactions if the combination is judged strictly necessary. The CHMP requested the MAH to propose a harmonised DDL to alert clinicians to maintain a high level of awareness for didanosine-related complications in patients treated with tenofovir+didanosine regardless the dose of didanosine and multitherapies used, the DDL was adopted during the February 2005 CHMP meeting.

	Package Leaflet				
II/0046	Quality changes	17/02/2005	22/02/2005		
IB/0047	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	25/01/2005	n/a	SmPC	
II/0043	To update section 4.4 "Special warnings and special precautions for use" and 4.8 "Undesirable effects" of the Summary of Product Characteristics (SPC) and section 2 "Before you take Viread" of the Package Leaflet (PL), to implement the class labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP in July 2004. Update of Summary of Product Characteristics and Package Leaflet	18/11/2004	10/01/2005	SmPC and PL	In patients treated with any type of combination antiretroviral therapy (CART), an inflammatory response to indolent or residual opportunistic infections may occur, when the immune system responds to treatment. In most cases the inflammatory reaction towards the opportunistic pathogens is not foreseen since the opportunistic infection has not been detected/ diagnosed. If diagnosed prior to the institution of CART, the treatment against the opportunistic infection (OI) is usually given priority. In particular, this is true for the complications most feared in this context; CMV-retinitis, generalised mycobacterial infections and Pneumocystis carinii pneumonia. An additional reason for treating the OI and the HIV-infection sequentially is the great risk of adverse events (toxicity or lack of effect) due to drug interactions. The clinical consequence of the reactivation of the immune system in patients starting CART cannot be prevented and the early recognition and diagnose of these inflammatory reaction is considering to be important for the clinical handling of the patients. Therefore, further to the assessment of the MAH's responses and discussions held at the Pharmacovigilance working party and CHMP, the CHMP adopted a class labelling text regarding the reactivation of the immune system of HIV-infected patients treated with

					any type of combination antiretroviral therapy (CART) to be implemented in the product information of all anti-retroviral medicinal products.
II/0039	Update of Summary of Product Characteristics and Package Leaflet	21/10/2004	06/12/2004	SmPC and PL	This was a double-blind, randomised, placebo-controlled study comparing tenofovir DF administered in combination with lamivudine and efavirenz versus stavudine, lamivudine and efavirenz in antiretroviral-naïve HIV 1 infected patients. This study is the follow-up of the 48 week pivotal double blind GS-99-903 study supportive of the treatment with tenofovir DF in antiretroviral naïve patients. The 144-week efficacy data showed a sustained virological response in both treatment arms and especially the emergence of the critical K65R associated mutation to tenofovir DF phenotypic resistance remain limited (<3%). The long-term safety profile of tenofovir DF was comparable to the safety profile observed through the first 48 weeks of treatment. No new safety signals were identified in the tenofovir DF group. The frequent monitoring of the renal function was however considered still necessary, particularly during the first year of treatment (i.e. every 4 weeks). No clinically significant bone abnormalities were associated with prolonged use of tenofovir. However, tenofovir induces significant decreases in bone mineral density, mainly during the first year of treatment, without aggravation over the time. The effects on bone biomarkers were statistically significantly higher with TDF than with stavudine. The long term safety profile regarding lipodystrophy was favourable to the tenofovir regimen compared with the stavudine regimen, respectively 3% vs 19%. Sections 4.4, 4.8, 5.1 of the SPC and sections 2 and 4 of

					the PL have been update to include these results.
IA/0045	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	11/11/2004	n/a		
II/0041	Update of the section 4.4 (Special warnings and special precautions for use) of the Summary of Product Characteristics (SPC) of Viread 245 mg film-coated tablets, to implement the class warning text regarding the high rate of virological failure and emergence of resistance at an early stage with triple combinations involving tenofovir disoproxil fumarate (Tenofovir DF) and two Nucleoside Reverse Transcriptase Inhibitors (NRTI's), as adopted by the CHMP in July 2004. Update of Summary of Product Characteristics	16/09/2004	28/10/2004	SmPC	A high rate of virological failure and emergence of resistance has been observed at an early stage of treatment with triple combinations involving tenofovir and 2NRTIs (tenofovir, lamivudine and abacavir, study ESS30009 and tenofovir, lamivudine, didanosine, Jemsek study) used as a once daily regimen in antiretroviral naïve patients. Two EMEA public statements have been issued (July and October 2003) relating to this topic. Further discussions on these findings have been held at the CHMP as well as at the EMEA HIV Ad Hoc Group. Based on the in vivo and in vitro data submitted by the MAHs a class labelling warning has been adopted by the CHMP in July 2004 to be implemented in section 4.4 of the SPC harmonising the information at the present stage of knowledge.
IA/0042	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	04/10/2004	n/a		
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/08/2004	n/a	PL	
S/0035	Annual re-assessment.	22/04/2004	02/08/2004	Annex II	
IB/0038	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	14/07/2004	n/a		

IB/0037	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	29/06/2004	n/a		
II/0034	Update of section 4.4 (Special warnings and special precaution for use) of the Summary of Product Characteristics (SPC) and section 2 of the Package Leaflet (PL) under subheading "Pregnancy", to implement the class labelling for Nucleotide/Nucleoside Reverse Transcriptase Inhibitors (NRTIs) regarding mitochondrial toxicity in children with in utero and post-natal exposure, as adopted by the CPMP in November 2003. Moreover, the MAH has taken this opportunity to update section 6.4 (Special precautions for storage) of the SPC and section 5 of the PL (Storing Viread) in line with the Appendix III to the QRD template for human medicinal products. In addition, the MAH has updated and completed the list of local representatives in the PL in accordance with EMEA/QRD templates, to include the 10 accession countries. Update of Summary of Product Characteristics and Package Leaflet	24/03/2004	10/06/2004	SmPC and PL	The issue of mitochondrial toxicity in children of in utero and/ or post-natal exposure to NRTIs was first raised in 1999 following the identification of 8 cases of mitochondrial dysfunction in uninfected children included in a clinical trial. The MAHs for all NRTIs were asked to provide preclinical data on the mitochondrial toxicity and a review of adverse reactions potentially attributable to mitochondrial toxicity in children exposed in utero and / or post-natally to NRTIs. Following the assessment of data submitted and discussions held at the PhVWP and CPMP, a class wording was agreed at the November 2003 CPMP meeting, to be implemented in the product information of all NRTIs.
II/0033	The Marketing Authorisation Holder (MAH) applied for the update of the section 4.4 (Special warning and special precaution for use) and 4.5 (Interactions with other medicinal products and other forms of interaction) of the Summary of Product Characteristics (SPC) of Viread 245 mg film-coated	24/03/2004	10/06/2004	SmPC	Three open-label, randomised pharmacokinetic studies (GS-01-940, FTC-114 and GS-02-1037) all performed in healthy volunteers exploring the interactions of tenofovir with adefovir, ribavirin and emtricitabine, respectively did not show any clinically significant interaction. As the clinical safety of the co-administration of tenofovir and

	tablets to implement the results from three pharmacokinetic drug-interaction studies that investigate the potential interactions of tenofovir disoproxil fumarate (TDF) with other antiviral products (adefovir dipivoxil, emtricitabine and ribavirin). Moreover the MAH made a proposal to change section 4.4 (Special warnings and special precautions for use) of the SPC, in view of results from the study conducted with adefovir dipivoxil. In addition, further to the request of the CPMP, the MAH has taken this opportunity to update section 4.5 of the SPC with regard to the interaction between TDF and lopinavir/ritonavir (study GS-01-943) and with regard to the interaction between TDF and atazanavir. Update of Summary of Product Characteristics				adefovir particularly the potential for renal effects is unknown further data will be collected by the MAH and provided to the CHMP. The SPC was updated in section 4.4 and 4.5 to reflect these data. In addition, section 4.5 of the SPC for Viread was amended to reflect the decrease in atazanavir concentration observed when co-administrated with tenofovir. Furthermore as requested by the CHMP further to the assessment of study GS-01-943 the text regarding the interaction with lopinavir/ritonavir has been amended to reflect the fact that the pharmacokinetic parameters of lopinavir and ritonavir are not affected by tenofovir.
IB/0036	IB_10_Minor change in the manufacturing process of the active substance	05/05/2004	n/a		
II/0032	Update section 5.3 (Preclinical safety data) of the Summary of Product Characteristics (SPC) of Viread 245 mg film-coated tablets in view of the results obtained from long-term carcinogenicity studies in the rat and mouse. The submission of this final report was requested by the CPMP, as Specific Obligation stated in the MAH's letter of undertaking dated 17 October 2001. Update of Summary of Product Characteristics	20/11/2003	30/01/2004	SmPC	

II/0030	Update of the section 4.2 (Posology and method of administration), section 4.4 (Special warnings and special precautions of use) and 5.2 (Pharmacokinetic properties) of the Summary of Product Characteristics (SPC) of Viread 245 mg film-coated tablets to implement the class labelling on liver impairment adopted by the CPMP for all anti-retroviral medicinal products on 25 April 2003. In addition, the MAH proposes changes to sections 5.2 and 4.2, based on pharmacokinetic from the final report on Study GS-01-931 (PK data in non-infected subjects with either normal hepatic function or varying degrees of hepatic impairment) as well as the inclusion, in section 4.4, of a warning regarding the potential risk of hepatitis flares following discontinuation of Viread in patients co-infected with hepatitis B. Changes to the Package Leaflet (PL) in accordance with the proposed changes to the SPC have also been proposed. Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	30/01/2004	SmPC and PL	
II/0029	The Marketing Authorisation Holder (MAH) applied to amend section 4.8 (Undesirable effects) of the Summary of Product Characteristics (SPC) of Viread 245 mg film-coated tablets to incorporate the additional adverse drug reaction of "acute renal failure" and "proteinuria" to the post-marketing	25/09/2003	14/01/2004	SmPC	

	experience information. This variation also aims to modify this same section to use MedDRA System Organ Class headings rather than the COSTART Bodysystem headings currently used as requested by the CPMP further to the assessment of variation EMEA/H/C/419/II/07. Update of Summary of Product Characteristics				
II/0018	Update of Summary of Product Characteristics and Package Leaflet	24/07/2003	17/10/2003	SmPC and PL	
I/0031	11_Change in or addition of manufacturer(s) of active substance	22/08/2003	17/09/2003		
S/0020	Annual re-assessment.	25/04/2003	05/08/2003	Annex II	
I/0028	12_Minor change of manufacturing process of the active substance	09/07/2003	17/07/2003		
I/0027	12_Minor change of manufacturing process of the active substance	09/07/2003	17/07/2003		
I/0026	12_Minor change of manufacturing process of the active substance	09/07/2003	17/07/2003		
I/0025	12_Minor change of manufacturing process of the active substance	09/07/2003	17/07/2003		
I/0023	12_Minor change of manufacturing process of the active substance	09/07/2003	17/07/2003		

II/0019	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	09/07/2003	SmPC and PL	
II/0015	Update of Summary of Product Characteristics	19/03/2003	09/07/2003	SmPC	
II/0014	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	09/07/2003	SmPC and PL	
II/0013	to introduce a statement on the feasibility of patients desintegrating Viread film-coated tablets in liquids for ingestion by drinking Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	09/07/2003	SmPC and PL	
I/0021	01_Change in the name of a manufacturer of the medicinal product	31/05/2003	09/07/2003	Annex II and PL	
I/0022	01_Change in the name of a manufacturer of the medicinal product	31/05/2003	11/06/2003		
II/0009	Update of Summary of Product Characteristics and Package Leaflet	20/02/2003	19/05/2003	SmPC and PL	
II/0008	Extension of Indication	20/02/2003	19/05/2003	SmPC and PL	
II/0007	Update of Summary of Product Characteristics and Package Leaflet	20/02/2003	19/05/2003	SmPC and PL	
II/0010	Update of Summary of Product Characteristics	21/11/2002	27/03/2003	SmPC	

I/0017	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	22/02/2003	04/03/2003		
I/0016	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	22/02/2003	04/03/2003		
N/0012	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/02/2003	06/02/2003	Labelling and PL	
I/0011	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	10/12/2002	12/12/2002		
II/0006	Update of Summary of Product Characteristics and Package Leaflet	19/09/2002	05/12/2002	SmPC and PL	
I/0005	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	06/08/2002	30/08/2002		
I/0004	15_Minor changes in manufacture of the medicinal product	08/04/2002	11/04/2002		
I/0003	15_Minor changes in manufacture of the medicinal product	08/04/2002	11/04/2002		
I/0002	16_Change in the batch size of finished product	08/04/2002	11/04/2002		
I/0001	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	13/02/2002	06/03/2002		