Emtriva

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0141	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)	18/04/2023		SmPC and PL	
WS/2331	This was an application for a variation following a worksharing procedure according to Article 20 of	10/11/2022		SmPC and PL	

[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).

	Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
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		
IG/1412	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	28/07/2021	n/a		
N/0137	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/05/2021	17/06/2021	PL	
IB/0135/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) A.5.b - Administrative change - Change in the name	06/11/2020	n/a		

	and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
PSUSA/1209/202004	Periodic Safety Update EU Single assessment - emtricitabine	29/10/2020	n/a		PRAC Recommendation - maintenance
IA/0136/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) A.7 - Administrative change - Deletion of manufacturing sites	27/10/2020	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.	18/06/2020	17/06/2021	Annex II, Labelling and PL	

	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
IG/1236	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	04/05/2020	n/a		
PSUSA/1209/201904	Periodic Safety Update EU Single assessment - emtricitabine	31/10/2019	n/a		PRAC Recommendation - maintenance
IB/0130	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/04/2019	21/10/2019	SmPC, Labelling and PL	
II/0127	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	29/11/2018	n/a		
WS/1466/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or	29/11/2018	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place				
IG/1001	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	23/11/2018	n/a		
PSUSA/1209/201804	Periodic Safety Update EU Single assessment - emtricitabine	31/10/2018	n/a		PRAC Recommendation - maintenance
IG/0995	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2018	21/10/2019	SmPC	
N/0125	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/07/2018	21/10/2019	Labelling	
T/0123	Transfer of Marketing Authorisation	25/04/2018	04/06/2018	SmPC, Labelling and PL	
PSUSA/1209/201704	Periodic Safety Update EU Single assessment - emtricitabine	26/10/2017	n/a		PRAC Recommendation - maintenance

IB/0122	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	29/08/2017	n/a		
IA/0121	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/0799	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	14/07/2017	n/a		
N/0118	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/05/2017	04/06/2018	PL	
IA/0117	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)	03/03/2017	n/a		
IG/0745	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	28/11/2016	n/a		
II/0113	Update of sections 4.2, 4.4 and 4.8 of the SmPC in	15/09/2016	03/11/2016	SmPC and PL	Renal insufficiency: Emtricitabine is eliminated by renal

	order to allow administration of Emtriva 200 mg hard capsule every 24 to 48 hours in patients with renal impairment (eGFRCG ≥ 30 mL/min) and corresponding update the SmPC for Emtriva 10mg/ml oral solution. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				excretion and exposure to emtricitabine was significantly increased in patients with renal insufficiency. Dose or dose interval adjustment is required in all patients with creatinine clearance < 30 ml/min. Table 1 in section 4.2 Posology and method of administration of the SmPC provides dose interval adjustment guidelines for the 200 mg hard capsules according to the degree of renal insufficiency. The safety and efficacy of the dose interval adjustments to every 72 or 96 hours in patients with creatinine clearance < 30 ml/min have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in these patients. Renal function Emtricitabine is principally eliminated by the kidney via glomerular filtration and active tubular secretion. Emtricitabine exposure may be markedly increased in patients with severe renal insufficiency (creatinine clearance < 30 ml/min) receiving daily doses of 200 mg emtricitabine as hard capsules or 240 mg as the oral solution. Consequently, either a dose interval adjustment (using Emtriva 200 mg hard capsules) or a reduction in the daily dose of emtricitabine (using Emtriva 10 mg/ml oral solution) is required in all patients with creatinine clearance < 30 ml/min. The safety and efficacy of the dose interval adjustment guidelines provided in section 4.2 are based on single dose pharmacokinetic data and modelling and have not been clinically evaluated. Therefore, clinical response to treatment and renal function should be closely monitored in patients treated with emtricitabine at prolonged dosing intervals.

					Patients with renal impairment: Emtricitabine is eliminated by renal excretion and exposure to emtricitabine was significantly increased in patients with renal insufficiency. Dose or dose interval adjustment is required in all patients with creatinine clearance < 30 ml/min).
PSUSA/1209/ 201604	Periodic Safety Update EU Single assessment - emtricitabine	27/10/2016	n/a		PRAC Recommendation - maintenance
IG/0725	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	21/10/2016	n/a		
WS/0860/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	26/05/2016	n/a		
WS/0792	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	01/04/2016	24/06/2016	SmPC and PL	Nucleos(t)ide analogues may impact mitochondrial function to a variable degree, which is most pronounced with stavudine, didanosine and zidovudine. There have been reports of mitochondrial dysfunction in HIV negative infants

	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				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.
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	24/06/2016	SmPC and PL	
IB/0109	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	24/11/2015	n/a		
IG/0613	B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	14/10/2015	n/a		

PSUSA/1209/201504	Periodic Safety Update EU Single assessment - emtricitabine	08/10/2015	n/a		PRAC Recommendation - maintenance
IG/0614	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	02/10/2015	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		
IB/0103	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/06/2015	24/06/2016	SmPC, Labelling and PL	
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	30/03/2015	Annex II and PL	
IB/0101/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/12/2014	n/a		

PSUV/0096	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IG/0479	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	17/09/2014	n/a		
IG/0469	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	07/08/2014	n/a		
IG/0448	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	02/07/2014	n/a		
IG/0422	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	28/03/2014	n/a		
WS/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	20/03/2014	30/03/2015	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

	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				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.
IG/0378	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	29/11/2013	n/a		
IA/0092/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)	27/11/2013	n/a		
IG/0368	B.I.a.2.a - Changes in the manufacturing process of	07/11/2013	n/a		

	the AS - Minor change in the manufacturing process of the AS				
WS/0422	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. This is a type IB variation application following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008, to introduce an alternative manufacturer and release testing site of the active substance emtricitabine. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	24/10/2013	n/a		
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	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.

	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				
IA/0089	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	03/05/2013	n/a		
IG/0294	A.7 - Administrative change - Deletion of manufacturing sites	03/04/2013	n/a		
IG/0290	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	03/04/2013	n/a		
IA/0085	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	28/08/2012	n/a		
IG/0203	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	03/08/2012	n/a		
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	13/04/2012	n/a		

	the pharmacovigilance system				
IB/0082	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	20/01/2012	n/a		
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 the pharmacovigilance system	17/10/2011	n/a		
WS/0115	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of the Product information (PI) in line with the SmPC Guideline, revision 2, September 2009 and the current QRD template version 7.3.1. The MAH took this opportunity to harmonize the PI across the products Viread, Emtriva, Truvada and Atripla. Following CHMP request, section 4.6 "fertility, pregnancy and lactation" of the SmPC was updated	23/06/2011	27/07/2011	SmPC, Annex II, Labelling and PL	The MAH took this opportunity to harmonize the PI across the products Viread (tenofovir disoproxil fumarate), Emtriva (emtricitabine), Truvada (emtricitabine and tenofovir disoproxil fumarate) and Atripla (efavirenz, emtricitabine and tenofovir disoproxil fumarate). Following CHMP request section 4.6 of the SmPC on fertility, pregnancy and lactation was revised. A moderate amount of data mainly from the Antiretroviral Pregnancy Registry on pregnant women (between 300-1000 pregnancy outcomes) indicate no malformations or foetal / neonatal toxicity associated with tenofovir disoproxil fumarate nor with emtricitabine.

	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				
IG/0078	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	14/07/2011	n/a		
IA/0077	A.7 - Administrative change - Deletion of manufacturing sites	18/04/2011	n/a	Annex II and PL	
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	10/03/2011	n/a	Annex II	

	system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system				
WS/0048	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/10/2010	21/10/2010		
II/0074	Update of section 4.4 of the SmPC to include a recommendation not to discontinue Emtriva in patients co-infected with HIV and HBV with advanced liver disease or cirrhosis. Update of section 4.8 to add angioedema. Furthermore, following CHMP request this section was fully revised to be in line with the SmPC guideline. Sections 3 and 4 of the PL were updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	22/07/2010	26/08/2010	SmPC and PL	Emtricitabine shows clinical and in vitro activity against HBV. Post-treatment hepatic flares were reported following discontinuation of emtricitabine. Therefore, section 4.4 of the SmPC was updated to not to discontinue Emtriva in patients co-infected with HIV and HBV with advanced liver disease or cirrhosis since post treatment exacerbations of hepatitis may lead to hepatic decompensation. The term 'angioedema', was included in section 4.8 following a review of angioedema. This review was submitted by the MAH for Truvada (emtricitabine/tenofovir DF) and identified two cases of angioedema with Truvada, with indirect evidence of a causal association with emtricitabine (a negative rechallenge to the tenofovir component of Truvada). In addition, there were four cases of a positive rechallenge to Truvada which should also be considered as possibly causally related, as the positive result could have been in response to either the tenofovir DF or the emtricitabine component. This adverse reaction, which was identified through post-

					marketing surveillance, was not observed in randomised controlled clinical trials in adults or paediatric HIV clinical trials of emtricitabine. The frequency category of uncommon was estimated from a statistical calculation based on the total number of patients exposed to emtricitabine in these clinical studies. Furthermore, following CHMP request the MAH has compiled a summary of the safety data supporting each ADR term in Section 4.8 of the Emtriva SmPC, which were previously submitted and approved by the CHMP. All ADRs (except angioedema) currently in section 4.8, were identified in the pivotal clinical HIV studies for Emtriva (in adults), and were included in the SmPC at the time of authorisation. Section 4.8 was fully revised to be in line with the SmPC guideline.
IA/0076	C.I.9.i - Changes to an existing pharmacovigilance system as described in the DDPS - Change(s) to a DDPS following the assessment of the same DDPS in relation to another medicinal product of the same MAH	13/08/2010	n/a	Annex II	
IA/0075	IA_09_Deletion of manufacturing site	20/11/2009	n/a		
IA/0073	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	29/05/2009	n/a	Annex II and PL	
IA/0072	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	29/05/2009	n/a		

IA/0070	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	12/05/2009	n/a		
IB/0069	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	20/04/2009	n/a		
II/0062	The Marketing Authorisation Holder applied for the addition of two manufacturing sites as a manufacturing and testing sites for emtricitabine active substance. Consequential addition of alternative specifications for reagents were also proposed. Change(s) to the manufacturing process for the active substance	22/01/2009	26/01/2009		
IA/0065	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	10/11/2008	n/a	Annex II and PL	
IA/0066	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	05/11/2008	n/a		
IA/0068	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	04/11/2008	n/a		
IA/0067	IA_05_Change in the name and/or address of a manufacturer of the finished product	04/11/2008	n/a		
IA/0064	IA_22_a_Submission of TSE Ph. Eur. certificate for	04/11/2008	n/a		

	exc. - Approved/new manufacturer				
IA/0063	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	04/11/2008	n/a		
IA/0061	IA_09_Deletion of manufacturing site	04/11/2008	n/a		
IA/0060	IA_09_Deletion of manufacturing site	04/11/2008	n/a		
IA/0059	IA_09_Deletion of manufacturing site	04/11/2008	n/a		
R/0055	Renewal of the marketing authorisation.	24/07/2008	22/09/2008	SmPC, Annex II, Labelling and PL	Based on the review of the avilable 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 sufficientely demonstrated and therefore considered that the benefit risk of Emtriva continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity.
IB/0057	IB_33_Minor change in the manufacture of the finished product	29/07/2008	n/a		
IB/0056	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	29/07/2008	n/a		
IA/0058	IA_09_Deletion of manufacturing site	07/07/2008	n/a		
IA/0054	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	31/03/2008	n/a		

IA/0053	IA_05_Change in the name and/or address of a manufacturer of the finished product	20/02/2008	n/a		
IA/0052	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	19/10/2007	n/a		
IA/0051	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	19/10/2007	n/a		
IA/0050	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	19/10/2007	n/a		
IB/0048	IB_38_c_Change in test procedure of finished product - other changes	14/09/2007	n/a		
II/0044	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.8 of the SPC and section 4 of the PL to list anaemia as an adverse drug reaction to emtricitabine treatment in adult patients, as requested by the CHMP in March 2007. Update of Summary of Product Characteristics and Package Leaflet	19/07/2007	22/08/2007	SmPC and PL	In a cumulative review of anaemia cases in adult patients on treatment with emtricitabine, 28 cases were identified up to 19 June 2006. Based on these cases a causal relationship between emtricitabine and anaemia was reasonably suspected. However, detailed description of the analysis performed in adult study data was needed to draw a definitive conclusion. The additional data provided from 3 trials suggested that emtricitabine can cause Grade 1 and Grade 2 anaemia, which occurs in between 0.5 and 1.0% of patients. Based on the available data, it was agreed to add "anaemia" to the list of uncommon adverse reactions to emtricitabine treatment in adult patient. Anaemia was already listed as common adverse reaction with emtricitabine treatment in paediatric patients.
IB/0049	IB_38_c_Change in test procedure of finished product - other changes	19/07/2007	n/a		

IB/0047	IB_33_Minor change in the manufacture of the finished product	19/07/2007	n/a		
IB/0045	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	19/07/2007	n/a		
IA/0046	IA_32_b_Change in batch size of the finished product - downscaling down to 10-fold	03/07/2007	n/a		
II/0043	Quality changes - change to the synthesis process of the active substance. Change(s) to the manufacturing process for the active substance	21/06/2007	27/06/2007		
II/0040	Update of sections 4.2 and 5.2 of the SPC to reflect results of a study evaluating the pharmacokinetics and safety of emtricitabine in neonates and young infants over the first 3 months of life, at CHMP request further to the assessment of this study in November 2006. Update of Summary of Product Characteristics	22/03/2007	25/04/2007	SmPC	An open label pharmacokinetic study of emtricitabine over the first 3 months of life following multiple dose administration in children born to HIV 1 infected mothers was completed by 20 of the 22 neonates enrolled. All the 20 neonates received two 4-day courses of emtricitabine oral solution between the first week of life and 3 months of age at a dose level of 3 mg/kg once daily (half of the approved dose for infants aged more than 4 months). Results showed that steady state clearance increased with age over the first 3 months of life and AUC decreased in parallel. Moreover, plasma emtricitabine exposure (AUC) in infants up to 3 months of age who received 3 mg/kg emtricitabine once daily was similar to that observed using 6 mg/kg daily doses in HIV-infected adults and children aged 4 months and over. This information is now included

					in the SPC. Furthermore, it is also mentioned that there is no efficacy data and only very few data in terms of safety are available for infants aged below 4 months. Therefore, Emtriva is not recommended for use in those aged less than four months.
IA/0042	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		
II/0039	Update of sections 4.2 and 4.4 of the SPC in regard of the potential Hepatitis B Virus reactivation after treatment discontinuation with emtricitabine. Section 4.4 is updated to not recommend the concomitant use with other products containg emtricitabine or lamivudine. Section 4.8, in line with the MedDRA - system organ class, was updated with regards nervous system disorders and psychiatric disorders.The PL has been updated accordingly. The MAH has amended the SPC, Annex II, labelling and the PL in line with the latest QRD templates and have introduced minor linguistic changes to the some EU languages, as relevant. Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/02/2007	27/03/2007	SmPC, Annex II, Labelling and PL	The results of an evaluation of post-treatment exacerbations of hepatitis performed by the MAH across 3 randomised, double-blind clinical trials of emtricitabine in patients with chronic hepatitis B were discussed in an article by Mondou et al, in Clinical Infectious Diseases, 2005; 41(5): e45-47. Based on these results the Company Core Safety Information for Emtriva was updated and now the SPC to specify that hepatitis B virus reactivation after discontinuation of treatment with emtricitabine could lead to more severe liver disease, including hepatic decompensation and liver failure. The fact that Emtriva should not be taken with any other medicinal product containing emtricitabine or lamivudine, including fixed combination products has been included in section 4.4 of the SPC and section 2 of the PL.
IA/0041	IA_01_Change in the name and/or address of the marketing authorisation holder	14/03/2007	n/a	SmPC, Labelling and PL	

II/0038	Update of sections 4.4 and 4.8 of the SPC and section 2 of the PL to implement the class labelling text on osteonecrosis, agreed by the CHMP in September 2006. Section 6 of the PL was updated with the local representatives in Bulgaria and Romania and in Belgium and Luxembourg. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	12/01/2007	SmPC and PL	Cases of osteonecrosis (death of the bone tissue resulting from an insufficient blood supply) have been reported in HIV-infected patients since the end of the 80's. Although the cause of this disease could be due to multi factors (including the use of corticosteroids, alcohol consumption, severe immunosuppression, higher body mass index) it has occurred specially in patients with HIV advanced disease and/or in patients with long term use of combination antiretroviral therapy (CART). Further to the review of all available data the CHMP agreed that this information should now be included in the SPC and PL of all antiretroviral medicinal products. Patients should be warned to seek medical advice in case they experience joint stiffness, aches and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.
IB/0034	IB_31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits	27/09/2006	n/a		
IB/0032	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	23/08/2006	n/a		
IB/0031	IB_33_Minor change in the manufacture of the finished product	23/08/2006	n/a		
IA/0036	IA_23_b_Change in source of excip./reagent to veg./synthetic material - other cases	10/08/2006	n/a		
IA/0035	IA_32_b_Change in batch size of the finished product - downscaling down to 10-fold	10/08/2006	n/a		

IA/0033	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	08/08/2006	n/a		
IA/0037	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	04/08/2006	n/a		
N/0030	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	31/07/2006	n/a	PL	
IA/0029	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	17/05/2006	n/a		
II/0026	Quality changes Quality changes	23/03/2006	27/04/2006	SmPC	
IA/0028	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	24/03/2006	n/a		
IA/0027	IA_05_Change in the name and/or address of a manufacturer of the finished product	24/03/2006	n/a		
N/0025	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/01/2006	n/a	PL	
IB/0024	IB_10_Minor change in the manufacturing process of the active substance	05/12/2005	n/a		
II/0023	Update sections 4.8, 5.1 and 5.2 of the SPC and	13/10/2005	15/11/2005	SmPC and PL	Further to the 24-week data results of two paediatric

	section 4 of the PL to reflect the results of 48 week data from three clinical studies in HIV infected paediatric patients. Update of Summary of Product Characteristics and Package Leaflet				studies submitted for the initial MA application the MAH provided the 48-week results of these studies and of an additional study (final report) evaluating also the pharmacokinetics, safety and antiviral effect of emtricitabine in HIV infected children. The provided data further substantiates the use of emtricitabine in HIV-1 infected children older than 4 months and the viral suppression achieved throughout the 48 weeks (89% achieved < 400 copies/ml and 77% < 50 copies/ml). A part from anaemia and skin discolouration commonly and very commonly, respectively reported in paediatric population, the pattern of adverse events reported in theses three studies is comparable with the already known for adult patients. Sections 4.8 and 5.1 of the SPC and section 4 of the PL have been updated to reflect this data.
II/0016	To update of section 4.4 "Special warnings and special precautions for use" of the Summary of Product Characteristics of Emtriva hard capsules and oral solution, to reflect the current status of the Emtriva Hepatitis B Virus development program. In addition the MAH took this opportunity to introduce minor linguistics changes to the Norwegian, Slovak, Italian, Portuguese, Spanish, Greek, Estonian, Lithuanian, Spanish, Czech, Latvian and Hungarian SPC, Package Leaflet, Labelling and Annex II, as relevant. Update of Summary of Product Characteristics, Labelling and Package Leaflet	27/07/2005	07/09/2005	SmPC, Annex II, Labelling and PL	

IA/0022	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	10/05/2005	n/a		
IA/0021	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	10/05/2005	n/a		
IA/0020	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	10/05/2005	n/a		
IA/0019	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	10/05/2005	n/a		
IA/0018	IA_23_b_Change in source of excip./reagent to veg./synthetic material - other cases	10/05/2005	n/a		
IA/0017	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	27/04/2005	n/a		
N/0015	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." Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/04/2005	n/a	PL	
II/0014	Update of section 5.2 of the SPC, to reflect the results of a study on the effect of food on the pharmacokinetics of emtricitabine following the	20/01/2005	03/03/2005	SmPC and PL	Following the assessment of the results of a study performed to evaluate the effect of food on absorption of emtricitabine from the oral solution, the CHMP in

	administration of Emtriva 10mg/ml oral solution, as requested by the CHMP. In addition, section 2 of the Portuguese PL was amended regarding a spelling correction. Update of Summary of Product Characteristics and Package Leaflet				September 2004 concluded that having demonstrated that there is no effect on the pharmacokinetics, the MAH should amend the SPC in accordance. Therefore, section 5.2 of the SPC was updated to reflect that the oral solution can, as the hard capsules, be administered with or without food.
II/0013	To update section 4.4 and 4.8 of the SPC and section 2 of the PL, to implement the class labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP. In addition the Greek PL was amended regarding spelling corrections. Update of Summary of Product Characteristics and Package Leaflet	18/11/2004	17/12/2004	SmPC	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 reactions towards the opportunistic pathogens in question cannot be foreseen since the opportunistic infection has not yet been detected/diagnosed. If diagnosed prior to 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 to the clinical

					handling of the patients. Therefore, the CHMP further to the assessment of MAH's responses and discussions held at the Pharmacovigilance working party and CHMP, a class labelling text regarding the reactivation of the immune system of HIV-infected patients treated with any type of combination antiretroviral therapy (CART) was agreed to be implemented in all anti-retroviral product information.
II/0012	Changes related to the active substance emtricitabine (i.e. changes related to the synthesis, control, specification and packaging). Quality changes	21/10/2004	27/10/2004		
N/0011	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	16/08/2004	n/a	PL	
II/0006	Update of section 5.3 of the SPC with new preclinical safety information following the completion of two years carcinogenicity studies. In addition the PL and Labelling were updated to be in line with the latest EMEA/QRD templates. Minor linguistic changes were introduced in the Dutch PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	23/06/2004	02/08/2004	SmPC, Labelling and PL	When the initial MA was granted, long term carcinogenicity studies were ongoing. The submission of these long-term studies reports fulfil the commitment made by the MAH within the initial MA and are the basis for the application of this type II variation. The preclinical safety data section of the SPC was update to reflect the negative carcinogenic potential results of these studies.
IB/0010	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	19/07/2004	n/a	SmPC	
IB/0009	IB_42_a_02_Change in shelf-life of finished product - after first opening	19/07/2004	n/a	SmPC, Labelling and	

				PL	
II/0005	Update of section 4.4 of the SPC and section 2 of the PL, to implement the class labelling text regarding the mitochondrial toxicity in children with in utero and post-natal exposure to Nucleotide/Nucleoside Reverse Transcriptase Inhibitors (NRTIs), as adopted by the CPMP. In addition, section 6.4 of the SPC and sections 5 and 6 of the PL were updated in line with the latest EMEA/QRD templates. Update of Summary of Product Characteristics and Package Leaflet	26/03/2004	23/06/2004	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 events potentially attributable to mitochondrial toxicity in children exposed in utero and / or post-natally to NRTIs. Following the assessment of the submitted data and discussions held at the PhVWP and CPMP, a class labelling wording was agreed by the CPMP in November 2003 to be implemented in all NRTIs product information. In addition, the storage conditions in section 6.4 of the SPC and section 5 of the PL were updated in line with EMEA/QRD templates. The list of the local representatives for the current European Members States and for the 10 new accession Members was introduced in section 6 of the PL.
IB/0008	IB_14_b_Change in manuf. of active substance without Ph. Eur. certificate - new manufacturer	08/06/2004	n/a		
II/0001	Change(s) to the test method(s) and/or specifications for the finished product	22/01/2004	26/01/2004		
IA/0004	IA_13_a_Change in test proc. for active substance - minor change	17/11/2003	n/a		
IA/0003	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	17/11/2003	n/a		

IA/0002	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	17/11/2003	n/a		