Sustiva

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
N/0161	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/05/2023		PL	
IB/0160	C.I.3.z - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the	31/03/2023		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).

	assessment done under A 45/46 - Other variation				
PSUSA/1200/202204	Periodic Safety Update EU Single assessment - efavirenz	01/12/2022	n/a		PRAC Recommendation - maintenance
IAIN/0158	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/10/2022		SmPC and PL	To update sections 4.4 and 4.6 of the SmPC and section 2 of the PL to implement the recommendation of the CHMP to remove the disease information relating to sexual transmission of HIV and to amend the sections related to breast-feeding.
IB/0156	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	11/08/2021	12/08/2022	SmPC and PL	To update section 4.5 of the SmPC to align with the wording for products containing Efavirenz from the CMDh Meeting Report EMA/CMDh/70731/2020, following the PSUSA procedure on metamizole.
IB/0155	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	27/01/2021	n/a		
IB/0154/G	This was an application for a group of variations. 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 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	09/07/2020	n/a		

IAIN/0153	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	28/01/2020	n/a		
PSUSA/1200/201904	Periodic Safety Update EU Single assessment - efavirenz	28/11/2019	n/a		PRAC Recommendation - maintenance
IA/0152/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	27/09/2019	n/a		
IAIN/0150/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	07/05/2019	23/04/2020	Annex II and PL	

IAIN/0149	A.1 - Administrative change - Change in the name and/or address of the MAH	27/02/2019	28/03/2019	SmPC, Labelling and PL	
PSUSA/1200/201804	Periodic Safety Update EU Single assessment - efavirenz	13/12/2018	20/02/2019	SmPC	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1200/201804.
IA/0147	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	26/10/2018	n/a		
II/0145/G	This was an application for a group of variations. Update of sections 4.3 and 4.5 of the SmPC in order to add contraindication with elbasvir/grazoprevir due to the potential for significant decreases in plasma concentrations of elbasvir and grazoprevir, based on the post-approval and literature data, the Package Leaflet is updated accordingly. Update of sections 4.4 and 4.5 to include warnings in relation to the co-administration of efavirenz and sofosbuvir/velpatasvir; efavirenz and vepatasvir/sofosbuvir/voxilaprevir and efavirenz and glecaprevir/pibrentasvir; based on the post-approval and literature data, 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 C.I.4 - Change(s) in the SPC, Labelling or PL due to	20/09/2018	25/10/2018	SmPC and PL	

	new quality, preclinical, clinical or pharmacovigilance data				
IAIN/0148	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2018	20/02/2019	SmPC	
WS/1117/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.4 (Type II) - Update of sections 4.3, 4.4, 4.5 and 5.1 of the SmPC in order to add a warning and update the safety information on QTc prolongation based on the final results from study AI266959; this is an interventional study to determine the concentration-electrocardiographic effects of efavirenz in healthy subjects enriched for cyp2b6 polymorphisms; the Package Leaflet is updated accordingly. The RMP version 8 has also been submitted. C.I.4 (Type II) – Update of sections 4.4 and 4.8 to add catatonia as a Psychiatric symptom following an assessment of catatonia cases reported in the literature and via the United States (US) Food and Drug Administration Adverse Event Reporting System (FAERS). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	09/11/2017	15/12/2017	SmPC and PL	The new contraindication has been included in section 4.3 of SmPC for patients with: - family history of sudden death or of congenital prolongation of the QTc interval on electrocardiograms, or with any other clinical condition known to prolong the QTc interval. - a history of symptomatic cardiac arrythmias or with clinically relevant bradycardia or with congestive cardiac failure accompanied by reduced left ventricle ejection fraction. - severe disturbances of electrolyte balance e.g. hypokalemia or hypomagnesemia. The contraindication is also included for the patients taking drugs that are known to prolong the QTc interval. SmPC sections 4.4, 4.5 and 5.1 have been updated in order to add a warning and update the safety information on QTc prolongation. SmPC sections 4.4 and 4.8 have been updated to add catatonia as a Psychiatric symptom, with frequency uncommon. The Package leaflet has been updated accordingly.

	data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/1200/ 201704	Periodic Safety Update EU Single assessment - efavirenz	30/11/2017	n/a		PRAC Recommendation - maintenance
IA/0143	B.II.d.2.f - Change in test procedure for the finished product - To reflect compliance with the Ph. Eur. and remove reference to the outdated internal test method and test method number	01/06/2017	n/a		
II/0142/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.3.b - Change in batch size (including batch size	01/06/2017	n/a		

	ranges) of AS or intermediate - Downscaling down to 10-fold				
IA/0141	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	30/03/2017	n/a		
IA/0140	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	24/02/2017	n/a		
PSUSA/1200/201604	Periodic Safety Update EU Single assessment - efavirenz	27/10/2016	n/a		PRAC Recommendation - maintenance
IB/0138/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP -	21/10/2016	13/02/2017	PL	

	Replacement/addition of a site where batch control/testing takes place B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter				
IA/0137	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	01/07/2016	n/a		
IA/0135	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	01/07/2016	n/a		
WS/0893	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	13/02/2017	SmPC and PL	

PSUSA/1200/201504	Periodic Safety Update EU Single assessment - efavirenz	03/12/2015	n/a		PRAC Recommendation - maintenance
II/0126/G	This was an application for a group of variations. Extension of indication for the treatment of HIV-1 to include children from 3 months to 3 year of age and weighing at least 3.5kg and removal of the oral solution pharmaceutical form for Sustiva (efavirenz). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2, and 6.6 of the Summary of Product Characteristics (SmPC) are updated. The Package Leaflet is updated accordingly. In addition, the SmPC, Labelling and Package Leaflet of the 30 mg/ml oral solution is deleted. The requested group of variations proposed amendments to the SmPC, Labelling and Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one C.I.7.a - Deletion of - a pharmaceutical form	26/02/2015	08/04/2015	SmPC, Labelling and PL	Please refer to scientific discussion Sustiva-H-C-249-II-126-G.
IA/0132	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	08/12/2014	n/a		
WS/0604	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	20/11/2014	08/04/2015	SmPC and PL	The MAH presented in this variation drug interaction data on concomitant administration of simeprevir (Olysio) with efavirenz, likely due to CYP3A induction by efavirenz.

	Update of section 4.5 of the SmPC to include information about the potential interaction between simeprevir with efavirenz, likely due to CYP3A induction by efavirenz. The Package Leaflet has been updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Concomitant administration of simeprevir with efavirenz resulted in significantly decreased plasma concentrations of simeprevir due to CYP3A induction by efavirenz, which may result in loss of therapeutic effect of simeprevir. Co-administration of simeprevir with efavirenz is not recommended.
IA/0131	A.7 - Administrative change - Deletion of manufacturing sites	29/09/2014	n/a		
II/0128	Addition of an alternative manufacturing process for the synthesis of the active substance. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product	25/09/2014	n/a		
IAIN/0127/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of	30/04/2014	08/04/2015	Annex II and PL	

	manufacturing sites B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.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				
R/0120	Renewal of the marketing authorisation.	20/02/2014	23/04/2014	SmPC, Labelling and PL	
II/0125	Submission of the final study reports for paediatric studies AI266913 and AI266914 included in the Oral Liquid Expanded Access Program (LEAP) in fulfilment of post authorisation measures for Sustiva required in the RMP. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	20/03/2014	n/a		The data from these 2 LEAP studies show that EFV oral solution was generally safe and tolerable in paediatric subjects. The observed safety profile of the oral solution in this population is consistent with the well described safety and tolerability profile of efavirenz and no new safety signal was identified. Therefore, no update of the product information for Sustiva is needed in the view of these data.
WS/0475	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.6 of the SmPC on the number of pregnancies and on the number of Neural Tube	20/03/2014	08/04/2015	SmPC and PL	As of July 2013, the Antiretroviral Pregnancy Registry (APR) has received prospective reports of 904 pregnancies with first trimester exposure to efavirenz-containing regimens, resulting in 766 live births. The total number of retrospective reports consistent with neural tube defects identified in the children or fetuses of

	Defects (NTD) cases reported in subjects exposed to efavirenz-based products to reflect the Antiretroviral Pregnancy Registry (APR) reports. Section 2 of the PL was updated accordingly. This submission addresses the CHMP request following additional questions coming from the assessment of the last submitted PSUR. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				mothers exposed to efavirenz during the first trimester of pregnancy were updated to add an identified neural tube defect in a fetus that reached a gestational age of 22 weeks. The number of identified retrospective neural tube defects changed from 6 to a total of 7 for mothers exposed to efavirenz containing regimens in the first trimester (excluding any efavirenz-containing fixed-dose combination tablets). Furthermore two cases (1 prospective and 1 retrospective) including events consistent with neural tube defects associated with fixed-dose combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate (Atripla) have been added to the SmPC.
WS/0486	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 to include information that concomitant use with Ginkgo biloba extracts is not recommended, as requested in the PRAC recommendation, dated 3 October 2013. The PL is updated accordingly. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/01/2014	23/04/2014	SmPC and PL	Two published cases suggested an interaction between efavirenz and Ginkgo biloba extracts with a negative impact on efavirenz concentration and/or on viral load. A deleterious pharmacokinetic interaction between efavirenz and Ginkgo biloba extracts is plausible. Ginkgo biloba extracts can induce enzymes that may give rise to decreased plasma concentrations of efavirenz. This information was reflected in the product information of efavirenz-containing medicinal products by stating that concomitant use of Gingko biloba extracts is not recommended.
WS/0434	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	23/01/2014	23/04/2014	SmPC and PL	A literature review indicated that efavirenz may interfere with the results of a number of commercially available tests used for routine screening of cannabinoid use, and not just one test as had been previously included in the SmPC. The

	Update of sections 4.5 and 4.8 of the SmPC concerning information on false positive results in screening tests for cannabinoid metabolites. The PL is updated to include minor amendments for clarity. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				CHMP agreed to move the information on false positive results in screening tests for cannabinoid metabolites from section 4.8 to section 4.5 of the SmPC. Section 4.5 was updated with a more general statement (mention of specific assays was removed) and with a recommendation for confirmation of positive screening tests by a more specific method, such as GC/MS.
IB/0124/G	This was an application for a group of variations. B.I.b.1.h - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition or replacement (excl. Biol. or immunol. substance) of a specification parameter as a result of a safety or quality issue B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	17/01/2014	n/a		
IAIN/0121/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site	18/11/2013	23/04/2014	Annex II and PL	

	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing				
WS/0435	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.5 of the SmPC with information on the drug-drug interaction with artemether/lumefantrine. Additionally, section 4.4. was updated to clarify that, while co-administration of efavirenz with the fixed combination tablet containing efavirenz, emtricitabine, and tenofovir disoproxil fumarate is not recommended, it can be considered if needed for dose adjustment. The Package Leaflet was updated accordingly. In addition, the PI was brought in line with the latest QRD template version 9.0, and the list of local representatives in the PL was updated to include contact details for the representative of Croatia. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/10/2013	23/04/2014	SmPC, Annex II and PL	In a drug-drug interaction study in healthy volunteers coadministration of efavirenz with the antimalarial artemisinin-based combination therapy artemether/lumefantrine resulted in reduced exposure (AUC) to artemether, its metabolite dihydroartemisinin, and lumefantrine. Since reduced drug concentrations may result in decreased antimalarial efficacy, caution is recommended when efavirenz and artemether/ lumefantrine are coadministered. In addition, the MAH clarified that efavirenz can be exceptionally coadministered with the fixed-dose combination of efavirenz, emtricitabine and tenofovir disoproxil fumarate, if needed for dose-adjustment (for example with rifampicin).
WS/0433	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.6 of the SmPC in order to include	24/10/2013	23/04/2014	SmPC	Routine pharmacovigilance activities of the MAH identified a published study analysing the levels of efavirenz in plasma and breast milk of 13 breast-feeding mothers and in the plasma of their non-antiretroviral-treated infants. Results from this study demonstrated that efavirenz passes easily

	information on the excretion of efavirenz into human breast milk. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				into human milk, with a strong correlation between the levels in maternal plasma and breast milk, as well as between the levels in milk and plasma levels in breast-feeding infants. There is insufficient information on the effects of efavirenz in newborns/infants. Importantly, HIV-infected mothers should not breast-feed under any circumstances to avoid HIV transmission to the infant.
WS/0388	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 PL was updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the PL. 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 and PL	Upon review of safety data and literature on immune disorders in association with antitretrovirals 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.
WS/0357	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. To update section 4.5 of the SmPC to include the	21/03/2013	29/04/2013	SmPC, Annex II and PL	This procedure aimed to update section 4.5 of the SmPC to include information on the interaction with rifabutin and the new HCV NS3 protease inhibitors telaprevir and boceprevir. The Package Leaflet was updated accordingly. In the assessment of the last PSURs the CHMP requested

	interaction with rifabutin and the new HCV protease inhibitors telaprevir and boceprevir. The Package Leaflet was updated accordingly. In addition, one of the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the WSA proposed this opportunity to bring the PI in line with the QRD template version 8.2. The requested variation work-sharing procedure proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				these changes from Sustiva and Stocrin MAHs. Within this procedure, the drug-drug interaction information on concomitant use of efavirenz with either boceprevir or telaprevir was updated consistently with their respective SmPCs. Additionally, the SmPC was updated to inform prescribers that the recommended dose adjustments for rifabutin when coadministered with efavirenz have not been clinically evaluated. The requested variation work-sharing procedure proposed amendments to the Summary of Product Characteristics, Annex II and Package Leaflet.
IG/0254	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	17/12/2012	n/a		
WS/0210	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 4.5 and 5.2 of the SmPC on mechanism of interactions and in particular on interactions with darunavir, bupropion, rifampicin, atovaquone/proguanil and acenocoumarol. Update of section 4.8 to add to the list of adverse reactions the	24/05/2012	27/06/2012	SmPC, Annex II, Labelling and PL	The interaction with darunavir was updated in line with Prezista (darunavir) SmPC. Efavirenz in combination with darunavir/ritonavir 800/100 mg once daily may result in suboptimal darunavir Cmin. If efavirenz is to be used in combination with darunavir/ritonavir, the darunavir/ritonavir 600/100 mg twice daily regimen should be used. A dose adjustment for efavirenz to 800 mg for patients with body weights ≥ 50 kg when co-administered with rifampicin

	increase in lipids and liver enzymes. This variation was requested by the CHMP following evaluation of the PSUR covering the period from 17 April 2010 to 16 April 2011. The Package leaflet was updated accordingly. In addition, the MAH updated the Product Information in line with the latest QRD template (version 8) and the list of local representatives in the PL. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				is recommended. Results on the interaction with atovaquone/proguanil were introduced in the interactions table. Concomitant administration of atovaquone/proguanil with efavirenz reduces the concentrations of atovaquone/proguanil and should be avoided whenever possible. The interaction of efavirenz with acenocumarol was included in the interactions table. A dose adjustment of acenocumarol may be required. Results on the interaction with Bupropion were introduced in the interactions table. Increases in bupropion dosage should be guided by clinical response, but the maximum recommended dose of bupropion should not be exceeded. No dose adjustment is necessary for efavirenz.
IA/0112/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer	09/12/2011	n/a		
IB/0110	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	26/08/2011	n/a		

IA/0111/G	This was an application for a group of variations. B.III.1.b.2 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - New certificate for a starting material/reagent/intermediate/or excipient from a new or an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	26/08/2011	n/a		
WS/0116	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of SmPC and PL following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.6 of the SmPC on the use of efavirenz during pregnancy (as requested by the CHMP following evaluation of FUM 70 for Sustiva and FUM 61 for Stocrin). The contact details of the PL were updated. Translations errors in the Bulgarian product information were corrected within this variation. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	19/05/2011	13/07/2011	SmPC and PL	As of July 2010, the Antiretroviral Pregnancy Registry has received prospective reports of 718 pregnancies with first trimester exposure to efavirenz-containing regimens, resulting in 604 live births. One child was reported to have a neural tube defect, and the frequency and pattern of other birth defects were similar to those seen in children exposed to non efavirenz containing regimens, as well as those in HIV negative controls. The incidence of neural tube defects in the general population ranges from 0.5 1 case per 1,000 live births. All together there have been six retrospective reports of findings consistent with neural tube defects, including meningomyelocele, all in mothers exposed to efavirenz containing regimens in the first trimester. A causal relationship of these events to the use of efavirenz has not been established, and the denominator is unknown. As neural tube defects occur within the first 4 weeks of foetal development (at which time neural tubes are sealed), this potential risk would concern women exposed to efavirenz during the first trimester of pregnancy. The SmPC was updated to reflect these data and the

					restriction for women with childbearing potential for efavirenz was revised as follows: Efavirenz should not be used during pregnancy, unless the patient's clinical condition requires such treatment. Additionally, women of childbearing potential should undergo pregnancy testing before initiation of efavirenz. Prescribers are referred to section 5.3 to relevant preclinical safety data.
IA/0109	A.7 - Administrative change - Deletion of manufacturing sites	08/07/2011	n/a	Annex II and PL	
IA/0108/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer 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	20/06/2011	n/a		
IA/0107	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	16/03/2011	n/a	Annex II	

	pharmacovigilance obligations and described in the DD				
II/0104	Update of sections 4.2, 4.4, 4.8 and 5.2 of the SmPC based on a PK study in HIV-infected patients with our without hepatic impairment, as well as on a cumulative review of severe hepatic events in patients with no known history of hepatic disease or impairment as requested by the CHMP following the assessment of follow-up measure 066. In addition, the MAH took this opportunity to update section 4.8 of the SmPC in line with Rev. 2 of the Guideline o SmPC. Finally, the SmPC was updated in light of the latest (7.3) QRD template. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	23/09/2010	03/11/2010	SmPC and PL	Update of sections 4.2, 4.4, 4.8 and 5.2 of the SmPC based on a PK study in HIV-infected patients with or without hepatic impairment, as well as on a cumulative review of severe hepatic events in patients with no known history of hepatic disease or impairment as requested by the CHMP following the assessment of follow-up measure 066. In addition, the MAH took this opportunity to update section 4.8 of the SmPC in line with Rev. 2 of the Guideline of SmPC. Finally, the SmPC was updated in light of the latest (7.3) QRD template. Therefore the frequencies now for cerebellar coordination and balance disturbances and flushing is 'common', 'uncommon' for psychosis, tremor, and tinnitus, and 'rare' for delusion, neurosis, completed suicide, hepatic failure, and photoallergic dermatitis. The PL was updated accordingly. Furthermore the local representatives of Belgium/Luxembourg, Malta, Denmark, Netherlands, Austria, Cyprus and Latvia have been updated.
IA/0106	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	09/09/2010	n/a	Annex II	
IA/0105/G	This was an application for a group of variations. C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the	12/03/2010	n/a	Annex II	

	contact details of the QPPV 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				
II/0097	Update of section 4.5 of the SmPC to add interaction information on warfarin with efavirenz following the CHMP conclusion on PSUR 12. The MAH also took the opportunity to update section 4.8 of the SmPC to include 3 adverse drug reactions: flushing, tinnitus and tremor to bring the SmPC in line with the company core data sheet. The PL was updated accordingly. In section 4.8, the MAH also reordered the MedDRA system organ class listing of events from clinical trials according to the most recent version (Version 12.0, February 2009). Minor typographical amendments have been made to SmPC and PL. Update of Summary of Product Characteristics and Package Leaflet	22/10/2009	09/12/2009	SmPC and PL	Following assessment of PSUR 12, the CHMP recommended to amend the SPC of efavirenz in order to include a interaction information with the anticoagulant warfarin. No interaction study has been performed. Warfarin is administered as a racemate; the S-enantiomer provides most of the anticoagulation effect and is metabolized by CYP2C9 while the R-enantiomer is metabolized by CYP3A4. Efavirenz is an inducer of CYP3A4 and in vitro data have indicated that it is also an inhibitor of CYP2C9. Due to these dual properties of efavirenz, the following information was added: an increase or decrease in warfarin exposures and effects could be observed if co administered with efavirenz. Dose adjustment of warfarin may be required. The PL was updated accordingly. In addition, a review of the MAH safety database has shown the following additional adverse reactions to occur in association with efavirenz-containing antiretroviral treatment regimens: flushing, tinnitus, and tremor. These were therefore added to the SPC. The PL was updated accordingly. The MAH took the opportunity to also reorder the MedDRA system organ class listing of events from clinical trials according to the most recent version (Version 12.0, February 2009).
IB/0102	IB_33_Minor change in the manufacture of the finished product	12/11/2009	n/a		

IA/0103	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	04/11/2009	n/a	Annex II and PL	
IB/0098	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	16/09/2009	n/a		
IA/0101	IA_36_ b_Change in shape or dimensions of the container/closure - other pharm. forms	28/08/2009	n/a		
IA/0099	IA_32_b_Change in batch size of the finished product - downscaling down to 10-fold	21/08/2009	n/a		
IA/0100	IA_36_ b_Change in shape or dimensions of the container/closure - other pharm. forms	20/08/2009	n/a		
IA/0096	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	30/06/2009	n/a		
IA/0095	IA_08_a_Change in BR/QC testing - repl./add. of batch control/testing site	10/06/2009	n/a		
II/0083	Update of section 4.5 "Interaction with other medicinal products and other forms of interaction" of the Summary of Product Characteristics (SPC) with information on the use of efavirenz with hormonal contraceptives based on results from clinical studies AI266145, ACTG5093, published literature and on data from pharmacovigilance reports. The update also includes amendment of section 4.6 "Pregnancy	23/04/2009	02/06/2009	SmPC and PL	In Study AI266145, the coadministration of efavirenz (600 mg once daily) with an orally administered hormonal contraceptive containing ethinyloestradiol (EE) and norgestimate (NGM) did not have a significant impact on EE exposures; however, significantly reduced exposures to norelgestromin (NGMN) and levonorgestrel (LNG), the active metabolites of NGM, were observed. The exact mechanism of this interaction is not elucidated, but is

	and lactation" of the SPC further to the update of the Antiretroviral Pregnancy Registry. The Package leaflet was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				possibly due to inhibition and induction of multiple metabolic pathways. The reduced exposures raise concern as to the potential negative impact on the efficacy of the hormonal combination. Consequently it is recommended that for patients taking EFV 600 mg once daily a reliable method of barrier contraception must be used in addition to oral hormonal contraceptives. In a study reported in the published literature, no significant differences in depo-medroxyprogesterone acetate (DMPA) pharmacokinetic parameters were found between subjects receiving EFV-containing antiretroviral therapy and subjects receiving no antiretroviral therapy. Similar results were found in study ACTG 5093 (although the DMPA plasma levels were found to be more variable). In these studies, plasma progesterone levels for subjects receiving EFV and DMPA remained low consistent with suppression of ovulation. However due to the global limited information available, a reliable method of barrier contraception must be used in addition to injectable hormonal contraceptives containing DMPA. The interaction between EFV and the implantable hormonal contraceptive, etonogestrel, has not been studied; however, there have been reports of unplanned pregnancies in women taking both, possibly due to induction of metabolic enzymes such as CYP3A4 by EFV. Thus, a reliable method of barrier contraception must be used in addition to implantable hormonal contraceptives when taking EFV.
R/0089	Renewal of the marketing authorisation.	19/02/2009	22/04/2009	SmPC, Annex II and PL	Based on the CHMP review of the available information , 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 Sustiva continues to be favourable. The CHMP recommends the renewal of the Marketing Authorisation for Sustiva but requires an additional five-year renewal on the basis of pharmacovigilance grounds. The hepatic toxicity is a known risk but is a remaining concern. The number of spontaneous reports on hepatic toxicity and acute or sub-acute chronic hepatitis potentially serious and fatal presented in subject without other known risk factors is a matter of concern in particular in view of the evolving therapeutic management of HIV infected patients. As newer therapeutic options for the treatment of HIV infection become available, the benefit/risk balance should be continuously reassessed in light of the introduction of these new options into treatment regimens.
IA/0094	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	10/03/2009	n/a		
IA/0093	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	10/03/2009	n/a		
IA/0092	IA_08_b_02_Change in BR/QC testing - repl./add. manuf. responsible for BR - incl. BC/testing	10/03/2009	n/a	Annex II and PL	
II/0085	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Changes to QPPV Update of DDPS (Pharmacovigilance)	22/01/2009	09/03/2009	Annex II	The MAH updated the DDPS to include a change in the Qualified Person for Pharmacovigilance (QPPV) in the EEA. In addtion, the MAH took the opportunity to notify other minor changes to the DDPS performed since the last approved version. Annex II of the Product Information has been updated using standard text including the new version

					number for the DDPS (version 3.0).
IB/0090	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	04/02/2009	04/02/2009	SmPC, Labelling and PL	
IA/0091	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	22/01/2009	n/a		
II/0076	Update of section 4.2, 4.4, 4.5, 4.6, 4.8, 5.1 and 5.2 of the SPC to align the product information with Atripla. The package leaflet is updated accordingly. Furthermore the contact details of the Czech, Danish, Maltese, and Icelandic local representatives in the PL are updated. The MAH also takes the opportunity to make some linguistic changes to the Slovakian Product Information Update of Summary of Product Characteristics and Package Leaflet	23/10/2008	01/12/2008	SmPC and PL	The Efavirenz SPC has been harmonised to be in line with the SPC of Atripla (a triple fixed-combination medicinal product containing efavirenz, emtricitabine and tenofovir disoproxil fumarate). Of note, the use of adequate contraceptive measures is recommended for 12 weeks after discontinuation of EFV to provide adequate protection against exposure of a fetus to EFV. Furthermore, changes were made focusing on drug elimination and gender differences based on updated EFV pharmacokinetics data. Taking into account the potential differences in exposure to EFV related to gender/ethnic/gene polymorphism, an increase in frequency/severity of AEs cannot be strictly ruled out, but this is unlikely to have a significant clinical impact.
II/0082	The Marketing Authorisation Holder applied to introduce four alternative in-process analytical methods and one alternative starting material method used in the synthesis of the active substance, efavirenz. Quality changes	20/11/2008	27/11/2008		

IA/0088	IA_09_Deletion of manufacturing site	25/11/2008	n/a		
IA/0087	IA_09_Deletion of manufacturing site	25/11/2008	n/a		
IA/0086	IA_09_Deletion of manufacturing site	25/11/2008	n/a		
II/0079	Update of section 4.2 and 5.2 of the SPC to incorporate bioequivalence results of the open capsules, further to request of the CHMP made in the context of the evalution of PSUR 10 (covering the period of 17.09.05 to 16.09.06). The package leaflet is updated accordingly. The MAH also updates the Detailed Description of the Pharmacovigilance System. Update of Summary of Product Characteristics and Package Leaflet	24/07/2008	15/09/2008	SmPC, Annex II and PL	Study AI266059 was conducted to evaluate the pharmacokinetics of efavirenz when the contents of the capsules are administered with food vehicles. Based on the results of this study, administration of the capsule contents with a small amount of food (e.g 1-2 teaspoons of applesauce, grape jelly, yogurt, or infant formula) may be considered as an alternative for adults and for children aged 3 years or older and weighing 13 kg or more, who are unable to tolerate the Sustiva oral solution or swallow intact Sustiva capsules. This option should not be recommended for general use in the paediatric population in lieu of the oral solution.
IA/0081	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	09/09/2008	n/a		
II/0074	Update of section 4.8 of the SPC to include the adverse reaction "cerebellar coordination and balance disturbances". The package leaflet is updated accordingly. Furthermore the Detailed Description of the Phamacovigilance system is updated in Module 1.8.1. Update of Summary of Product Characteristics and Package Leaflet	30/05/2008	11/07/2008	SmPC and PL	A review of cases relating to cerebellar function, including all spontaneous, literature and clinical trial (regardless of causality) reports up until March 2007 in which efavirenz was considered a suspect or interacting medicinal product was carried out. Based on the review and taking into account the distribution and heterogeneity of terms for the reported events, the High Level Term "cerebellar coordination and balance disturbances" has been included in the SPC. The package leaflet is updated accordingly.

IB/0080	IB_14_a_Change in manuf. of active substance without Ph. Eur. certificate - change in manuf. site	01/07/2008	n/a		
IB/0078	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	10/06/2008	n/a		
IA/0077	IA_20_a_Change in test procedure for an excipient - minor change to approved test procedure	21/04/2008	n/a		
IA/0075	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	21/02/2008	n/a		
IB/0072	IB_10_Minor change in the manufacturing process of the active substance	19/02/2008	n/a		
IA/0073	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	06/02/2008	n/a		
IA/0071	IA_23_b_Change in source of excip./reagent to veg./synthetic material - other cases	05/10/2007	n/a		
II/0069	Update section 5.2 of the SPC as requested by the CHMP further to the assesment of an integrated pharmacogenomic/pharmacokinetic report for efavirenz, in February 2007. Section 4.8 of the SPC and section 4 of the PL are updated in line with the MedDRA version 8.2. Furthermore, the Danish, Dutch, Hungarian and Spanish version of the annexes were amneded in line with the QRD/EMEA template version 7.2	19/07/2007	23/08/2007	SmPC and PL	Following the assessment of an integrate report from three efavirenz studies (AI266919, AI266926 and AI266928) concerning associations between genetic polymorphism of CYP2B6, CYP 3A4/5 and MDR-1 genes and the pharmacokinetics of efavirenz it was agreed that a reference to the possibility of increased efavirenz exposure (with possible increased incidence and severity of specific adverse events, namely pertaining to the central nervous system) in patients carrying the CYP2B6 G516T

	Update of Summary of Product Characteristics and Package Leaflet				homozygoty should be reflected in the efavirenz product information. This observation, supported by the current published data could not be disregarded as potentially affecting clinical practice and therefore it is now reflected in the efavirenz product information.
II/0068	Update of sections 4.2, 4.3 and 4.5 of the SPC to include a recommendation on dose adjustment for efavirenz and voriconazole when co-administration is deemed necessary, as requested by the CHMP. Section 2 of the PL is updated accordingly. Section 6 was updated for the local representatives in Spain and Malta. Update of Summary of Product Characteristics and Package Leaflet	24/05/2007	02/07/2007	SmPC and PL	Based on the results of a pharmacokinetic study conducted in 16 healthy volunteers a dose adjustment recommendation can be made to both efavirenz and voriconazole when the co-administration is necessary. Efavirenz and voriconazole can only be used in combination if the voriconazole maintenance dose is increased to 400 mg twice daily and the efavirenz dose is reduced to 300 mg once daily. Once the treatment with voriconazole is stopped, the initial dosage of efavirenz should be restored. This information is included in section 4.2 and 4.5 of the SPC. The PL is updated to reflect this information.
II/0067	Update of section 4.8 of the SPC and section 4 of the PL by adding "gynaecomastia" to the list of uncommon adverse reactions to efavirenz, as agreed by the CHMP in December 2006. Update of Summary of Product Characteristics and Package Leaflet	22/03/2007	02/05/2007	SmPC and PL	Based on the safety data provided in the Periodic Safety Update Report (PSUR) for efavirenz covering the period 17.09.04 - 16.09.05 and on data from an integrated safety summary, a total of 9 gynaecomastia cases was identified among the 840 male patients. Five of the 9 cases were classified as at least possibly related with efavirenz. Gynaecomastia, under the System Organ Class heading "Reproductive System and Breast Disorders" is now included in section 4.8 of the SPC with a MedDRA frequency convention "uncommon".
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.	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

	Section 6 of the PL was updated with the local representatives in Bulgaria and Romania and in Norway. Update of Summary of Product Characteristics and Package Leaflet				(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.
IA/0066	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	12/12/2006	n/a		
IA/0064	IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	16/11/2006	n/a		
II/0063	Update of section 4.5 of the SPC and section 2 of the PL to include information on the interaction between efavirenz and itraconazole. Update of Summary of Product Characteristics, Labelling and Package Leaflet	21/09/2006	26/10/2006	SmPC, Annex II, Labelling and PL	Efavirenz decreases itraconazole plasma levels when given in combination for the treatment of HIV and fungal co-infection. Itraconazole levels are decreased by 39%, 37%, and 44% respectively, and the hydroxyitraconazole (the active metabolite of itraconazole) by 37%, 35%, and 43% % for AUC, Cmax and Cmin respectively, when compared to itraconazole administered alone. The pharmacokinetics of efavirenz were considered not affected by itraconazole. Since no dose adjustment for itraconazole can be recommended at this stage, alternative antifungal treatment should be considered. Section 4.5 of the SPC under subheading "Antifungal agents" reflects this information. The PL was consequently updated in section 2.

II/0062	Update of section 4.5 of the SPC and section 2 of the PL to include information on the interaction between efavirenz and diltiazem. The list of the local representatives in the PL was updated. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	01/09/2006	SmPC and PL	The plasma levels of efavirenz are slightly increased by 11%, 16%, and 13% with respect to AUC, Cmax and Cmin, respectively, when efavirenz is co-administered with diltiazem. This increase is considered not clinically relevant. Diltiazem levels decreased by 69%, 60%, and 63% when co-administered with efavirenz than when administered alone with respect to AUC, Cmax and Cmin, respectively. Diltiazem dose adjustment following co-administration with efavirenz should be guided by clinical response. Section 4.5 of the SPC under subheading "calcium channel blockers" reflects this information. The PL was consequently updated in section 2.
II/0055	Update of section 4.5 "Interaction with other medicinal products and other forms of interaction" of the Summary of Product Characteristics (SPC) and section 2 "Before you take Sustiva" of the Package Leaflet (PL) to include information on the interaction between efavirenz and atazanavir in line with the atazanavir product information. In addition, the MAH took this opportunity to introduce minor linguistic changes in the Danish, German, Spanish, Estonian, Icelandic, Italian, Norwegian, Polish and Portuguese SPC and/or PL, as relevant. Update of Summary of Product Characteristics and Package Leaflet	17/11/2005	23/12/2005	SmPC and PL	As stated in the product information of atazanavir (Reyataz), the co-administration of efavirenz with atazanavir in combination with low-dose ritonavir decreases the exposure of atazanavir. A dosage adjustment of atazanavir is therefore recommended although no efficacy and safety data are available to support the proposed increased atazanavir dose to 400 mg with ritonavir when co-administrated with efavirenz. Limited data further suggest that using efavirenz in a regimen including low dose ritonavir, may cause an increase in the incidence of efavirenz-associated adverse events. This information has been included in section 4.5 of the SPC and reflected in section 2 of the PL.
II/0058	The Marketing Authorisation Holder (MAH) applied to amend section 4.5 "Interaction with other medicinal	15/09/2005	25/10/2005	SmPC and PL	The need to characterise the pharmacokinetics of the concomitant use of statins and efavirenz was addressed in

	products and other forms of interaction" of the the Summary of Product Characteristics (SPC) and point 2 " Before you take Sustiva2 of the Package Leaflet (PL) to include data on the interaction between efavirenz and statins (atorvastatin, pravastatin and simvastatin). Update of Summary of Product Characteristics and Package Leaflet				an open-label, phase I, four arm study evaluating the effect of efavirenz and simvastatin, atorvastatin and pravastatin at steady state in uninfected volunteers. The results showed that efavirenz decreased the AUC and Cmax at steady-state by 69% and 76% for simvastatin, 43% and 12% for atorvastatin, 40% and 18% for pravastatin. These significant decreases were accompanied by small but significant changes in LDL cholesterol which may not be clinically relevant however, as the HMG COA-reductase inhibitors are generally titrated, this should be able to be clinically managed. Further to the assessment of these data the CHMP agreed that these results and observation should be reflected in section 4.5 under a new subheading "Lipid-lowering agents" of the SPC and section 2 of the PL.
II/0057	The Marketing Authorisation Holder (MAH) applied to amend sections 4.4 " Special warnings and special precautions for use" and 4.8 "Undesirable effects" of the Summary of product Characteristics (SPC) regarding lipids following a wider review in lipodystrophy. Update of Summary of Product Characteristics	15/09/2005	25/10/2005	SmPC	A wider review on the effect of efavirenz on lipid profiles and fat redistribution from several clinical studies, including data in antiretroviral naive patients, was performed and has been provided to further monitor and characterised lipodystrophy. The results of this review confirmed that the long-term treatment with efavirenz is associated with increases in total and HDL cholesterol (21-31% and 23-34%, respectively) and showed increases in triglycerides (23%) and LDL (18%). Although the clinical significance of this small increase in triglycerides is yet uncertain, this new information is now being reflected in section 4.8 of the SPC. Multivariate analyses evaluating how efavirenz performs against other potential risk factors, either treatment-related or disease-related were not done. Also, demographic variables such as age and gender were not analysed. The provided data support findings from previous data that

					efavirenz-based regimens may be independently associated with new or worsening lipodystrophy in a small percentage of patients.
II/0056	The Marketing Authorisation Holder (MAH) applied to amend section 4.4 "Special warnings and special precautions for use" and section 4.5 "Interaction with other medicinal products and other forms of interaction" of the Summary of Product Characteristics (SPC) and point 2 "Before you take Sustiva" of the Package Leaflet (PL) to include data on the interaction between efavirenz and carbamazapine. Additionally, the MAH updates section 4.5 of the SPC to comply with QRD guidelines Update of Summary of Product Characteristics and Package Leaflet	15/09/2005	25/10/2005	SmPC and PL	The plasma levels of both efavirenz and carbamazepine when co-administrated are decreased remaining however, unchanged for the carbamazepine active metabolite as shown in a study performed in healthy volunteers. On average the decreases of AUC, Cmax and Cmin at steady state were of 36%, 21% and 47% for efavirenz and 27%, 20% and 35% for carbamazepine. The available data does not allow any recommendation for dosage adjustment. However, intensification of therapeutic monitoring considered, when efavirenz is added to a regimen of carbamazepine. Section 4.4 under subheading "seizures" and section 4.5 subheading "anticonvulsivants" of the SPC are amended to reflect this information. Section 2 of the PL is updated in accordance. The majority of the adverse events reported were consistent with those for individual medicinal products. The overall incidence of the adverse events for each drug alone and for the combination was similar.
IA/0061	IA_01_Change in the name and/or address of the marketing authorisation holder	02/09/2005	n/a	SmPC, Labelling and PL	
II/0054	Update of section 4.6 "Pregnancy and lactation" of the Summary of Product Characteristics and section 2 of the Package Leaflet under subheading "Pregnancy" regarding recent information from the Antiretroviral Pregnancy Register and following the CHMP assessment of PSUR 8 covering the period	23/06/2005	09/08/2005	SmPC and PL	In line with the CHMP recommendations further to the assessment of the 9th and 10th efavirenz PSURs and with the long-term data from the antiretroviral pregnancy registry (APR) the MAH applied to update the efavirenz's pregnancy information. Pregnancy testing is now recommended before the initiation of therapy with

	from 17.09.03 to 16.09.04. Update of Summary of Product Characteristics and Package Leaflet				efavirenz. Efavirenz should only be started during pregnancy if there are no other treatment options as, a small number of neural tube defects have been reported although no causality with efavirenz has been established. The existing data in animals is consistent with a reproductive toxicity of efavirenz.
II/0053	Update of sections 4.2, 4.4 and 4.8 of the SPC for Sustiva hard capsules and film-coated tablets to include information on the food effect and differences with respect to both solid formulations as requested by the CHMP. A cross reference to section 4.4 is proposed for inclusion in section 5.2. Relevant sections of the PL are updated accordingly. In addition, MAH has taken this opportunity to amend the SPC and PL in line with the latest EMEA/QRD templates and to introduce minor linguistic changes in the Finnish and Polish SPC. Furthermore, the contact details for the local representative in Slovak Republic and France are being updated. Update of Summary of Product Characteristics and Package Leaflet	23/06/2005	09/08/2005	SmPC and PL	It was known that the absorption rate of efavirenz was positively affected when the hard capsules were taken in the fed state and that for the tablets the impact seemed even greater. As a post-renewal commitment the MAH submitted a safety comparison between the hard capsules and the film-coated tablets derived from clinical trials, spontaneous and literature reports. Following the assessment of this data the CHMP concluded that in the presence of food an increase of efavirenz serum concentration and an increase of the frequency of adverse reactions was observed. As this effect could be more evident for the film-coated tablets than for the hard capsules, the CHMP requested the update of the SPC and PL of both solid formulations to recommend the administration of Sustiva on an empty stomach preferable at bedtime to improve the tolerability of nervous system undesirable effects.
IA/0060	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	29/07/2005	n/a		
IA/0059	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	29/07/2005	n/a		
IA/0052	IA_23_b_Change in source of excip./reagent to	17/03/2005	n/a		

	veg./synthetic material - other cases				
II/0050	Update of section 4.3 "Contraindications" and 4.5 "Interaction with other medicinal products and other forms of interaction" of the Summary of Product Characteristics and section 2 "Before you take Sustiva" of the Package Leaflet, to include information on the interaction between efavirenz and voriconazol as requested by the CHMP in August 2004. Furthermore, the Marketing Authorisation Holder applied for the update of section 4.5 of the Summary of Product Characteristics to clarify the safety concerns of the interaction between efavirenz and CYP450 metabolised products. The MAH has taken this opportunity to amend the Summary of Product Characteristics, Labelling and Package Leaflet to reflect the unit dose blister presentation, to specify the type of container, in accordance with the latest EMEA/QRD templates and to update the list of the local representatives in the Package Leaflet. In addition the labelling texts for Sustiva hard capsules of bottle and blister outer carton are being merged and the bottle label of hard capsules and film-coated tablets are being separate from the outer carton text. Moreover, the Czeck, Danish, Greek, Estonian, Finish, Portuguese, Swedish and Iceland, Norwegian SPC and/or PL are being amended to ensure	20/01/2005	07/03/2005	SmPC, Labelling and PL	

	consistence in all the languages. The detail changes are highlighted in Annex 1 to this assessment report. Update of Summary of Product Characteristics, Labelling and Package Leaflet				
II/0049	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 Sustiva" 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	05/01/2005	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 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 the product information of all anti-retroviral medicinal products.
II/0048	To update the Summary of Product Characteristics (SPC) in section 4.5 (Interaction with other medicinal products and other forms of interaction) to include information on pharmacokinetic data from the study report 906-01 and of section 4.8 (Undesirable effects) to include percentage data for the occurrence of asymptomatic amylase elevations as requested by the CPMP after the Assessment of Study AI266049 in July 2003. In addition the MAH has taken this opportunity to merge the labelling texts for Sustiva film-coated tablets of bottle label and outer carton and blister outer carton. Update of Summary of Product Characteristics, Labelling and Package Leaflet	21/10/2004	06/12/2004	SmPC, Labelling and PL	
IA/0051	IA_09_Deletion of manufacturing site	18/11/2004	n/a		
II/0047	Quality changes	21/10/2004	28/10/2004		
II/0046	Quality changes	16/09/2004	29/09/2004		
II/0040	Update of sections 4.8 and 5.1 of the SPC to include the results of the long-term (168 week) safety and efficacy data from the clinical study AI266006.	03/06/2004	13/07/2004	SmPC and PL	This study was an open-label, randomized designed to compare the antiretroviral activity and tolerability of three different combination regimens efavirenz (EFV)+indinavir

	The list of local representatives in the PL is being updated to include the contacts of the new European Member States. Update of Summary of Product Characteristics and Package Leaflet				(IDV), EFV+zidovudine (ZDV)+lamivudine (3TC), IDV+ZDV+3TC in HIV-infected, NNRTI-, 3TC- and Protease Inhibitors (PI)- naïve patients. This study is the follow-up of the original 006 EFV pivotal study supportive of the initial Marketing Authorisation for Sustiva. The long-term (168 weeks) efficacy results suggest durability of response in terms of proportion of patients with HIV RNA < 400 copies/ml (48% in the EFV+3TC+ZDV group, n = 422; 30% in the IDV+3TC+ZDV group, n = 415), HIV RNA <50 copies/ml (42% in the EFV+3TC+ZDV group, n = 422; 23% in the IDV+3TC+ZDV group, n = 415) and of mean changes from baseline CD4 cell counts (329 cells/mm3 in the EFV+3TC+ZDV group, n = 422; 329 cells/mm3 in the IDV+3TC+ZDV group, n = 415). Section 5.1 was updated to reflect these results. The long-term safety of the EFV+ZDV+3TC treatment regimen was not different from the already defined safety profile of EFV. The incidences of nervous system symptoms and rash beyond the 48 week of treatment were low. The long-term safety profile in patients with HCV and/or HBV co-infection was not different from the previously profile known in this subset of patients. Section 4.8 of the SPC, subheading "nervous system symptoms" and "laboratory test abnormalities" were updated in regard of these observations.
R/0043	Renewal of the marketing authorisation.	26/02/2004	29/04/2004	SmPC, Annex II, Labelling and PL	
II/0038	Update of the section 4.4 (Special warnings and special precautions of use) and 5.2 (Pharmacokinetic	20/11/2003	05/02/2004	SmPC and PL	

	properties) of the Summary of Product Characteristics (SPC) to implement the class labelling on liver impairment adopted by the CPMP for all anti-retroviral medicinal products on 25 April 2003. Furthermore, the MAH has taken this opportunity to update section 4.4 of the SPC, by reordering the wording on lactose (for the 300 and 600 mg tablet formulations only), on cholesterol and on lipodystrophy. The MAH also updated the SPC according to the latest EMEA/QRD templates with regard to the expression of cross references between sections. In addition, the MAH has proposed to update the Package leaflet (PL) in line with the proposed changes of the SPC and to include the wording on lipodystrophy as adopted by the CPMP on 24 March 2003. Update of Summary of Product Characteristics and Package Leaflet				
IA/0045	IA_09_Deletion of manufacturing site IA_07_b_01_Replacement/add. of manufacturing site: Primary packaging site - Solid forms	30/01/2004	n/a		
IA/0044	IA_09_Deletion of manufacturing site	27/01/2004	n/a		
IA/0042	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	17/11/2003	n/a		
I/0039	10a_Addition or replacement of measuring device for	16/10/2003	23/10/2003		

	oral liquid dosage forms and other dosage forms				
I/0037	15_Minor changes in manufacture of the medicinal product 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	07/07/2003	22/07/2003		
II/0035	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	09/07/2003	SmPC and PL	
I/0036	20_Extension of shelf-life as foreseen at time of authorisation	08/05/2003	25/06/2003	SmPC	
II/0034	Update of Summary of Product Characteristics and Package Leaflet	20/02/2003	19/05/2003	SmPC and PL	
N/0033	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/11/2002	09/12/2002	PL	
II/0027	Update of Summary of Product Characteristics and Package Leaflet	27/06/2002	30/09/2002	SmPC and PL	
II/0029	Update of Summary of Product Characteristics	30/05/2002	30/08/2002	SmPC	
X/0018	X-3-iv_Change or addition of a new pharmaceutical form	30/05/2002	22/08/2002	SmPC, Annex II, Labelling and PL	
X/0017	X-3-iv_Change or addition of a new pharmaceutical form	30/05/2002	22/08/2002	SmPC, Annex II, Labelling and PL	

N/0032	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/06/2002	10/07/2002	PL	
N/0031	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/05/2002	20/06/2002	PL	
I/0030	01_Change following modification(s) of the manufacturing authorisation(s)	09/04/2002	07/05/2002	Annex II and PL	
II/0019	Update of Summary of Product Characteristics	13/12/2001	12/04/2002	SmPC	
T/0028	Transfer of Marketing Authorisation	28/02/2002	02/04/2002	SmPC, Labelling and PL	
I/0024	03_Change in the name and/or address of the marketing authorisation holder 01_Change following modification(s) of the manufacturing authorisation(s)	31/10/2001	21/03/2002	SmPC, Labelling and PL	
I/0023	03_Change in the name and/or address of the marketing authorisation holder	31/10/2001	21/03/2002	SmPC, Labelling and PL	
I/0025	01_Change following modification(s) of the manufacturing authorisation(s)	31/10/2001	06/03/2002		
I/0022	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	26/11/2001	06/03/2002		
I/0021	31_Change in container shape	24/10/2001	07/01/2002		

I/0020	26_Changes to comply with supplements to pharmacopoeias	21/09/2001	23/10/2001		
X/0007	X-3-iv_Change or addition of a new pharmaceutical form	27/06/2001	18/10/2001	SmPC, Annex II, Labelling and PL	
II/0014	Update of Summary of Product Characteristics	31/05/2001	20/09/2001	SmPC	
II/0012	Update of Summary of Product Characteristics and Package Leaflet	01/03/2001	14/06/2001	SmPC and PL	
II/0011	Change(s) to the manufacturing process for the active substance	01/03/2001	14/06/2001		
I/0016	26_Changes to comply with supplements to pharmacopoeias	28/03/2001	05/05/2001		
I/0010	13_Batch size of active substance	24/11/2000	n/a		
II/0008	Update of Summary of Product Characteristics and Package Leaflet	29/06/2000	13/10/2000	SmPC and PL	
II/0006	Update of Summary of Product Characteristics	29/06/2000	13/10/2000	SmPC	
II/0009	Change(s) to the manufacturing process for the active substance	27/07/2000	12/10/2000		
II/0004	Update of Summary of Product Characteristics	19/01/2000	24/05/2000	SmPC	
I/0005	20a_Extension of shelf-life or retest period of the active substance	02/02/2000	11/05/2000		

II/0002	Update of Summary of Product Characteristics and Package Leaflet	23/09/1999	31/01/2000	SmPC and PL	
I/0001	20_Extension of shelf-life as foreseen at time of authorisation	08/07/1999	23/08/1999		
I/0003	08_Change in the qualitative composition of immediate packaging material	11/08/1999	17/08/1999		