Viramune

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/0165	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/10/2024		SmPC, Annex II, Labelling and PL	
IA/0164/G	This was an application for a group of variations. B.II.c.1.c - Change in the specification parameters	12/09/2024	n/a		

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.c - Change in the specification parameters and/or limits of an excipient - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method B.II.c.1.b - Change in the specification parameters and/or limits of an excipient - Addition of a new specification parameter to the specification with its corresponding test method				
IA/0163	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	28/02/2024	n/a		

IB/0162/G	This was an application for a group of variations. B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation A.7 - Administrative change - Deletion of manufacturing sites	23/02/2024	n/a		
IA/0161	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)	25/07/2023	n/a		
IB/0158	B.IV.1.b - Change of a measuring or administration device - Deletion of a device	20/04/2023	04/08/2023	SmPC and PL	
IA/0160	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	28/02/2023	n/a		
IA/0159	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	27/02/2023	n/a		
IB/0157	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/02/2023	n/a		

IB/0156	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	16/12/2022	n/a		
IAIN/0155	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/08/2022	04/08/2023	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
IA/0154	A.7 - Administrative change - Deletion of manufacturing sites	24/06/2022	n/a		
IAIN/0153/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.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	02/06/2022	01/07/2022	Annex II and PL	
IB/0152/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.7.b - Deletion of - a strength	07/03/2022	01/07/2022	SmPC, Annex II, Labelling and PL	
PSUSA/2147/ 202105	Periodic Safety Update EU Single assessment - nevirapine	13/01/2022	n/a		PRAC Recommendation - maintenance

IB/0151	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	13/10/2021	n/a		
IA/0149	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	26/07/2021	n/a		
II/0147	Update of sections 4.4 and 5.2 of the SmPC in order to remove wording on precautionary measures related to reassuring that tablet remnants in faeces have no impact on the therapeutic response of Viramune, based on additional clinical and pharmacovigilance data that have become available; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.2. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	08/07/2021	01/07/2022	SmPC, Labelling and PL	The data submitted with this application provides no evidence that additional monitoring is needed in patients who report tablet remnants of Viramune XR. As a result of this variation, sections 4.4 and 5.2 of the SmPC and the corresponding section of the PL of the extended release (XR) formulation for Viramune were updated to delete wording related to actions to take in case of occurrence of tablet remnants in faeces. For more information, please refer to the Summary of Product Characteristics.
IA/0148	B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	11/05/2021	n/a		
IAIN/0146/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a	30/09/2020	18/11/2020	Annex II and PL	

	manufacturing site for the FP - Secondary packaging site 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				
IB/0145	B.IV.1.z - Change of a measuring or administration device - Other variation	26/05/2020	n/a		
IB/0144/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 - Replacement/addition of a site where batch control/testing takes place 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	18/03/2020	n/a		

	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
IA/0143	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	24/01/2020	n/a		

II/0141/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.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure	12/12/2019	n/a		
IB/0142	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/11/2019	18/11/2020	SmPC, Labelling and PL	
IAIN/0140	B.IV.1.a.1 - Change of a measuring or administration	01/08/2019	n/a		

	device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking				
IA/0139	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)	17/04/2019	n/a		
IAIN/0138	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	14/03/2019	n/a		
IA/0137/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	08/03/2019	n/a		
IAIN/0136/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	15/02/2019	n/a		

	B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)				
PSUSA/2147/ 201805	Periodic Safety Update EU Single assessment - nevirapine	17/01/2019	n/a		PRAC Recommendation - maintenance
IAIN/0135	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	13/09/2018	29/10/2018	SmPC	
IA/0133/G	This was an application for a group of variations. B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer B.III.1.a.2 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	31/05/2018	n/a		
N/0132	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/05/2018	29/10/2018	Labelling and PL	
IA/0131	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	06/03/2018	n/a		
IB/0130	C.I.7.b - Deletion of - a strength	13/11/2017	29/10/2018	SmPC, Annex II, Labelling	

				and PL	
IA/0129	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	18/08/2017	n/a		
IA/0128	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	18/07/2017	n/a		
IA/0127/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.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	08/11/2016	n/a		
IA/0126	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	24/10/2016	n/a		
IA/0125/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	14/09/2016	n/a		

	and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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) 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.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.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				
IB/0124/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.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.e - Change in test procedure for AS or	06/09/2016	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition)				
IB/0123	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/01/2016	09/01/2017	SmPC and PL	
PSUSA/2147/ 201505	Periodic Safety Update EU Single assessment - nevirapine	14/01/2016	n/a		PRAC Recommendation - maintenance
IB/0122	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/11/2015	n/a		
IB/0120/G	This was an application for a group of variations. B.III.1.a.3 - Submission of a new/updated or deletion of Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - New certificate from a new manufacturer (replacement or addition) B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of	17/10/2014	n/a		

	specification limits B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method 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.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				

IA/0119	B.II.c.3.z - Change in source of an excipient or reagent with TSE risk - Other variation	04/08/2014	n/a		
II/0112	Update of sections 4.4 and 5.2 of the SmPC regarding remnants of prolonged release tablets in the stool. The Package Leaflet is updated accordingly. The MAH has taken the opportunity of this change to make minor editorial amendments to the SmPC and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	03/07/2015	SmPC and PL	The MAH has provided data gathered from clinical trials and from post-marketing experience on the occurrence of remnants or prolonged release (XR) tablets of Viramune in faeces. The analysis of this data does not point to a decreased efficacy of Viramune XR in patients with tablet remnants in their stool.
IB/0118	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	16/07/2014	03/07/2015	SmPC and PL	To update SmPC section 4.4 and the Package Leaflet with new information on the risk of HIV transmission as requested by the CHMP for all HIV medicines. Based on new data available the recommendation for post-exposure prophylaxis should be updated. Furthermore, the MAH takes the opportunity to introduce minor linguistic changes to the French and Latvian annexes.
IG/0432	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	16/04/2014	n/a		
IA/0115	A.7 - Administrative change - Deletion of manufacturing sites	21/01/2014	n/a		
II/0114	Update of information on adverse reactions in section	21/11/2013	10/04/2014	SmPC and PL	The MAH had recalculated the frequencies of adverse

	4.8 of SmPC for the prolonged release formulations of nevirapine, based on results from study extension up to 114 weeks. In addition, minor linguistic changes are implemented in the SmPC and the PI is updated to the QRD template version 9.0. Minor linguistic changes are made also in the German PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				reactions following completion of the extension phases up to 114 weeks of two studies (1100.1486 and 1100.1470). For the prolonged release formulation, the frequency group of adverse reactions of diarrhoea and vomiting has been updated from 'uncommon' to 'common'. In addition, information regarding rash, Stevens Johnson Syndrome and hepatic events has also been updated in the SmPC of prolonged release formulation, not impacting the frequency groups of those reactions.
II/0113/G	This was an application for a group of variations. Update of SmPC section 4.5 with information that Viramune can be co-administered with emtricitabine and abacavir without dose adjustment and update of SmPC section 4.5. with information that coadministration with elvitegravir in combination with cobicistat is not recommended. The PL is being updated in accordance. In addition, the SmPC section 4.4 list of medicines not recommended for coadministration is being updated in line with information in section 4.5 and editorial changes are being implemented in section 4.5. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/11/2013	10/04/2014	SmPC and PL	Since both emtricitabine and abacavir are not inhibitors of human CYP 450 enzymes, they can be co-administered with nevirapine without dose adjustment of any of the products. The co-administration of elvitegravir/cobicistat with nevirapine should not be recommended as cobicistat can affect concentration of nevirapine. This combination is already not recommended in the product information of elvitegravir/cobicistat/emtricitabine/tenofovir fixed dose combination product.

IA/0111/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	19/08/2013	n/a		
II/0108	Update of information on interactions with other NNRTIs (delavirdine, eltravirine, rilpivirine) and antivirals for chronic hepatitis B and C (adefovir, boceprevir, entecavir, interferons, ribavirin, telparevir, telbivudine) in SmPC section 4.5 and shortening of SmPC section 5.1, as requested by the CHMP. Information regarding nelfinavir has been deleted from SmPC. Redundant information has been deleted from PL section 1. In addition, minor editorial changes are implemented in the SmPC, Annex II, Labelling and Package Leaflet. Furthermore, Annex II is brought in line with the latest QRD template version and improvements are made in translations of Finnish and French product information. 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	25/07/2013	10/04/2014	SmPC, Annex II, Labelling and PL	The MAH introduced changes in the PI as requested by the CHMP following assessment of procedure R/0107. In particular, information on interactions has been updated in SmPC section 4.2 and SmPC section 5.1. has been shortened, deleting information that was deemed not relevant for the prescriber. Information regarding nelfinavir has been deleted from SmPC as this product is no longer authorised.

IB/0110	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)	25/06/2013	10/04/2014	SmPC	
IB/0109	To include information on a class labelling for all antiretrovirals to revise section 4.4 and section 4.8 of the SmPC to include information regarding Autoimmune Disorders under Immune Reactivation Syndrome. The changes have also been reflected 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	19/04/2013	10/04/2014	SmPC and PL	
R/0106	Renewal of the marketing authorisation.	18/10/2012	20/12/2012	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of Viramune continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Viramune continues to be favourable. The CHMP concluded that the MAH should submit the PSUR on a 3-yearly basis. The CHMP is of the opinion that the renewal be granted with unlimited validity.
IG/0211	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/09/2012	n/a		
IB/0105/G	This was an application for a group of variations.	12/06/2012	n/a		

	B.I.d.1.a.1 - Stability of AS - Change in the re-test period/storage period - Reduction B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
WS/0255/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. Update of the Description of Pharmacovigilance System (DDPS). C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation C.I.9.f - Changes to an existing pharmacovigilance system as described in the DDPS - Deletion of topics covered by written procedure(s) describing pharmacovigilance activities C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure 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	24/05/2012	24/05/2012		Changes to an existing pharmacovigilance system as described in the DDPS. The MAH update the Detailed Description of the Pharmacovigilance System (DDPS) for Aptivus, MicardisPlus, Mirapexin, Onduarp, Pradaxa, Sifrol, Trajenta, Twynsta and Viramune.

II/0100/G	This was an application for a group of variations. Changes to the manufacturing process and in-process controls for the active substances nevirapine anhydrous and nevirapine hemihydrate 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.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - 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 B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised B.I.b.2.a - Change in test procedure for AS or	16/02/2012	16/02/2012		

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0103	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	19/01/2012	23/08/2012	SmPC, Labelling and PL	
IAIN/0101/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.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	16/11/2011	n/a		
IA/0102/G	This was an application for a group of variations. B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	15/11/2011	n/a		
X/0095	Annex I_2.(d) Change or addition of a new pharmaceutical form Annex I_2.(c) Change or addition of a new strength/potency	21/07/2011	16/09/2011	SmPC, Annex II, Labelling and PL	The prolonged-release formulation (XR) met the PK target levels, demonstrated non-inferior efficacy in comparison to nevirapine immediate release (IR) and exhibited similar safety. Therefore, the advantage of the once daily convenience of the prolonged-release formulation could be beneficial for patients. For further information please refer to the variation

					assessment report Viramune-H-C-000183-X-0095.
IB/0099/G	This was an application for a group of variations. B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation A.7 - Administrative change - Deletion of manufacturing sites 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	15/08/2011	n/a		
II/0098	Update of section 4.8 of the SmPC and section 4 of the PL in order to include two new side effects ("Blood pressure increased" and "Blood phosphorus decreased") and updated frequencies/ frequency categories. Furthermore, within the scope of Viramune extension variation EMEA/H/C/183/X/95, QRD comments were received on the Viramune XR labelling. Some of these comments are also applicable to the labelling of Viramune immediate release dosage forms. These changes are introduced with this variation. The MAH also takes the opportunity to introduce minor linguistic and administrative changes to the English language Annexes and to the Annexes for Finland, France, Greece and Romania. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-	19/05/2011	23/06/2011	SmPC and PL	The MAH updates the SmPC regarding the adverse events of "Blood pressure increased" and "Blood phosphorus decreased". The update is based on post-hoc analysis of data from a Phase 4 comparative trial of Viramune (clinical trial 1100.1470; ARTEN). The MAH noted a small increase in the patient population means for systolic and diastolic blood pressure in patients treated with nevirapine. In the same study a decrease in patient population means of blood phosphorus was also noted. These signals triggered a retrospective analysis of relevant Viramune clinical trials, complemented by an analysis of post-marketing case reports (both healthcare professional confirmed cases and consumer reports) performed in the Global Pharmacovigilance Database. Also the frequencies of the other known Viramune side effects have been recalculated, which has led to changes in frequencies and/or frequency categories.

	clinical, clinical or pharmacovigilance data				The Package leaflet has been updated accordingly.
IB/0096/G	This was an application for a group of variations. B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition)	19/01/2011	n/a		
IA/0097/G	This was an application for a group of variations. B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification	15/12/2010	n/a		

	parameter to the specification with its corresponding test method B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure				
II/0094	Update of the sections 4.4 and 4.6 of the SmPC, and section 2 of the Package Leaflet in order to give a better characterisation of the patient groups that are at greater risk of developing hepatotoxicity following evaluation of an analysis made by an expert panel. Furthermore the Product Information has been updated according to the new QRD template. The MAH took the opportunity to introduce minor linguistic changes to the annexes in Austria/Germany, Denmark, Finland, Latvia, Norway, Portugal, Slovenia and Spain. 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	22/07/2010	26/08/2010	SmPC, Labelling and PL	The MAH update the SmPC regarding the CD4+ threshold. The update is based on the new analysis provided by an external Expert Panel via FUM, and which the CHMP considered relevant in order to give a better characterisation of the patient groups that are at greater risk of developing hypersensitivity reactions, specifically those concerning the liver. Therefore the section 4.4 of the SmPC has been updated to highlight that female gender and higher CD4 counts (>250/mm3 in adult females and >400/mm3 in adult males) at the initiation of Viramune therapy are associated with a greater risk of hepatic adverse events if the patient has detectable plasma HIV-1 RNA - i.e. a concentration ≥ 50 copies/ml - at the initiation of Viramune. Furthermore in the section 4.8, the frequency of drug rash with eosinophilia and systemic symptoms and anaphylactic reaction has changed from not known to uncommon under the SOC immune system disorder. The Package leaflet has been updated accordingly.
IA/0093/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of	26/04/2010	n/a		

	the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
IA/0092	A.7 - Administrative change - Deletion of manufacturing sites	24/03/2010	n/a		
IB/0091	IB_33_Minor change in the manufacture of the finished product	07/01/2010	n/a		
IA/0090	IA_32_a_Change in batch size of the finished product - up to 10-fold	04/12/2009	n/a		
II/0083	Update of section 4.4 "Special warnings and precautions for use" of the Summary of Products Characteristics (SPC) with regards to the effect of nevirapine on the plasma lipid profile based on clinical studies and published literature review. Update of Summary of Product Characteristics	23/04/2009	29/05/2009	SmPC	In clinical studies, nevirapine has been associated with an increase in HDL- cholesterol and an overall improvement in the total to HDL-cholesterol ratio. The exact mechanism remains unclear but there is some evidence that this effect could be independent from the antiretroviral activity as shown in controlled clinical studies NILE. However, in the absence of specific studies with nevirapine on modifying the cardiovascular risk in HIV infected patients, the clinical impact of these findings is not known. The selection of antiretroviral drugs must be guided primarily by their antiviral efficacy.
II/0082	Update of section 5.1 "Pharmacodynamic properties" of the Summary of Products Characteristics (SPC) in line with the recommendations of Annex B of the revision CHMP Guideline on the clinical development of medicinal products for the treatment of HIV	23/04/2009	29/05/2009	SmPC and PL	Section 5.1 was updated based on published data and study report when available. The mechanism of action section was shortened in order to clearly describe the non-competitive mechanism of action of nevirapine (NVP) to inhibit the HIV-1 reverse transcriptase (RT). The antiviral

	infection (CPMP/EWP/633/02, Rev. 2) as requested by the CHMP during the marketing authorisation renewal procedure (EMEA/H/C/183/R/74). The Package Leaflet (PL) has been updated to reflect the outcome of a readability user testing. Update of Summary of Product Characteristics and Package Leaflet				activity in vitro section was also shortened in order to focus on the antiviral activity of NVP against several HIV isolates from HIV infected patients instead on the cell line used in protocols. The resistance section describing phenotypic and genotypic changes in HIV-1 isolates from patients receiving either NVP or NVP in combination with other RT inhibitors was rewritten to focus on mutations that emerged in vitro or in vivo. In the cross resistance section a generic statement, not mentioning individual mutations or mutation scores regarding cross-resistance was introduced. For the clinical aspect section data on both naive and experienced patients were presented. In order to increase the clinical utility of the information to the prescriber, the proposed information on efficacy were completed with safety information. Data on perinatal transmission were updated to reinforce the current knowledge on the NVP resistance development after single dose. In women previously treated with single-dose NVP alone for prevention of mother to child transmission of HIV-1, the efficacy of NVP as part of a combination therapy which the women receive for their own health may be reduced. Implications on infant virologic failure has been also included in the SPC wording in order to complete the information: in infants previously treated with single-dose NVP alone for prevention of mother to child transmission of HIV-1, the efficacy of NVP as part of a combination therapy which they receive for their own health may be reduced.
II/0088	Update of sections 4.2 and 4.4 of the SPC following the CHMP conclusion on PSUR 15 to add a precautionary statement to prevent exacerbation of the rash, to warn on the risk of underexposure and	19/03/2009	07/05/2009	SmPC	In patients from 16 years of age the recommended dose of NVP is one 200 mg tablet daily for the first 14 days. This lead-in period should be used because it has been found to lessen the frequency of rash. There are currently few

	resistance development and to encourage treating physicians to consider alternative treatment in case where there is a prolonged use of the lead-in treatment dosing regimen. Update of Summary of Product Characteristics				clinical data to link the development of viral resistance with lower plasma levels of NVP with the lead-in dose nevertheless the risk cannot be excluded. As a consequence a precautionary statement is added to the SPC to encourage alternative treatment in these cases of prolonged lead-in treatment dosing regimen not only to prevent an exacerbation of the rash but also to prevent the development of resistances due to underexposure. Patients experiencing rash during the 14 day lead-in period of 200 mg/day should not have their NVP dose increased until the rash has resolved. The 200 mg once daily dosing regimen should not be continued beyond 28 days at which point in time an alternative treatment should be sought due to the possible risk of underexposure and resistance.
IB/0089	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	02/03/2009	02/03/2009	SmPC, Labelling and PL	
II/0075	Update of section 4.5 of the SPC with interactions between nevirapine and other recently approved HIV products. Section 4.5 is also updated in line with the draft revision guideline Guideline on the clinical development of medicinal products for the treatment of HIV infection (CPMP/EWP/633/02, Rev. 2). The PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/12/2008	27/01/2009	SmPC and PL	Based on a literature review existing and new information of section 4.5 has been tabled as recommended in Guideline on the clinical development of medicinal products for the treatment of HIV infection (CPMP/EWP/633/02, Rev. 2). As studies for newer classes of antiretrovirals and recently approved antiretroviral medicinal products are not available in all cases, SPCs of the recently approved antiretroviral products were used as reference document. For products where the pathway of metabolism is similar to nevirapine, the information was added that their plasma concentration may decrease when co-administered with nevirapine and that careful monitoring of their effectiveness is recommended. In the first column of the interaction section the dosage of the respective co-administered

					medicinal products has been specified. The interaction data is presented in the second column as geometric mean value with 90% confidence interval (90% CI) whenever these data were available. This facilitates the use of the interaction section for the treating physician. Recommendations to the treating physician concerning the co-administration are given in the third column. Where applicable, the recommendation concerning co-administration has been worded uniformly as: "product concerned" and Viramune can be co-administered without dose adjustments. Overall, the description of the interaction follows a single pattern for all drugs which increases the legibility.
II/0084	The MAH applied to introduce several changes related to the active substance (nevirapine) which include: minor changes to the manufacturing process, a change in the specification of the active substance, and change in the test procedures for the active substance. Change(s) to the test method(s) and/or specifications for the active substance	23/10/2008	27/10/2008		
IB/0087	IB_33_Minor change in the manufacture of the finished product	26/09/2008	n/a		
IB/0086	IB_32_c_Change in batch size of the finished product - other situations	26/09/2008	n/a		
IB/0085	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	26/09/2008	n/a		

II/0076	To update section 4.6 of the SPC based on a review of available data in pregnant women receiving antiretroviral therapy that includes nevirapine. In addition, minor linguistic changes have been made to the product information for the Netherlands. Update of Summary of Product Characteristics	24/07/2008	02/09/2008	SmPC	Following a review of available data on the use of Viramune in pregnancy, some data suggests that nevirapine exposure in the first trimester is not associated with a rate of birth defects above the expected one. This is consistent with preclinical data, which did not suggest a teratogenic effect. It thus seems reasonable for the SPC to state that there is no evidence of teratogenic effects with nevirapine. The already existing warning in section 4.4 regarding the higher frequency of liver toxicity in women with CD4 cell counts above 250 cells/mm3 was linked to this section to reinforce this potentially problematic issue in the target population.
R/0074	Renewal of the marketing authorisation.	15/11/2007	10/01/2008	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, the safety and the efficacy of this Viramune continues to be adequately and sufficiently demonstrated and therefore considers that the benefit/risk profile of Viramune continues to be favourable. However, the low genetic barrier of nevirapine, associated with a significant number of "drug ineffective" reports, are a matter of concern in particular in view of the evolving therapeutic management of HIV infected patients. The emergence of resistance to nevirapine and associated virological failure should be carefully controlled in order to permanently ensure an optimal therapeutic management of HIV infected patients. In addition, serious adverse events associated with the use of nevirapine, in particular hepatic and cutaneous reactions, should continue to be monitored. Based on these issues, the CHMP concluded that the MAH should continue to submit yearly PSURs. Furthermore, the CHMP is of the opinion that one additional five-year renewal on the basis of pharmacovigilance grounds is required.

IB/0073	IB_30_b_Change in supplier of packaging components - replacement/addition	16/07/2007	n/a		
II/0068	Update of section 4.5 of the SPC with interaction between nevirapine and tripanavir co-administered with ritonavir based on results of a pharmacokinetic study. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/05/2007	29/06/2007	SmPC and PL	Results from pharmacokinetic studies appeared to suggest that there is no significant interaction between nevirapine and tipranavir co-administered with ritonavir. However, these current data are limited and do not allow to draw a definitive conclusion on the interaction between nevirapine and tipranavir (co-administered with low dose ritonavir). Caution should be used when combining these drugs. The product information was updated to reflect this information.
II/0066	Update of section 5.1 of the SPC with in vitro HIV susceptibility to nevirapine based on results of three nonclinical studies conducted by the Marketing Authorisation Holder. Update of Summary of Product Characteristics	22/03/2007	29/06/2007	SmPC	The in vitro HIV susceptibility to nevirapine against non-clade (genetic subtypes of HIV groups) B virus was assessed in non-clinical studies. The SPC section 5.1 was updated to reflect that nevirapine exhibited antiviral activity in vitro against group M HIV-1 isolates from different clades. However, no antiviral activity in vitro was observed against isolates from group O HIV-1 and HIV-2. When studied in combination with other drugs, nevirapine exhibited a strong antagonistic (opposite) anti-HIV-1 activity with efavirenz and was additive to antagonistic with ritonavir or enfuvirtide. Nevirapine exhibited additive to synergistic (combined effect was greater than the sum of the individual effects) anti-HIV-1 activity in combination with amprenavir, atazanavir, indinavir, lopinavir, nelfinavir, saquinavir and tipranavir, abacavir, didanosine, emtricitabine, lamivudine, stavudine, tenofovir and zidovudine. The anti-HIV-1 activity of nevirapine was antagonised by adefovir and ribavirin. The interactions section of the SPC was also updated to

					reflect that nevirapine in combination with efavirenz showed antagonistic anti-HIV-1 activity in vitro.
II/0065	Update of section 4.5 of the SPC with interaction between nevirapine and depomedroxyprogesterone acetate (DMPA) based on results of a pharmacokinetic interaction study between DMPA and selected protease inhibitors and non-nucleosides reverse transcriptase inhibitors therapies among HIV-infected women. Update of Summary of Product Characteristics	22/03/2007	29/06/2007	SmPC	An investigator initiated study on non-oral contraceptives provided new information about the interaction between nevirapine (NVP) and depo-medroxyprogesterone acetate (DMPA). This study showed that DMPA pharmacokinetic parameters (AUC, Cmax, Cmin, and half-life) did not changed in the presence of nevirapine. Nevirapine co-administration did also not alter the ovulation suppression effects of DMPA. Nevirapine pharmacokinetic parameters AUC and Cmax increased by 20% in the presence of DMPA; while statistically significant, this change is considered not clinically relevant.
II/0067	Update of section 4.4 of the SPC to reflect the occurrence of rhabdomyolysis in patients experiencing skin and/or liver reactions associated with nevirapine therapy, as requested by the CHMP in November 2006. Update of Summary of Product Characteristics	26/04/2007	30/05/2007	SmPC	A cumulative review performed up to July 2006 identified 14 rhabdomyolysis related, health professionals confirmed case reports associated with nevirapine treatment. Of these 12 were reported as serious, 1 non-serious and another with no information. In all, except one (with limited information) rhabdomyolysis was accompanied by either hepatitis or severe cutaneous skin reactions. Acute renal failure in five cases seems to present a typical complication of rhabdomyolysis. Based on these findings, the warning section in the SPC for Viramune under subheadings "Cutaneous reactions" and "Hepatic reactions" is amended to reflect this association.
IA/0072	IA_05_Change in the name and/or address of a manufacturer of the finished product	15/05/2007	n/a	PL	
II/0064	Update of section 5.2 of the SPC to reflect the lower nevirapine clearance observed in women in a	22/03/2007	02/05/2007	SmPC	The published pharmacokinetic substudy of the double non-nucleoside (2NN) study, analysed the pharmacokinetics of

	pharmacokinetic sub study of the double non-nucleoside (2NN) study. Update of Summary of Product Characteristics				nevirapine and efavirenz from 1077 treatment naïve, HIV infected patients from several study sites in Europe, South Africa, Canada, United States, Argentina, Brazil, Australia and Thailand with HIV RNA > 5000 copies/ml at baseline. All patients received also lamivudine and stavudine. Results showed that gender, hepatitis B and geographical region were involved in the variability of the nevirapine pharmacokinetic parameters. Clearance of nevirapine was lower in females (13,8%) than in male patients. Since neither body weight nor body mass index were shown to have an influence on the clearance of nevirapine the effect of gender cannot solely be explained by body size. Section 5.2 of the SPC reflects the results of this study.
II/0063	Update of section 5.2 of the SPC with information obtained in a pharmacokinetic study assessing nevirapine levels in HIV-1 infected patients with impaired hepatic function. Consequently sections 4.3 and 4.4 were amended, in accordance. Update of Summary of Product Characteristics	22/02/2007	02/05/2007	SmPC	A pharmacokinetic study comparing forty six (46) HIV infected patients with different degrees of hepatic impairment and on nevirapine (200 mg twice daily) as part of a stable antiretroviral therapy showed that approximately 15 % of these patients had nevirapine trough concentrations 2-fold above (9,000 ng/ml) the usual mean trough. These patients should therefore, be under closely monitoring for any evidence of nevirapine induced toxicity. In addition, historical data from a single dose pharmacokinetic study in HIV negative patients with mild to moderate hepatic impairment suggested that patients with worsening hepatic function and ascites may be at risk of accumulating nevirapine. This information has been included in section 5.2 of the SPC, sections 4.3 and 4.4 have been consequently updated.
IB/0069	IB_42_a_02_Change in shelf-life of finished product - after first opening	16/04/2007	n/a	SmPC, Labelling and	

				PL	
IA/0071	IA_11_a_Change in batch size of active substance or intermediate - up to 10-fold	11/04/2007	n/a		
IA/0070	IA_09_Deletion of manufacturing site	30/03/2007	n/a	Annex II and PL	
II/0062	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	15/01/2007	SmPC and PL	Cases of osteonecrosis (death of the bone tissue resulting from an insufficient blood supply) have been reported in HIV-infected patients since the end of the 80's. Although the cause of this disease could be due to multi factors (including the use of corticosteroids, alcohol consumption, severe immunosuppression, higher body mass index) it has occurred specially in patients with HIV advanced disease and/or in patients with long term use of combination antiretroviral therapy (CART). Further to the review of all available data the CHMP agreed that this information should now be included in the SPC and PL of all antiretroviral medicinal products. Patients should be warned to seek medical advice in case they experience joint stiffness, aches and pain especially of the hip, knee and shoulder or if they experienced any difficulty in movement.
II/0061	Update of section 5.2 of the SPC to reflect paediatric pharmacokinetic data obtained during the review of several clinical studies. Update of Summary of Product Characteristics	21/09/2006	27/10/2006	SmPC	Data from the 48 weeks data from a study performed in 123 antiretroviral naïve paediatric patients (3 months to 16 years) evaluating the pharmacokinetic, efficacy and safety parameters of nevirapine 150mg/m2 (body surface area) and nevirapine 4/7mg/Kg (body weight) was compared with historical data from five Paediatric AIDS Clinical Trials Group (PACTG) studies and a combined analysis of nevirapine pharmacokinetic in paediatric patients was presented. It was concluded that either dosing method for

					nevirapine oral suspension (body surface area or body weight) the plasma concentrations observed were within the range of the observed for adults. Section 5.2 of the SPC reflects the results of these studies.
II/0060	Update of section 4.2 and section 4.4 of the SPC and section 1, 2 and section 3 of the PL to include body surface area as an additional dosage regimen calculation for paediatric patients, as requested by the CHMP further to the assessment of a study that evaluated nevirapine dose regimen calculation by body surface area versus body weight in antiretroviral naïve paediatric patients. Minor linguistic comments were introduced in the PL for some of the EU languages, as relevant. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	27/10/2006	SmPC and PL	The 48 weeks data from a study performed in 123 antiretroviral naïve paediatric patients (3 months to 16 years) evaluating the pharmacokinetic, efficacy and safety parameters of nevirapine 150mg/m2 (body surface area) and nevirapine 4/7mg/Kg (body weight) when administered in combination with zidovudine and lamivudine were sufficient to allow the recommendation of the dose calculation for nevirapine to be based also by body surface area. The posology and the method of administration section of the SPC (section 4.2) for the tablets and the oral suspension is amended to clearly indicate the calculation of nevirapine dosage by body surface area or by body weight for the paediatric patients. Section 4.4 was amended to reflect this changes as well as the relevant section in the PL.
II/0058	Update of section 5.3 of the SPC to reflect the results of the 14 day gene expression toxicity study in the mouse on phenobarbital and nevirapine, as agreed by the CHMP. Minor linguistic amendments were introduced in some EU languages versions of the product information, as relevant. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	01/09/2006	SmPC and PL	The results of a 14 days gene expression toxicity study in mice were consistent with previous results obtained in other studies to conclude on the liver enzyme induction ability of nevirapine in mice. The SPC for Viramune was amended to reflect that the hepatic tumours induced by nevirapine in rat and mice are not due to a genotoxic mechanism of action but rather to nevirapine's ability to increase gene expression of liver enzymes. Section 5.3 of the SPC was updated in accordance.

II/0059	Change(s) to the manufacturing process for the finished product	27/07/2006	14/08/2006		
II/0054	Update of Summary of Product Characteristics. Update of section 4.5 of the SPC to reflect the results of a pharmacokinetic study evaluating the interaction between nevirapine and methadone in HIV-1 infected, opioid-dependent adults on stable methadone maintenance therapy. Update of Summary of Product Characteristics	27/04/2006	31/05/2006	SmPC	The provided study confirmed the fact that nevirapine decreases the plasma concentrations of methadone when given in co-administration. Additional pharmacokinetic information on this interaction was shown in this study: plasma concentration of methadone are reduced by 65 % (mean AUC) and by 50 % (mean Cmax) with 95 % prediction interval. In addition, it was determined that nevirapine causes a 3-fold increase in the clearance of oral methadone. Based on these results, the interaction section (4.5) of the SPC has been amended in accordance.
II/0053	Update of Summary of Product Characteristics and Package Leaflet. Update of section 4.5 of the SPC and section 2 of the PL to reflect pharmacokinetics results following a statistical re-analysis of the existing drug-drug interaction studies. In addition, section 4.6 is updated to include a cross reference to section 4.4 as requested by the CHMP. Update of Summary of Product Characteristics and Package Leaflet	27/04/2006	31/05/2006	SmPC and PL	Results of twelve studies that investigated nevirapine's pharmacokinetic interactions in co-administration with didanosine, efavirenz, indinavir, nelfinavir, ritonavir, saquinavir, stavudine, zalcitabine, zidovudine, clarithromycin, ethinyl estradiol, norethindrone, fluconazole, ketoconazole, rifabutin and rifampin were re-analysed by the MAH using a different statistical test. Although no new data has been provided the interaction section of the SPC (section 4.5) has been updated to reflect these revised results. Section 2 of the PL was updated in accordance. In addition, the pregnancy and lactation section of the SPC (section 4.6) is amended to include a cross reference to the warning section (4.4) as requested by the CHMP further to the assessment of previously submitted paediatric data.
II/0055	Update of Summary of Product Characteristics (SPC) and Package Leaflet (PL) Update of section 4.5 of the SPC to include published information on	13/10/2005	25/11/2005	SmPC and PL	Based on pharmacokinetic published data, a statistically significant decrease in lopinavir AUC by 27 % was observed in adult patients receiving nevirapine 200 mg and

	pharmacokinetic data on the combination of nevirapine with lopinavir/ritonavir in adults and paediatric patients. Minor linguistic comments were introduced in the SPC and/or PL for some of the EU languages, as relevant. The local representatives were updated in the PL. Update of Summary of Product Characteristics and Package Leaflet				lopinavir/ritonavir 400/100 mg twice daily when compared with historical data. An increase of the lopinavir/ritonavir dose to 533/133 mg twice daily is therefore recommended in combination with nevirapine. The co-administration of nevirapine with lopinavir/ritonavir 300/75 mg/m2 decreased the lopinavir AUC by 22% (AUC ratio 0.78; 0.56-1.09) and Cmin by 55% % (Cmin ratio 0.45; 0.25-0.82), in paediatric patients. Therefore, increase of the lopinavir/ritonavir dose to 300/75 mg/m2 should be considered in combination with nevirapine. Section 4.5 of the SPC has been updated to reflect this data.
IA/0057	IA_05_Change in the name and/or address of a manufacturer of the finished product	18/08/2005	n/a		
IA/0056	IA_05_Change in the name and/or address of a manufacturer of the finished product	18/08/2005	n/a		
IB/0052	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	12/07/2005	n/a	SmPC	
IB/0051	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	12/07/2005	n/a	SmPC	
II/0047	Change(s) to the manufacturing process for the active substance	26/05/2005	10/06/2005		
IB/0050	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	19/05/2005	19/05/2005	SmPC, Labelling and PL	

II/0049	To update section 4.1 and 4.4 of the Summary of Product Characteristics and section 2 "Before you take Viramune" of the Package Leaflet, to strengthen the warning regarding the use of Viramune tablets and oral solution in specific risk populations for hepatic adverse reactions, as agreed by the CHMP in January 2005. Furthermore, information on the identification and corresponding actions for hepatic, skin and hypersensitivity reactions are strengthened in section 4.4. Finally, the recommendations on rash-associated hepatic events under cutaneous and hepatic reactions subheadings are revised to read now symptomatic hepatic events with often rash-associated. In addition, the MAH has taken this opportunity to update the address of the local representative in Iceland in the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	16/03/2005	20/04/2005	SmPC and PL	
II/0048	Quality changes	16/03/2005	22/03/2005		
II/0045	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. 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 inflamatory 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.
IA/0046	IA_23_b_Change in source of excip./reagent to veg./synthetic material - other cases	17/11/2004	n/a		
II/0043	To update section 4.4 to implement a general statement discouraging the use of nevirapine in Post-Exposure-Prophylaxis (PEP), as requested by the CHMP following the assessment of PSUR 9 & 10 and MAH responses. Update of Summary of Product Characteristics	16/09/2004	15/10/2004	SmPC	The use of nevirapine in PEP is an unlabelled use, however section 4.4 of the SPC describes the risks associated with a nevirapine based regimen for PEP. Based on the assessment of the MAH responses to PSUR 9 and 10 the CHMP requested the MAH to strengthen the warning regarding the use of nevirapine in PEP by implement a general statement strongly discouraging the use in the

					corresponding paragraph of section 4.4. A contra-indication was not requested, as it would no be in consistence with the national recommendations of some Member States. Section 4.4 was update accordingly under the new sub-heading "Post-Exposure-Prophylaxis".
IA/0044	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 IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	25/08/2004	n/a	Annex II and PL	
IB/0042	IB_17_a_Change in re-test period of the active substance	30/07/2004	n/a		
II/0039	To move adverse events from section 4.4 to 4.8 of the SPC and to add information on frequency of adverse events in children. Update of corresponding sections of the PL, in accordance with the CHMP request further to the assessment of PSUR 9 and 10. In addition, section 6 of the PL was completed. Update of Summary of Product Characteristics and Package Leaflet	03/06/2004	13/07/2004	SmPC and PL	Following the assessment of PSUR 9 and 10 the CHMP requested the MAH to revise section 4.8 of the SPC to reflect that anaemia occurs more frequently in the paediatric population and to move the paragraph describing adverse events reported when nevirapine is used in combination with other anti-retroviral agents from section 4.4 to section 4.8.. The corresponding sections 2 and 4 of the PL were updated in accordance and in addition, the list of local representatives in section 6 was completed with the contacts of the new European Members States.
II/0040	Quality changes	03/06/2004	08/06/2004		A new synthesis site for nevirapine anhydrous: Boehringer Ingelheim Pharma GmbH & Co KG - Binger Strasse 173 - 55216 Ingelheim am Rhein - Germany was added to the Marketing Authorisation. As a consequence, minor adaptations to the synthesis process and changes to the specifications of the starting materials, of the intermediates

					and of the active substance have been made. The specifications of the starting materials and of the intermediates for nevirapine hemihydrate have been updated accordingly.
IA/0041	IA_43_a_01_ Add./replacement/del. of measuring or administration device - addition or replacement	28/04/2004	n/a		
II/0038	Update of section 4.2 (Posology and method of administration), 4.4 (Special warnings and special precautions of use), 4.8 (Undesirable effects), 4.9 (Overdose) and 5.2 (Pharmacokinetic 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 and to include the conclusions of a new integrated analysis of hepatic reactions as well as, in section 4.4, information about the risk factors for hepatic adverse events, namely female gender and higher CD4 cell count, further to the review of the 10th PSUR covering the period from 09 July 2002 to 08 July 2003. Furthermore, the MAH has taken this opportunity to updated section 4.8 of the SPC according to the latest EMEA / QRD templates. In addition, changes to the Package Leaflet (PL), which are consistent with the proposed changes to the SPC have also been proposed, and the PL wording on lipodystrophy, as adopted by the CPMP on 24 March 2003, has been incorporated. Update of Summary of Product Characteristics and	20/11/2003	04/02/2004	SmPC and PL	

	Package Leaflet				
II/0033	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	09/07/2003	SmPC and PL	
II/0035	Change(s) to the test method(s) and/or specifications for the finished product	26/06/2003	01/07/2003		
I/0037	28_Change in test procedure of immediate packaging	12/06/2003	25/06/2003		
I/0036	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	12/06/2003	25/06/2003		
I/0034	01_Change in the name of a manufacturer of the medicinal product	14/04/2003	19/05/2003	Annex II and PL	
R/0032	Renewal of the marketing authorisation.	21/11/2002	17/02/2003	SmPC, Annex II, Labelling and PL	
II/0031	Update of Summary of Product Characteristics	19/09/2002	05/12/2002	SmPC	
II/0030	Update of Summary of Product Characteristics and Package Leaflet	19/09/2002	05/12/2002	SmPC and PL	
II/0029	Change(s) to the test method(s) and/or specifications for the active substance	19/09/2002	07/10/2002		
S/0028	Annual re-assessment.	25/04/2002	11/07/2002	Annex II	
II/0025	Update of or change(s) to the pharmaceutical documentation	25/04/2002	30/04/2002		

II/0027	Quality changes	18/10/2001	17/12/2001		
II/0024	Update of Summary of Product Characteristics and Package Leaflet	26/07/2001	30/11/2001	SmPC and PL	
II/0023	Update of Summary of Product Characteristics and Package Leaflet	26/07/2001	30/11/2001	SmPC and PL	
II/0022	Update of Summary of Product Characteristics and Package Leaflet	26/07/2001	30/11/2001	SmPC and PL	
S/0020	Annual re-assessment.	26/04/2001	13/08/2001	Annex II	
I/0021	04_Replacement of an excipient with a comparable excipient	30/03/2001	04/05/2001		
II/0018	Update of Summary of Product Characteristics	27/07/2000	18/11/2000	SmPC	
II/0017	Update of Summary of Product Characteristics	27/07/2000	18/11/2000	SmPC and PL	
II/0016	Update of Summary of Product Characteristics and Package Leaflet	27/07/2000	18/11/2000	SmPC and PL	
II/0015	Update of Summary of Product Characteristics and Package Leaflet	29/06/2000	30/10/2000	SmPC and PL	
II/0012	Update of Summary of Product Characteristics and Package Leaflet	18/11/1999	16/03/2000	SmPC and PL	
II/0011	Update of Summary of Product Characteristics and Package Leaflet	18/11/1999	16/03/2000	SmPC and PL	

I/0013	10a_Addition or replacement of measuring device for oral liquid dosage forms and other dosage forms	15/10/1999	28/12/1999	SmPC and PL	
I/0010	13_Batch size of active substance	24/06/1999	16/07/1999		
II/0007	Update of Summary of Product Characteristics and Package Leaflet	25/03/1999	08/07/1999	SmPC and PL	
II/0003	Update of Summary of Product Characteristics and Package Leaflet	21/10/1998	26/01/1999	SmPC and PL	
I/0006	25_Change in test procedures of the medicinal product	11/11/1998	n/a		
I/0005	25_Change in test procedures of the medicinal product	11/11/1998	n/a		
I/0004	15a_Change in IPCs applied during the manufacture of the product	29/09/1998	n/a		
I/0001	01_Change in the name of a manufacturer of the medicinal product	02/04/1998	15/06/1998	Annex II, Labelling and PL	