STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after1 March 2004 please refer to module 8B**.**

- On 25 February 1998, the Marketing Authorisation Holder (MAH) applied for a Type I variation in accordance with Commission Regulation (EC) 542/95. The MAH applied for a change in the content of the manufacturing authorisation. On 2 April 1998 the EMEA issued a notification.
- On 17 July 1998 the MAH submitted a Type II variation in accordance with the Commission Regulation (EC) No 542/95 as amended, related to the update of the SPC and as a consequence the Package Leaflet following the review of the first periodic safety update report (PSUR). The variation was adopted by the CPMP on 21 October 1998, and the respective Commission Decision was issued on 26 January 1999.
- On 1 September 1998, the MAH applied, in accordance to the Regulation, for a Type I variation related to the change in in-process controls during the manufacture of the product. The EMEA issued a notification on 29 September 1998.
- On 12 October 1998, the MAH applied, in accordance to the Regulation, for two Type I variations related to changes in the test procedure of the product. The EMEA issued two notifications on 11 November 1998.
- The MAH submitted on 26 June 1998 an application for a marketing authorisation for Viramune 50 mg/ 5 ml oral suspension under Annex II to Commission Regulation (EC) No 542/95 as amended. This oral suspension was intended to be indicated for children and adults who have difficulties to swallow. The procedure started on 24 July 1998 and the CPMP agreed on a consolidated list of questions on 19 November 1998. Additional data were submitted by the MAH on 12 January 1999. During its March meeting, the CPMP, in light of the overall data submitted and the scientific discussion within the Committee, issued by consensus a positive opinion for granting a Marketing Authorisation to Viramune 50 mg/5 ml oral suspension on 25 March 1999. The CPMP opinion was forwarded to the European Commission, which adopted the respective Decision on 18 June 1999.
- On 11 January 1999 the MAH submitted two Type II variation applications. The first variation application related to the update of the safety information of the SPC and as a consequence the Package Leaflet based on the evaluation of the second periodic safety update report (PSUR). The second variation application related to the update of the interaction information of the SPC and the Package Leaflet based on the evaluation of additional interaction study reports. The CPMP agreed the changes to be incorporated and adopted two Opinions on the Type II variation on 25 March 1999. The respective Commission Decisions were issued on 8 July 1999.
- Pursuant to Article 13(2) of Council Regulation (EEC) No. 2309/93 as amended and Part 4G of Annex to Council Directive 75/318/EEC, the MAH provided throughout the year additional efficacy and safety data as stated in Annex IIC to Commission Decision, which formed the basis of the annual re-assessment of the risk/benefit profile of Viramune (e.g. results from the clinical endpoint studies). On 11 February 1999, the MAH provided an updated expert report summarising the different specific obligations already submitted within the period February 1998-January 1999. The procedure started on 26 February 1999. During its April plenary meeting, the CPMP agreed with the Rapporteur's assessment report that the risk/benefit profile of Viramune remained favourable and that the MA should remain under exceptional circumstances until all the specific obligations are fulfilled. The CPMP adopted on 22 April 1999 an opinion on the annual re-assessment of the specific obligations and the risk/benefit ratio, stating that no amendments of Annexes I and III to the Community Marketing Authorisation were necessary. The Annex II has been updated. Respective Commission Decision was issued on 29 July 1999.
- On 19 May 1999, the MAH applied for a Type I variation related to change in batch size of the active substance. The EMEA issued a notification on 24 June 1999.

- On 2 August 1999, the MAH submitted a Type II variation application related to the update of the safety information of the Summary of Product Characteristics and as a consequence the Package Leaflet based on the evaluation of the third periodic safety update report (PSUR), and the newly available results of the animal carcinogenicity studies. The CPMP agreed on the changes to be incorporated and adopted the Opinion on the Type II variation on 18 November 1999. The respective Commission Decisions were issued on 16 March 2000.

- On 2 August 1999, the MAH submitted a Type II variation application related to the update of the SPC and as a consequence the Package Leaflet with paediatric information. The CPMP agreed on the changes to be incorporated and adopted the Opinion on the Type II variation on 18 November 1999. The respective Commission Decisions were issued on 16 March 2000.

- On 27 September 1999, the MAH applied for a Type I variation related to a change in the plastic adapter which fits between the bottle and oral syringe of the oral suspension dosage form. The EMEA issued a notification on 15 October 1999.

- On 12 April 2000, additional cases of severe and life-threatening cutaneous and hepatic reactions have been reported despite the warnings already included in the product information. The Marketing Authorisation Holder requested an update of the Summary of Product Characteristics and Package Leaflet through an Urgent Safety Restriction procedure in accordance with article 1(2) of Commission Regulation (EC) No. 542/95 as amended.

  The scope of the procedure was to reinforce the cutaneous and liver monitoring of patients treated with nevirapine. New warnings have been introduced in the Summary of Product Characteristics (sections 4.2 Posology and method of administration, 4.3 Contraindications, 4.4 Special warnings and special precautions for use and 4.8 Undesirable effects) and in the Package Leaflet.

- Pursuant to Article 13(2) of Council Regulation (EEC) No. 2309/93 as amended and Part 4G of Annex to Council Directive 75/318/EEC, the MAH provided throughout the year additional efficacy and safety data as stated in Annex IIC to Commission Decision, which formed the basis of the annual re-assessment of the risk/benefit profile of Viramune. On 8 February 2000, the MAH provided an updated expert report summarising the different specific obligations already submitted within the period February 1999-January 2000. The procedure started on 18 February 2000. During its April plenary meeting, the CPMP agreed with the Rapporteur's assessment report that the risk/benefit profile of Viramune remained favourable and that the MA should remain under exceptional circumstances until all the specific obligations are fulfilled. The CPMP adopted on 12 April 2000 an opinion on the annual re-assessment of the specific obligations and the risk/benefit ratio, stating that amendments of Annexes I and III to the Community Marketing Authorisation were necessary. The Annex II has been updated. Respective Commission Decision was issued on 27 July 2000.

- Pursuant to CPMP discussion on the potential of St John's wort (*Hypericum perforatum*) to interact with protease inhibitors (PIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs), the MAHs for the respective PIs and NNRTIs submitted to the EMEA an application for a Type II variation to include a class labelling wording in the Summary of Product Characteristics and Package leaflet. On 29 June 2000, the CPMP adopted an Opinion on this variation and the respective Commission Decision was issued on 30 October 2000.

- On 15 May 2000, the MAH submitted three Type II variation applications related to the update of the Summary of Product Characteristics and Package Leaflet when relevant. The changes concerned the safety information following the April 2000 urgent safety restriction procedure, new information on interactions with medicinal products and pharmacodynamic information on the perinatal transmission and resistance data. The CPMP agreed on the changes to be incorporated and adopted an Opinion on the three Type II variations on 27 July 2000. The respective Commission Decisions were issued on 18 November 2000.

Subsequent post Marketing Authorisation applications agreed upon are summarised in the table below:

Scope	Application number	Type of modification[1]	Notification/ Opinion issued on[2]	Commission Decision Issued/amended on
Annual reassessment	S/0020	S	25.04.01	13.08.01
Replacement of an excipient with a comparable excipient	I/0021	I	30.03.01	04.05.01
Update of section 4.4 (Special warnings and special precautions for use) of the SPC (Summary of Product Characteristics) concerning the introduction of a statement for use of nevirapine in Post-Exposure Prophylaxis (PEP), inclusion of hepatitis B and C as additional risk factors and addition in section 4.8 (undesirable effects) of neutropenia, anaemia and arthralgia as possible side-effects. The relevant changes have been introduced to the package leaflet. Update of section 5.1 (Pharmacodynamic properties) of the SPC concerning resistance data for perinatal transmission and cross-resistance data (with efavirenz). Update of sections 4.3 (Contra-indications), 4.4 (Special warnings and special precautions for use) and 4.5 (Interaction with other medicinal products and other forms of interaction) of the SPC referring to the interaction of nevirapine with the protease inhibitors lopinavir and saquinavir, the non-nucleoside reverse transcriptase inhibitor, efavirenz and with St. John's Wort (*Hypericum perforatum*). The information available in the SPC in sections 4.4 (Special warnings and special precautions for use) and 5.2 (Pharmacokinetic properties) regarding the effects of hepatic and renal dysfunction on the pharmacokinetic of nevirapine has been updated. Finally, a contra-indication in section 4.3 (Contra-indications) and new Special warnings and special precautions for use (section 4.4) concerning the concomitant use of nevirapine with rifampicin due to the pharmacokinetic interaction of these medicines have been added.	II/0022-0023-0024	II	26.07.01	30.11.01
Variation to demonstrate compliance with Commission Directive 1999/82/EC and the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products (CPMP/BWP/1230/98 rev.1).	II/0025	II	25.04.02	30.04.02
Change in the specification of the active substance.	II/0027	II	18.10.01	17.12.01
Annual reassessment	S/0028	S	25.04.02	11.07.02
Changes related to the active substance.	II/0029	II	19.09.02	07.10.02
Update of the SPC, to add interaction data with fluconazole and warfarin (section 4.5 of the SPC), and to alter the statement on severe liver impairment in the contra-indication section (section 4.3 of the SPC). In addition, an update of the SPC on the information related to the occurrence of Stevens-Johnson syndrome in children is proposed (section 4.8 of the SPC).	II/0030	II	19.09.02	05.12.02
Update of SPC, to add pharmacodynamic data (section 5.1 of the SPC): Revision of the wording related to cross-resistance among Non-Nucleoside Reverse Transcriptase Inhibitors (NNRTI) and inclusion of information resulting from the SAINT study on Perinatal Transmission.	II/0031	II	19.09.02	05.12.02
Renewal	R/0032	R	21.11.02	17.02.03
Update of the SPC to include the class labelling on Lipodystrophy in sections 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable Effects). Relevant changes are equally proposed for the Package Leaflet.	II/0033	II	19.03.03	09.07.03
Change in the name of a manufacturer of the medicinal product	I/0034	I	14.04.03	19.05.03
Change(s) to the test method(s) and/or specifications for an excipient	II/0035	II	26.06.03	01.07.03
Change in or addition of manufacturing site(s) for part or all of the manufacturing process	I/0036	I	12.06.03	25.06.03
Change in test procedure of immediate packaging	I/0037	I	12.06.03	25.06.03

[1] In accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended: **I** refers to a minor variation (Type I variation); **II** refers to a major variation (Type II variation); **I/II** refers to a minor variation following the procedure set out in Article 6, 7 and 8 of the Regulation; **X** refers to an Annex II application.
T refers to a transfer of a Marketing Authorisation in accordance with Commission Regulation (EC) No 2141/96 of 7 November 1996.
N refers to a notification in accordance with Article 10(3) of Council Directive 92/27/EEC of 31 March 1992.

[2] For Notifications and Type I variations, the date of entry into force of the change is the EMEA Notification date. The Commission Decision will be amended accordingly.

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, to include 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.	II-0038	II	20.11.03	04.02.04