STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 1 March 2004 please refer to module 8B**.**

- On 4 June 1999, the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation related to the extension of the shelf life. The EMEA approved this variation on 8 July 1999 which required amendments to Annexes of the Commission Decision.
- On 16 July 1999, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to the update of the Summary of Product Characteristics and Package Leaflet with new data based on 1) reports of genotyping of virus from clinical isolates, 2) updated clinical study reports and 3) revised safety information resulting from increased patient exposure. The CPMP, during its September plenary meeting, considered the changes acceptable, and adopted on 23 September 1999 a favourable opinion on the Type II variation. The corresponding Commission Decision was issued on 31 January 2000.
- On 28 July 1999, the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation related to a change in the qualitative composition of the immediate packaging material (bottles). The EMEA approved on 11 August 1999 this variation which did not require any amendments to Annexes of the Commission Decision.
- On 9 November 1999, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to the update of the Summary of Product Characteristics to reflect results from the 48 weeks paediatric study. The CPMP, during its January plenary meeting, considered the changes acceptable, and adopted on 19 January 2000 a favourable opinion on the Type II variation. The corresponding Commission Decision was issued 24 May 2000.
- On 28 January 2000, the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation related to an extension of the re-test period of the active substance. The EMEA approved on 2 March 2000 this variation, which did not require any amendments to Annexes of the Commission Decision.
- On 30 March 2000, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to the update of the Summary of Product Characteristics and Package Leaflet in particular to reflect new data on food interaction and safety information. The CPMP, during its June plenary meeting, considered the changes acceptable, and adopted on 29 June 2000 a favourable opinion on the Type II variation. The corresponding Commission Decision was issued 13 October 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 13 October 2000.
- On 10 May 2000, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to the introduction of an alternative route of synthesis of the active substance. The CPMP, during its July plenary meeting, considered the changes acceptable, and adopted on 27 July 2000 a favourable opinion on the Type II variation, which did not require any amendments to the Commission decision.
- On 24 October 2000, the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation related to a change of the batch size of the active substance. The EMEA approved on 24 November 2000 this variation, which did not require any amendments to Annexes of the Commission Decision.
- On 30 November 2000, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to the addition of an alternate manufacturer of the

active substance and to the redefinition of the starting material for the synthetic route of the active substance.
The CPMP, during its February plenary meeting, considered the changes acceptable, and adopted on 1 March 2001 a favourable opinion on the Type II variation, which did not require any amendments to the Commission decision.

- On 30 November 2000, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to the update of the Summary of Product Characteristics and Package Leaflet following the evaluation of the 2nd Periodic Safety Update Report and the availability of clinical data regarding the interaction between efavirenz and rifabutin. The CPMP, during its February plenary meeting, considered the changes acceptable, and adopted on 1 March 2001 a favourable opinion on the Type II variation. The corresponding Commission Decision was issued 14 June 2001.

- On 14 February 2001 The Marketing Authorisation Holder submitted to the EMEA an application for a type II variation related the update of the Summary of Product Characteristics to reflect results from indinavir/efavirenz steady state pharmacokinetics study. The procedure started on 2 March 2001. Supplementary information was supplied by the Marketing Authorisation Holder on 4 May 2001. The CPMP, during its May plenary meeting, considered the changes acceptable, and adopted on 31 May June 2001 a favourable opinion on the Type II variation. The corresponding Commission Decision was issued 20 September 2001.

- On 28 March 2000 The Marketing Authorisation Holder submitted to the EMEA an Annex II application Pursuant to Article 2(1) of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended, and Annex II point 3(iv) The procedure started on 14 April 2000, The CPMP, during its June plenary meeting, considered the changes acceptable, and adopted on 27 June 2001 a favourable opinion on the Type II variation. The corresponding Commission Decision was issued 18 October 2001.

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
Change 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)	I/16	I	28.03.01	05.05.01
The MAH submitted to the EMEA on 4 May 2001, an Annex II application. The existing numbers in the Community Register of Medicinal Products for Sustiva, are: EU/1/99/110/001-005	X/17	X	30.05.02	22.08.02
The MAH submitted to the EMEA on 4 May 2001, an Annex II application. The existing numbers in the Community Register of Medicinal Products for Sustiva, are: EU/1/99/110/001-005	X/18	X	30.05.02	22.08.02
The MAH applied for an update of the Summary of Product Characteristics (SPC) section 4.4 (Special warnings and special precautions for use) and section 5.3 (Preclinical safety data).	II/19	II	13.12.01	12.04.02
Changes to comply with supplements to pharmacopoeias	I/20	I	21.09.01	23.10.01
Change in container shape	I/21	I	24.10.01	07.01.02
Change in or addition of manufacturing site(s) for part or all of the manufacturing process and consequential change	I/22	I	26.11.01	06.03.02
Change in the name and/or address of the marketing authorisation holder	I/23	I	31.10.01	21.03.02
Change following modification(s) of the manufacturing authorisation(s).	I/24	I	31.10.01	21.03.02

[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 61(3) of Council Directive 2001/83/EC.

[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.

Change following modification(s) of the manufacturing authorisation(s)	I/25	I	31.10.01	06.03.02
The MAH applied for an update of the SPC sections 4.3, 4.4, 4.5 and 4.8 and corresponding sections of the Package leaflet (PL). The application is based on newly completed interaction studies and on two adverse events reported in the 4th efavirenz PSUR. In addition, a class wording on St-John's Wort is added, as agreed with CPMP.	II/27	II	27.06.02	30.09.02
Bristol-Myers Squibb Pharma (UK) Limited submitted to the EMEA on 21 January 2002 an application for the transfer of the Marketing Authorisation to Bristol-Myers Squibb Pharma EEIG	T/28	T	28.02.02	02.04.02
Update of the SPC for the oral solution in order to include information on the final results of study DMP266-111, "A Phase I, Open-label, Single-dose, Randomized; Two-period Crossover Study in Healthy Volunteers to Determine the Effect of Food on the Bioavailability of Efavirenz Oral Solution.	II/29	II	30.05.02	30.08.02
Change following modification(s) of the manufacturing authorisation(s)	I/30	I	09.04.02	07.05.02
Changes to the PL local representatives address for France, Finland and Ireland. The phone numbers for the local representatives in Greece and Germany are modified. Local representatives for Belgium, Luxembourg, Ireland and UK are listed individually in accordance with the latest QRD template.	N/31	N	20.06.02	20.06.02
Changes of the local representative name in Italy.	N/32	N	14.06.02	10.07.02
Changes of the local representative names in Italy and Spain. The phone number for the local representative in Ireland is modified.	N/33	N	18.11.02	04.12.02
To amend sections 4.4 and 4.8 of the SPC as requested by the CPMP on July 2002, following the assessment of PSUR 5, in order to adequately reflect the safety concerns with regard to suicide. In particular, the Marketing Authorisation Holder (MAH) was requested to delete "occasional" in sections 4.4 and 4.8 and "a causal relationship to the use of efavirenz cannot be determined from these reports" in sections 4.8. Moreover, the MAH took this opportunity to update the SPC and the PL of the 300mg and the 600mg film-coated tablet presentations, following variation II/27 for Sustiva, adopted at the June 2002 CPMP for the hard capsules and the oral solution presentation.	II/34	II	20.02.03	19.05.03
The MAH applied for an update of the SPC to include the class labelling on Lipodystrophy in sections 4.4 and 4.8. Relevant changes are equally proposed for the Package Leaflet.	II/35	II	19.03.03	09.07.03
Extension of shelf-life as foreseen at time of authorisation.	I/36	I	08.05.03	25.06.03
Minor changes in manufacture of the medicinal productChange in or addition of manufacturing site(s) for part or all of the manufacturing process	I/37	I	07.07.03	22.07.03
Update of section 4.4 (Special warnings and special precautions of use) and 5.2 (Pharmacokinetic properties) of the 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. In addition, the MAH has proposed to update the 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.	II/38	II	20.11.03	05.02.04
Addition or replacement of measuring device for oral liquid dosage forms and other dosage forms	I/39	I	16.10.03	23.10.03
Replacement/add. of manufacturing site: Secondary packaging site	IA/42	IA	17.11.03	-
Deletion of manufacturing site	IA/44	IA	27.01.04	-
Deletion of manufacturing site Replacement/add. of manufacturing site: Primary packaging site - Solid forms	IA/45	IA	30.01.04	-