STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 1 July 2005 please refer to module 8B**.**

- On 8 October 1996, the Marketing Authorisation holder (MAH) submitted two different applications for a Type I variation in accordance with Commission Regulation (EC) No. 542/95:

  1. The scope of the first variation related to the introduction of a new manufacturing site as an alternative manufacturer of the active substance.
  2. The scope of the second variation related to the change of the batch size of the active substance.

  On 30 October 1996, the EMEA considered both variations to be acceptable. These variations did not require any amendments to the Commission Decision.

- On 19 November 1996, the MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95, related to a change of the name of the manufacturer of the finished medicinal product and responsible for the batch release in the European Economic Area for Epivir oral solution. On 2 December 1996, the EMEA approved the variation, which required amendments to be incorporated in the relevant sections of the Commission Decision. The European Commission amended the Decision on 14 February 1997.

- On 28 November 1996, the MAH submitted two applications for a Type II variation in accordance with Commission Regulation (EC) No. 542/95:

  1. The scope of the first variation concerned the introduction of a 10 ml device syringe and a polyethylene adapter in each oral solution pack to facilitate its use. The CPMP considered the variation acceptable and adopted the Opinion on the Type II variation on 22 January 1997. The respective Commission Decision was issued on 15 April 1997.
  2. The scope of second variation concerned the update of the statement into the Summary of Product Characteristics related to the carcinogenicity and mutagenicity potential following the finalisation of the studies. The CPMP agreed on the wording to be implemented into the Summary of Product Characteristics and adopted the Opinion on the Type II variation on 19 February 1997. The respective Commission Decision was issued on 22 May 1997.

- On 23 January 1997, the MAH submitted two applications for a Type I variation in accordance with Commission Regulation (EC) No. 542/95, related to a change in the manufacturer(s) of the active substance. On 28 February 1997, the EMEA approved both variations, which did not require any amendments to the Commission Decision.

- On 1 April 1997, the MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95, related to a change in the manufacturer of the active substance. On 15 May 1997, the EMEA approved the variation, which did not require any amendments to the Commission Decision.

- On 23 June 1997, the MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95, related to a minor modification to the synthesis of the active substance. On 11 July 1997, the EMEA approved the variation, which did not require any amendments to the Commission Decision.

- Pursuant to Article 13(2) of Council Regulation (EEC) No 2309/93 and Part 4G of Annex to Council Directive 75/318/EEC, the MAH provided throughout 1997 additional efficacy and safety data as stated in the Annex IIC to the Commission Decision, which formed the basis of the annual re-assessment of the risk/benefit profile of Epivir (e.g. final results from the clinical endpoint study). On 14 July 1997 the MAH provided an updated expert report summarising the different specific obligations already submitted within the period August 1996-June 1997. The procedure started on 25 July 1997. During its September plenary CPMP meeting, the CPMP agreed with the Rapporteur's assessment report that the risk/benefit profile of lamivudine remained favourable and that there was no remaining grounds to keep the MA under

exceptional circumstances since all the specific obligations were fulfilled. The CPMP adopted on 24 September 1997, an Opinion on the annual re-assessment of the specific obligations and the benefit/risk ratio, stating that amendments of Annexes I, II and III to the Community Marketing Authorisation were necessary. The respective Commission Decision was issued on 7 January 1998. Subsequent applications for a Type II variation (update of the Summary of Product Characteristics and change in the formulation of the oral solution) were submitted by the MAH and Opinions were adopted by the CPMP on 24 September 1997. The respective Commission Decisions were issued on 16 December 1997.

- On 12 January 1998, the MAH submitted two applications for a Type II variation in accordance with Commission Regulation (EC) No. 542/95:

  1. The scope of the first variation concerned the extension of the indication to include paediatric patients.
  2. The scope of second variation concerned the update of the Summary of Product Characteristics to reflect the current clinical practice.

  The CPMP considered the changes related to both variation acceptable and issued on 25 March 1998 the Opinion on the two Type II variations. The respective Commission Decisions were issued on 7 July 1998.

- On 3 March 1998, the MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95, related to an extension of the shelf-life of Epivir oral solution to 24 months. On 20 March 1998, the EMEA approved the variation, which required amendments to be incorporated in Annex I of the Commission Decision. The European Commission amended the Decision on 7 July 1998.

- On 22 March 1999, the MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95, related to a minor change to the manufacturing process of the active substance. On 4 May 1999, the EMEA approved the variation, which did not require any amendments to the Commission Decision.

- On 12 April 1999, the MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95 relating to the update of the Summary of Product Characteristics and Package Leaflet following evaluation of the third and fourth Periodic Safety Update Report. The CPMP considered the changes related to the variation acceptable and issued on 23 June 1999 the Opinion on the Type II variation. The Commission Decision was issued on 10 November 1999.

- On 11 October 1999, the MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95, related to:

  - a change in supplier of an intermediate compound used in the manufacture of the active substance and consequently

  - a minor change of manufacturing process of the active substance.

  On 20 October 1999, the EMEA approved the variation, which did not require any amendments to the Commission Decision.

- On 20 March 2000, the MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95, related to the extension of the shelf-life of Epivir tablets to 36 months. On 14 April 2000, the EMEA approved the variation, which required amendments to be incorporated in Annex I of the Commission Decision. The European Commission amended the Decision on 27 July 2000.

- On 16 June 2000, the MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95 variation for an update of the Summary of Product Characteristics and Package Leaflet following the evaluation of the sixth and seventh Periodic Safety Update Report and following the review of post authorisation data on pharmacokinetics in infants. The CPMP considered the changes related to the variation acceptable and issued on

28 August 2000 the Opinion on the Type II variation. The Commission Decision was issued on 22 January 2001.

- On 4 September 2000, the MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95, related to an update of the Summary of Product Characteristics (sections "Special warnings and special precautions for use", "Interaction with other medicinal products and other forms of interaction" and "Undesirable effects", and as a consequence, an update of the Package Leaflet). The application addressed changes requested by the CPMP following the revision of the class labelling for nucleoside analogues in September 2000 and changes proposed by the MAH following the availability of new safety data. The CPMP considered the changes related to the variation acceptable and issued on 29 March 2001 the Opinion on the Type II variation. The Commission Decision was issued on 11 July 2001.

- On 4 September 2000, the MAH submitted an annex II application in accordance with Commission Regulation (EC) No. 542/95, related to the introduction of 300 mg film-coated tablets. The CPMP considered the application acceptable and issued on 26 July 2001 the opinion for granting a Marketing Authorisation for Epivir 300 mg film-coated tablets. The Commission Decision was issued on 15 November 2001.

- On 19 April 2001, the MAH submitted an application for the renewal of the Marketing Authorisation. In accordance with Article 13 of Council Regulation (EC) No. 2309/93. The CPMP was of the opinion that the quality, safety and efficacy of Epivir continued to be adequately and sufficiently demonstrated and adopted on 26 July 2001 the opinion on the renewal of the Marketing Authorisation. The Commission Decision was issued on 9 November 2001.

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

Scope	Application number	Type of modification[1]	Notification/ Opinion issued on[2]	Commission Decision Issued/amended on
To update the Summary of Product Characteristics (SPC), section 5.1 "Pharmacodynamic Properties" relating to the use of lamivudine as part of HAART and relating to an update of virological information, following the CPMP assessment of the renewal dossier of the Epivir Marketing Authorisation. Furthermore, to update section 4.8 "Undesirable Effects" to reflect the frequencies of the adverse drug reactions in accordance with the SPC guideline. Also, to update section 4.4 " Special warnings and special precautions" to reflect the class labelling statement for nucleoside analogues regarding lactic acidosis as revised by the CPMP. Finally, to update sections 4.2. "Posology", 4.4 " Special warnings and special precautions" and 5.2 " Pharmacokinetic properties" of the Epivir Oral solution to include a once a day dosing advice following the CPMP assessment of the once a day dosing scheme. The relevant sections of the Package Leaflet (PL) have been amended accordingly. Furthermore, some minor changes have been incorporated in the SPC and PL in order to bring the text in line with the latest QRD/ EMEA templates. In addition, the list of the Local Representatives has been updated.	II/0025	II	30.05.02	21.08.02
Change in specification of starting material or intermediate used in the manufacture of the active substance.	I/0026	I	08.05.02	17.05.02
Change in or addition of manufacturing site for part or all of the manufacturing process.	I/0027	I	05.09.02	24.09.02
Change in or addition of manufacturing site(s) for part or all of the manufacturing process.	I/0028	I	05.09.02	17.10.02
Change in the qualitative composition of immediate packaging material.	I/0029	I	05.09.02	24.09.02
Extension of shelf-life as foreseen at time of authorisation.	I/0030	I	09.10.02	12.11.02
Change in the test procedure of the medicinal product.	I/0031	I	20.11.02	25.11.02
To update the SPC sections 4.2 " Posology and method of administration" further to the CPMP assessment of 48 week data of a clinical study. In addition, the Marketing Authorisation Holder (MAH) proposed some minor linguistic changes to the language versions to improve the readability and to comply with the latest EMEA/ QRD templates.	II/0032	II	20.02.03	14.05.03
Registration of an alternative primary packaging material (PVC/aluminium blister) for Epivir 150 mg and 300 mg film-coated tablets.	II/0033	II	19.03.03	09.07.03
To update 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 PL.	II/0034	II	19.03.03	09.07.03
Change in test procedure of active substance.	I/0036	I	05.08.03	19.08.03

[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.

To update the sections 4.4 "Special warnings and special precautions for use" and 5.2 "Pharmacokinetic properties" of the SPC to implement the class labelling statement on liver impairment adopted by the CPMP for all anti-retroviral medicinal products in April 2003. The section 2 of the PL is amended accordingly. Furthermore, the MAH has taken this opportunity to implement minor changes in the sections 4.4 and 4.6 "Pregnancy and Lactation" of the SPC and to update the PL in section 4, revising the wording on lipodystrophy as adopted by the CPMP in March 2003.	II/0037	II	20.11.2003.	29.01.2004
Change in BR/QC testing - repl./add. of batch control/testing site.	I/0038	IA	29.10.03	
Replacement/add. of manufacturing site: Secondary packaging site.	I/0039	IA	19.12.2003	-
Minor change in the manufacturing process of the active substance.	I/0040	IB	10.02.2004	-
To update section 4.4 “Special warnings and special precaution for use” of the SPC and section 2 of the PL under subheading "Pregnancy", to implement the class labelling for nucleoside/nucleotide reverse transcriptase inhibitors (NRTIs) regarding mitochondrial toxicity in children with *in utero* and post-natal exposure as adopted by the CPMP in November 2003. In addition, the MAH completed the list of local representatives in the PL, including the 10 accession countries and changed the format according to the latest EMEA/QRD template.	II/0041	II	24.03.2004	01.06.2004
Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer.	I/0042	IA	01.03.2004	-
Change in the name and/or address of a manufacturer of the finished product.	I/0043	IA	29.07.2004	-
To update section 5.3 “Preclinical safety data” of the SPC of Epivir 150 mg tablets, 300 mg tablets and 10 mg/ml oral solution to include information on NRTI incorporation into cellular DNA.	II/44	II	21.10.2004	
To update section 4.4 “Special warnings and special precautions for use” of the SPC, to implement the class labelling text regarding the high rate of virological failure and emergence of resistance at an early stage with triple combinations involving tenofovir disoproxil fumarate (Tenofovir DF) and two Nucleoside Reverse Transcriptase Inhibitors (NRTI’s), lamivudine and abacavir as adopted by the CHMP in July 2004. Furthermore, the MAH took the opportunity of this variation to amend the address of the Estonian local representative in the PL.	II/45	II	21.10.2004	
Change in batch size of active substance or intermediate - up to 10-fold	IA/46	IA	03.09.2004	-
To update section 4.4 “Special warnings and special precautions for use” and 4.8 “Undesirable effects” of the SPC and section 2 “Before you take Epivir” of the PL, to implement the class labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP in July 2004. Furthermore, to update section 4.4 “Special warnings and special precautions for use” of Epivir oral solution, to move the sentence to advise diabetic patients on the amount of sucrose contained in each dose. Additionally, the MAH added side-headings, where appropriate to section 4.4 of the SPC to improve readability. The MAH took also the opportunity of this variation to amend the address of the Estonian local representative in the PL.	II/47	II	18.11.2004	