Steps taken after granting the Marketing Authorisation

- On 12 June 1998 the EMEA issued a Notification of a change to an aspect of the Labelling and Package Leaflet not connected to the Summary of Product Characteristics in accordance with Article 10(3) of Council Directive No 92/27/EEC of 31 March 1992.

- The MAH submitted on 10 July 1998 three applications for a Type I Variation in accordance with Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995 as amended, related to:

    - changes in the manufacturer of the active substance and to
    - a change in batch size of the active substance

  On 19 August 1998, the EMEA approved these variations which did not lead to any change to the Commission Decision as amended.

- The MAH submitted on 12 April 1999 an application for a Type I Variation in accordance with Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995 as amended, related to a change in specification of starting material or intermediate used in the manufacture of the active substance. On 25 May 1999 the EMEA approved this variation, which did not lead to any change 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. The scope of the variation concerned the update to the Summary of Product Characteristics (SPC) and Package Leaflet with regard to "Special Warnings and Precautions for Use" (to include a warning statement on lactic acidosis), and "Undesirable effects" (introduction of the adverse event rhabdomyolysis). Furthermore, some minor administrative changes have been incorporated in the SPC, Labelling and Package Leaflet in order to bring the text in line with the new QRD/EMEA templates. 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 16 November 1999.

- On 11 October 1999, the MAH submitted three applications for Type I variations 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 substances and consequently

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

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

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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
To update the Summary of Product Characteristics (SPC) and Package Leaflet (PL), section 4.8 "Undesirable effects" following the evaluation of PSUR 6 and 8 and the availability of other new safety data.	II/0010	II	28.08.00	27.12.00
To update the SPC and PL, sections 4.4 "Special Warnings and special precautions for use", 4.5 "Interaction with other medical products and other forms of interaction", 4.8 "Undesirable effects" and 5.3 "Preclinical Safety Data", following the CPMP adoption of a revised class labelling for nucleoside analogues in September 2000 and the availability of new safety data.	II/0011	II	29.03.01	31.07.01
To update the SPC, section 5.1 "Pharmacodynamic Properties" relating to the use of lamivudine and zidovudine as part of HAART and relating to an update of virological information. Furthermore, to update section 4.8 "Undesirable Effects", to include pure red cell aplasia, aplastic anaemia and hepatitis and 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. The relevant sections of the 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/0012	II	30.05.02	22.08.02
Minor change in manufacture of the medicinalproduct.	I/0013	I	05.03.02	13.03.02
Change in specification of starting material or intermediate used in the manufacture of the active substance.	I/0014	I	08.05.02	17.05.02
Change in manufacturer of active substance.	I/0015	I	23.08.02	29.08.02
Renewal of the Marketing Authorisation.	R-16	R	18.03.03	11.06.03
Manufacturing process for PhEur components verified by certificate of suitability from PhEur.	I/0018	I	08.08.03	20.08.03
Withdrawal of the manufacturing authorisation for a site of manufacture.	I/0019	I	18.07.03	22.07.03
Change in test procedure of active substance.	I/0020	I	05.08.03	20.08.03
To update the sections 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 in April 2003. The section 2 of the PL is amended accordingly. Furthermore, the Marketing Authorisation Holder (MAH) has taken this opportunity to implement minor changes in sections 4.4 and 4.6 "Pregnancy and Lactation" of the SPC and to clarify the wording in section 5.3 "Preclinical safety data". Furthermore, the MAH updated the PL, section 4, revising the wording on lipodystrophy as adopted by the CPMP in March 2003 and amended the telephone number of the German local representative.	II/0021	II	20.11.03	05.02.04
To update section 5.1 "Pharmacodynamic properties" of the SPC, to characterise the role of a "fixed combination" product based on resistance data, as requested by the CPMP further to the opinion on	II/0022	II	25.09.03	14.01.04

[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.

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the renewal of the Marketing Authorisation.				
To update section 5.3 " Preclinical safety data" of the SPC, to illustrate the results of a cohort pilot study showing that zidovudine may be incorporated into leukocyte DNA. Furthermore, the SPC has been updated in line with the latest EMEA/QRD template.	II/0023	II	25.09.03	14.01.04
Submission of a new or updated Ph. Eur. Certificate of Suitability for an active substance or starting material/reagent/intermediate in the manufacturing process of the active substance from a manufacturer currently approved.	I/0024	I	20.10.03	-
Minor change in the manufacturing process of the active substance.	IB/0025	IB	10.02.04	-
To update the 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 to include the 10 accession countries and changed the format according to the latest EMEA/QRD template.	II/0026	II	24.03.04	26.05.04
Submission of Ph. Eur. certificate for active substance - approved manufacturer.	IA/0027	IA	09.03.04	-
Change in the name and/or address of a manufacturer of the finished product.	IA/0028	IA	29.07.04	-
To update section 4.4 "Special warnings and special precautions for use" and 4.8 "Undesirable effects" of the Summary of Product Characteristics and section 2 "Before you take Combivir" of the Package Leaflet, to implement the class labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP in July 2004. Furthermore, the Marketing Authorisation Holder (MAH) took the opportunity of this variation to amend the address of the Estonian local representative in the PL. Additionally, the MAH added side-headings, where appropriate to section 4.4 of the SPC to improve readability.	II/0030	II	18.11.2004	05.01.2005

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