STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

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

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

  1. The change of the manufacture site responsible for the production of the capsules, for the importation of the powder for oral solution and for the batch release in the EEA of both pharmaceutical forms. On 10 October 1996, the EMEA approved the variation. This variation required amendments to be incorporated in the relevant sections of the Commission Decision. The respective Commission Decision was issued on 9 November 1996.
  2. The change of the manufacturing site for the labelling of the powder for oral solution. On 16 October 1996, the EMEA approved the variation. This variation did not require any amendments to the Commission Decision, as amended.
  3. The change of the batch size of the finished product for Zerit 15 mg capsules. On 7 November 1996, the EMEA approved the variation. This variation did not require any amendments to the Commission Decision, as amended.

- On 23 September 1996, 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 of the statement in the SPC related to *Pneumocysitiis carinii* pneumonia (PCP) prophylaxis. On 17 October 1996, the CPMP agreed on the wording to be implemented into the SPC and adopted the opinion on the type II variation. The respective Commission Decision was issued on 3 February 1997.

- On 16 January 1997, the MAH submitted in parallel three applications for a type II variation, in accordance with Commission Regulation (EC) No. 542/95. The MAH applied for:

  1. The extension of the therapeutic indication of Zerit to include paediatric patients
  2. The update of the SPC with additional data for the prescribing physician for patients with end-stage renal disease
  3. The update of the SPC related to the carcinogenic potential of Zerit following the finalisation of the studies.

  The CPMP considered these variations acceptable and agreed on the wording to be introduced into the appropriate sections of the SPC and reflected into the PL. The CPMP adopted on 16 April 1997 an opinion on the three type II variations. The respective Commission Decision was issued on 28 July 1997.

- On 17 July 1997, the MAH submitted an application for a type II variation, in accordance with Commission Regulation (EC) No. 542/95. The MAH applied for the update of the safety sections of the SPC with regard to the occurrence of cases of lactic acidosis and to the streamlining of some undesirable effects. The CPMP considered this variation acceptable and agreed on the wording to be introduced into the appropriate sections of the SPC. The CPMP adopted on 24 September 1997 an opinion on the type II variation, and the respective Commission Decision was issued on 12 December 1997.

  On 8 September 1997, the MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) 542/95 related to a minor change of the manufacturing process of the active substance. On 25 September 1997 the EMEA approved the variation. This variation did not require any amendments to the Commission Decision, as amended.

- In accordance with Article 10(3) of Council Directive 92/27/EEC of 31 March 1992, the EMEA issued on 4 March 1998 a Notification for amendment of the addresses of the local representatives mentioned in the Package Leaflet, as applied by the MAH. The Commission Decision was issued on 3 April 1998.

- On 14 April 1998, the MAH submitted an application for a type I variation in accordance with Commission Regulation (EC) 542/95 related to the change of the batch size of the finished product for Zerit capsules 20 mg. On 11 May 1998 the EMEA approved the variation, which did not lead to any changes to the Commission Decision.
- In accordance with Article 10(3) of Council Directive 92/27 EEC of 31 March 1992, the EMEA issued on 8 September 1998 a Notification for amendments of the addresses of the local representatives included in the package leaflet as applied by the MAH.

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/amendedon
Addition of alternative manufacturing process for the active substance.	II/12	II	21.10.98	-
To make a change in the address of the German and Dutch local representatives of the Marketing Authorisation holder (MAH), as stated in the Package Leaflet (PL).	N/13	N	08.09.98	09.10.98
To update the Summary of Product Characteristics (SPC) sections 4.4 "Special warnings and special precautions for use", 4.5 "Interactions with other medicinal products and other forms of interactions", 4.6 "Pregnancy and lactation", 4.8 "Undesirable effects", 5.1 "Pharmacodynamic properties" and relevant sections of the PL following the evaluation of PSUR 4 and the availability of new safety data.	II/14	II	23.09.99	21.02.00
Minor change of manufacturing process of the active substance.	I/15	I	16.07.99	-
Change in the batch size of finished product.	I/16	I	08.10.99	-
Changes in manufacture of the medicinal product.	I/17	I	08.10.99	-
Changes of the addresses of the local representatives included in the PL.	N/18	N	14.04.00	-
Changes of the addresses of the local representatives included in the PL.	N/19	N	09.06.00	-
Changes of the addresses of the local representatives included in the PL.	N/20	N	04.12.00	-
To update the SPC sections 4.4 "Special warnings and special precautions for use", 4.8 "Undesirable Effects" and relevant sections of the PL, further to changes requested by the CPMP following the adoption of the revised class labelling for nucleoside analogues in September 2000 and the availability of new safety data.	II/21	II	29.03.01	05.07.01
Addition of alternative manufacturing process for the active substance.	II/23	II	31.05.01	-
Renewal of the Marketing Authorisation.	R/24	R	29.03.01	08.06.01
To update the SPC sections 4.4 "Special warnings and special precautions for use" and relevant sections of the PL following reports of sometimes fatal, progressive, ascending muscular weakness in association with lactic acidosis among patients receiving stavudine.	II/26	II	20.09.01	28.01.02

[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 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.

Change in the name and/or address of the marketing authorisation holder.	I/27	I	05.10.01	21.11.01
Additional pharmaceutical presentations, namely prolonged release hard capsules.	X/28	X	25.07.02	12.11.02
Extension of shelf-life or retest period of the active substance.	I/29	I	25.01.02	04.02.02
Changes of the addresses of the local representatives included in the PL.	N-30	N	05.06.02	28.06.02
Replacement of an excipient with a comparable excipient.	I/31	I	06.08.02	10.09.02
Changes of the addresses of the local representatives included in the PL	N/32	N	30.10.02	20.11.02
To update and harmonise the SPC of the immediate release formulations for Zerit prolonged-release hard capsules. Changes relate to sections 4.1 "Therapeutic indications, 4.2 "Posology and method of administration", 4.3 "Contra-indications", 4.4 " Special warnings and special precautions for use", 4.5 " Interactions with other medicinal products and other forms of interaction", 4.6 " Pregnancy and lactation", 4.8 "Undesirable Effects", 5.1 "Pharmacodynamic properties", 5.2"Pharmacokinetic properties", 6.1 "List of excipients". Furthermore, section 4.8 of the SPC of the Zerit immediate release formulations and Zerit prolonged-release hard-capsules has been revised according to the SPC guideline. Relevant changes are equally proposed for the PL. In addition, the list of local representatives in the PL of the Zerit immediate release formulations and Zerit prolonged-release hard-capsules has been revised.	II/33	II	23.01.2003	16.05.2003
The extension of indication for Zerit hard capsules and Zerit powder for oral solution to include newborns based on new clinical data. Changes relate to sections 4.1 "Therapeutic indications, 4.2 "Posology and method of administration", 4.4 "Special warnings and special precautions for use", 4.6 "Pregnancy and lactation", 4.8 "Undesirable Effects", 5.1 "Pharmacodynamic properties", 5.2 "Pharmacokinetic properties", 5.3 "Preclinical Safety data" and 6.6 "Instructions for use and handling and disposal". Relevant changes are equally proposed for the PL. In addition, the list of local representatives in the PL has been revised.	II/34	II	24.07.2003	24.10.2003
To make an update in 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/35	II	19.03.2003	30.06.2003
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 on liver impairment adopted by the CPMP for oral anti-retroviral medicinal products in April 2003. Relevant changes are equally proposed for the PL. Furthermore, the MAH has taken this opportunity to update the section 4.2."Posology and method of administration" of the SPC to revise the paragraph on dose adjustment in case of peripheral neuropathy further to the CPMP assessment of variation II/33, and to update section 4.8 "Undesirable effects" to include macrocystosis further to the CPMP assessement of the PSURs, covering the period November 2000 - December 2001 and December 2001 - December 2002, respectively. Also, the MAH has updated the PL in section 4 to revise the wording on lipodystrophy as adopted by the CPMP in March 2003. Finally, the MAH has further harmonised the wording of the SPC and PL of the prolonged-release and immediate release formulations.	II/36	II	20.11.2003	27.01.2004
To update the section 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. The MAH also introduced minor editorial amendments to sections 4.4 and 4.8. In addition, the MAH has taken the opportunity to introduce minor linguistic changes in the Greek, Portuguese, Spanish and Norwegian language versions. Finally, 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/37	II	24.03.2004	28.04.2004
To amend the list of local representatives in the PL, namely to correct the address of the representatives in Cyprus, France, Latvia, Lithuania and Republic of Slovenia.	N/38	N	25.06.2004	
To update section 4.8 "Undesirable effects" of the SPC, to include hyperlactatemia in the postmarketing section, following assessment of PSUR 10 covering the period 24/12/2002-23/12/2003.	II/39	II	18.11.2004	20.01.2005

To update section 4.4 "Special warnings and special precautions for use" and section 4.8 "Undesirable effects" of the SPC and section 2 “Before you take Zerit” of the PL, to implement the class labelling text regarding the Immune Reactivation Syndrome, as adopted by the CHMP in July 2004.	II/40	II	18.11.2004	20.01.2005
To replace the current TSE Certificates of Suitability with the new Certificates of Suitability (ROP-CEP 2002-110 and ROP-CEP 2002-126) and to remove one of the gelatin sources from which Capsugel manufacturers their capsules shells (Gelita Group RO-CEP 200-50). The MAH took the opportunity to update the administrative data (previously part IA).	IA|/41	I	29.11.2004	
To gain approval for a larger batch size for Zerit Powder for Oral Solution of 150 kg.	IA/42	I	12.01.2005	
Deletion of a pharmaceutical form	IA/43	I	17.03.2005	
Change in the name and/or address of the MAH	IA/45	I	09/08/2005	
Update of SPC and PL The MAH submitted this variation to harmonise the stavudine SPC with the current Company Core Datasheet (CCDS) for stavudine, which includes a statement on the increased risk of pancreatitis (fatal and non fatal), fatal hepatic events and peripheral neuropathy (severe in some cases) in HIV infected patients receiving stavudine in association with didanosine and hydroxyurea.	II/44	II	27/07/2005	31/08/2005