STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

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

- On 29 August 1996, the EMEA approved the variation (Type I) submitted by the company relating to an additional manufacturing site as a site where the product assembly of bulk capsules imported from Abbott North Chicago takes place.
- On 11 December 1996, the Marketing Authorisation Holder (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 safety information in the Summary of Product Characteristics (SPC) and consequently the Package Leaflet (PL) based on post-marketing experience and new pharmacokinetic data. On 19 March 1997, the CPMP adopted an opinion on the Type II variation and the respective Commission Decision was issued on 22 July 1997.
- On 4 April 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 change in the storage recommendations for Norvir capsule. As a consequence to this change the Marketing Authorisation Holder applied also for lowering the assay specification at the end of shelf life. On 18 June 1997, the CPMP adopted an opinion on the Type II variation and the respective Commission Decision was issued on 30 September 1997.
- On 11 September 1997, the MAH submitted two applications for a Type I variation in accordance with Commission Regulation (EC) No. 542/95. The first variation related to the change in the manufacturer of the active substance meanwhile the second application concerned the amendment of the SPC with regard to the temperature at which the oral solution should be kept by the patient. On 6 November 1997, the EMEA approved both variations.
- 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 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 Norvir (e.g. results from the clinical endpoint studies). On 11 September 1997, the MAH provided an updated expert report summarising the different specific obligations already submitted within the period August 1996-August 1997. The procedure started on 26 September 1997. During its November plenary CPMP meeting, the CPMP agreed with the Rapporteur's assessment report that the risk/benefit profile of ritonavir remained favourable and that the MA remains under exceptional circumstances until all the specific obligations are fulfilled.
- The CPMP adopted on 19 November 1997 an Opinion on the annual re-assessment of the specific obligations and the risk/benefit ratio, stating that amendments of Annexes I, II and III to the Community Marketing Authorisation are necessary. Subsequent applications for a Type II variation (update of the statement in the SPC on the combination saquinavir/ritonavir and update of the SPC, including the implementation of a warning statement regarding the use of Norvir in diabetic patients) were submitted by the Marketing Authorisation Holder and Opinions were adopted by the CPMP on 19 November 1997. The respective Commission Decisions were issued on 17 March 1998.

  In July 1998 Abbott International notified the EMEA of manufacturing and batch release problems with the capsule due to the emergence of a new polymorphic form of ritonavir having a much-reduced solubility. This was considered by CPMP during the July 1998 meeting. Furthermore, a precipitation of the new polymorph had also been observed in the oral solution. Therefore, because of the foreseen supply shortage with the hard capsules, on 30 July 1998 the MAH submitted a request for an urgent safety restriction to the product literature for Norvir oral solution to enable patients to be transferred from the hard capsule to the oral solution. This request was to allow the oral solution to be stored out of the refrigerator, with a reduced shelf life and warning statements concerning storage and use. This urgent safety restriction was agreed on public health grounds in the interests of maintaining continuity of ritonavir therapy.

Revised, provisional SPC, label and package leaflet texts were adopted within the 24-hour timetable allowed for in this procedure. The hard capsules were subsequently no longer available for prescription.

- The MAH submitted a Type II variation application for Norvir 80 mg/ml oral solution, subsequent to the request by the MAH to introduce an urgent safety restrictions on 30 July 1998, in accordance to Commission Regulation (EC) 542/95 as amended. The CPMP adopted an Opinion on this variation on 16 September 1998 and the respective Commission Decision was issued on 11 January 1999.
- On 13 August 1998, the EMEA issued a notification on a Type I variation submitted by the MAH on 13 July 1998. This variation related to minor modifications to the synthetic process of ritonavir and as a consequence the tightening of the specification with respect to impurities.
- On 27 November 1998, the EMEA issued a notification on a Type I variation for Norvir 80 mg/ml submitted by the MAH on 18 September 1998. This variation related to the introduction of a new in-process control to confirm the absence of undissolved ritonavir crystals due to the low solubility of polymorphic Form II of ritonavir.
- The MAH submitted an application for a Type II variation on 14 April 1998 related to the extension of the indication for paediatric population. The variation procedure was extended in order to provided requested additional data on efficacy and safety to allow for further evaluation of the variation. On 19 November 1998, the CPMP adopted an Opinion on this variation and the respective Commission Decision was issued on 26 February 1999.
- The MAH submitted an application for variation on 15 October 1998 related to the update of the SPC (interaction section). On 19 November 1998, the CPMP adopted an Opinion on this variation and the respective Commission Decision was issued on 26 February 1999.
- Pursuant to CPMP discussion on cases of lipodystrophy and other metabolic disorders as reported from HIV infected patients and treated with protease inhibitors, the MAHs for the respective PIs submitted to the EMEA an application for a Type II variation to include a class labelling wording into the SPC. On 19 November 1998, the CPMP adopted an Opinion on this variation and the respective Commission Decision was issued on 26 February 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 as amended, the MAH provided throughout the year additional efficacy and safety data as stated in Annex II to Commission Decision, which formed the basis of the 2nd annual re-assessment of the risk/benefit profile of Norvir. On 1 September 1998, the MAH provided the documentation and the procedure for the annual re-assessment started on 18 September 1998. During its November CPMP plenary meeting, the CPMP agreed that the risk/benefit profile of Norvir remained favourable. The CPMP adopted on 19 November 1998 an Opinion on the annual re-assessment stating that no amendments to Annexes to Community Marketing Authorisation are necessary and that the MA should be kept under exceptional circumstances until all the specific obligations are fulfilled. The respective Commission Decision was issued on 23 February 1999.

Norvir 100 mg soft capsules

- The MAH submitted on 8 January 1999 an application for a marketing authorisation for Norvir 100 mg soft capsules under Annex II to Commission Regulation (EC) No 542/95 as amended. The procedure started on 29 January 1999 and the CPMP agreed on a consolidated list of questions on 21 April 1999.
- Additional data were provided by the MAH on 12 May 1999. The Inspection Services United Kingdom between 10-13 May 1999 carried out an inspection of the manufacturing site of the finished product (R.P. Scherer, USA) further to the request of the CPMP. The findings of the inspection are in compliance with the Community Good Manufacturing Practices requirements.
- An oral explanation was held before the CPMP on 27 July 1999 to address the quality of the product. The CPMP considered satisfactory the responses provided by the MAH. Amendments to the Summary of Product Characteristics and package leaflet were discussed and agreed.

- A letter of undertaking on the follow-up measures to be fulfilled post opinion was provided by the MAH on 27 July 1999.
- During its July CPMP meeting the CPMP in light of the overall data submitted and the scientific discussion within the Committee issued by consensus a positive opinion for the granting of a marketing authorisation for Norvir 100 mg soft capsules on 30 July 1999. The CPMP opinion was forwarded to the European Commission, which adopted the respective Decision on 29 November 1999.

Norvir 80 mg/ml and 100 mg soft capsules

- Pursuant to CPMP discussion on cases of rhabdomyolysis reported from HIV infected patients and treated with protease inhibitors, the Marketing Authorisation Holders for the respective protease inhibitors submitted to the EMEA an application for a Type II variation to include a class labelling wording into the SPC and consequently the Package Leaflet. On 30 July 1999, the CPMP adopted an opinion on this variation and the respective Commission Decision was issued on 29 November 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 as amended, the MAH provided throughout the year additional efficacy and safety data as stated in Annex II to Commission Decision, which formed the basis of the 3rd annual re-assessment of the risk/benefit profile of Norvir. On 25 August 1999, the MAH provided the documentation and the procedure for the annual re-assessment started on 24 September 1999. During its November CPMP plenary meeting, the CPMP agreed that the risk/benefit profile of Norvir remained favourable. The CPMP adopted on 12 November 1999 an Opinion on the annual re-assessment stating that no amendments to Annexes to Community Marketing Authorisation are necessary and that the MA should be kept under exceptional circumstances until all the specific obligations are fulfilled. The respective Commission Decision was issued on 9 March 2000.
- On 24 March 2000, the Commission issued a decision on the withdrawal of Norvir 100 mg hard capsules.
- 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 24 October 2000.
- On 8 May 2000, the MAH submitted two applications for a Type II variation. The first application related to an update the Summary of Product Characteristics to include new safety information following the evaluation of the previously submitted 5th and 6th Periodic Safety Update Reports for ritonavir. The second application related to the update of the Summary of Product Characteristics and Package Leaflet with respect to the therapeutic indication to reflect current medical practice for administration of protease inhibitors and with respect to the dosage recommendation to introduce a dose escalation regimen in order to improve the tolerance. Supplementary information was supplied by the Marketing Authorisation Holder on 7 September 2000 and on 4 January 2001. The CPMP adopted a favourable Opinion on 1 March 2001 and the respective Commission decision was issued on 14 June 2001.
- 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 as amended, the MAH provided throughout the year additional efficacy and safety data as stated in Annex II to Commission Decision, which formed the basis of the 4th annual re-assessment of the risk/benefit profile of Norvir. On 28 August 2000, the MAH provided the documentation and the procedure for the annual re-assessment started on 22 September 2000. During its December CPMP plenary meeting, the CPMP agreed that the risk/benefit profile of Norvir remained favourable. The CPMP adopted on 14 December 2000 an Opinion on the annual re-assessment stating that no amendments to Annexes to Community Marketing Authorisation are necessary and that there were no

remaining grounds for the Marketing Authorisation to be kept under exceptional circumstances since all specific obligations have been fulfilled. The respective Commission Decision was issued on 13 March 2001.

- On 29 September 2000, the MAH submitted an application for a Type I variation related to the change in test procedures of Norvir oral solution. On 15 November 2000, the EMEA approved the variation.
- On 2 November 2000, the MAH submitted an application for a Type I variation related to the introduction of a slightly different alternative method of manufacture of Norvir 100 mg soft capsules. On 12 January 2001, the EMEA approved the variation.
- On 1 December 2000, the MAH submitted an application for a Type I variation related to the addition of a manufacturing site for Norvir 100 mg soft capsules. On 5 January 2001, the EMEA approved the variation.

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
80 mg/ml oral solution only - Quality change (to introduce an alternative analytical method for the finished product)	II/0033	II	27.06.01	07.07.01
100 mg soft capsules only - Quality change (to comply with the European TSE Directive and Guidance)	II/0027	II	15.11.01	-
Renewal of the Marketing Authorisation	R/0029	R	27.06.01	12.11.01
The Marketing Authorisation Holder (MAH) applied to vary the Marketing Authorisation for Norvir 100 mg, Soft Capsules, by extending the shelf-life from 1 year to 2 years.	I/0034	I	26.10.01	17.12.01
The MAH applied to tighten the specification for 5-Wing HCl, one of the starting materials used in the manufacture of the ritonavir active substance, by tightening its purity limit, tightening all the limits for the impurities (specified and unspecified), tightening the limit for the residual solvent ethyl acetate, and specifying a new impurity.	I/0035	I	27.02.02	04.03.02
The MAH applied to amend the Summary of Product Characteristics (SPC) for 80 mg/ml oral Solution and 100 mg soft capsules with respect to section 4.5, "Interaction with other medicinal products and other forms of interaction". The proposed change is to add a statement on the interaction with amprenavir. The MAH have also taken this opportunity to make other minor changes and corrections to the SPC and the package leaflet.	II/0036	II	30.05.02	10.09.02
The MAH applied for a change in the GC method used for the identification and determination of Ethyl Alcohol in Norvir Soft Elastic Capsules and premix. The new GC method employs a capillary column instead of the packed column already used.	I/0037	I	3.10.02	10.10.02
The MAH applied for a change in the chromatographic conditions used for the content uniformity determination of retonavir in Norvir Soft Elastic Capsules.	I/0038	I	3.10.02	10.10.02
The MAH applied for a change in HPLC method for an improvement in the preparation procedure to reduce or eliminate interfering oleic acid excipient components. The chromatographic procedure remains unchanged.	I/0039	I	3.10.02	10.10.02

[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.

The MAH applied for an improvement of the identification of Polyoxyl 35 Castor Oil in Norvir Oral Solution and Norvir Soft Capsules. The current identification test (decolourisation of a bromide solution) is replaced by a GC method, monitoring the primary corresponding fatty acid methyl ester.	I/0040	I	3.10.02	10.10.02
The MAH applied for a change in HPLC method for the determination of related substances in Norvir Oral Solution.	I/0041	I	3.10.02	10.10.02
Changes to the Patient Leaflet local representatives address and telephone number for Greece, contact company name for Iceland and minor corrections in compliance with the template.	N/0043	N	17/10/02	07.11.02
The MAH applied to update section 4.4 and section 4.8 of the SPC further to the CPMP request to implement the class-labelling for "antiretroviral therapy (ART) and lipodystrophy" in the SPC. In addition, the MAH seeks to implement the CPMP recommendations on the 10th PSUR, affecting section 4.3 and 4.5 of the SPC. A change to the warfarin interaction statement in section 4.5 of the SPC is also proposed, further to the CPMP recommendations received on study report M01-291.	II/0044	II	19.03.03	14.07.03
The MAH applied to update section 4.2 and 4.4 of the SPC as a class labelling on liver impairment and anti-HIV products. Corresponding changes are made in the PIL, section 2 and 4. Lipodystrophy wording is also implemented in section 2 and 4 of the PL.	II/0045	II	20.01.03	27.01.04
The MAH applied to change the test method used to determine related substances in ritonavir.	I/0046	I	05.08.03	-
The MAH applied to change the name of manufacturing sites for Norvir soft capsule .	I/0047	I	07.10.03	-
The variation concerns an update to section 4.2 (Posology and method of administration) of the SPC, to mention the use of small ("baby") doses of ritonavir in combination with other antiretroviral therapy. Also, amendments to sections 4.5 to add the interaction with buspirone and 4.8 of the SPC, to include thrombocytopenia and menorrhagia. Consequential changes are included in sections 2 and 3 of the PL.	II/0048	II	21.01.04	25.03.04
To update section 4.5 "Interaction with other medicinal products and other forms of interaction" of the SPC to include an interaction with delavirdine. A consequential change is proposed in section 2 of the PL. In addition, SPC, PL and labelling have been updated to bring the storage conditions in line with current guidance. Minor typographical errors in the SPC are corrected and cross-references have been updated in line with QRD templates. In the PL, the list of local representatives has been updated to include the 10 new EU Member States and to update the address for the Spanish local representative.	II/0049	II	23.06.04	02.08.04
Change to batch release arrangements and quality control testing of the finished product – replacement or addition of a site where batch control/testing takes place	IA/0050	IA	21.09.04	-