STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

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

- On 9 January 1997, the Marketing Authorisation Holder (MAH) submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95. The MAH applied for a minor change to the manufacture of the active substance. The procedure was extended following the request of additional data and the EMEA approved on 20 March 1997 this variation.
- On 6 February 1997, the MAH submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 related to the addition of an alternative manufacturing site of the active substance. On 20 March 1997 the EMEA approved this variation.
- On 6 February 1997, the MAH submitted an application for a Type II variation in accordance with Commission Regulation (EC) No. 542/95 related to the implementation of a modified synthetic route of the active substance. This variation, which did not lead to any change to the Commission Decision, was adopted by the CPMP on 16 April 1997 and acknowledged by the Commission.
- 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 Invirase (e.g. results from the clinical endpoint studies). On 9 October, the MAH provided an updated expert report summarising the different specific obligations already submitted within the period October 1996-September 1997. The procedure started on 24 October 1997. During its January plenary CPMP meeting, the CPMP agreed with the Rapporteur's assessment report that the risk/benefit profile of Invirase remained favourable and that the MA should remain under exceptional circumstances until all the specific obligations are fulfilled. The CPMP adopted on 28 January 1998 an Opinion on the annual re-assessment of the specific obligations and the risk/benefit ratio, stating that amendments of Annexes I, II and IIIB to the Community Marketing Authorisation are necessary. Subsequent application for a Type II variation (update of the SPC) was submitted by the Marketing Authorisation Holder and the Opinion was adopted by the CPMP on 28 January 1998. Respective Commission Decision was issued on 12 May 1998.
- On 10 July 1998 the MAH submitted 4 applications for a Type I Variation in accordance with Commission Regulation (EC) No 542/95 as amended, related to changes in the test procedure of the active substance and extension of the shelf life. On 20 August 1998, the EMEA approved these variations.
- On 10 July 1998 the MAH submitted a Type II Variation in accordance with the Commission Regulation (EC) No 542/95 as amended, related to a change in the specification of the active substance. The variation, which did not lead to any change to the Commission Decision, was adopted by the CPMP on 16 September 1998, and acknowledged by the Commission.
- 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 second annual re-assessment of the risk/benefit profile of Invirase. On 9 October 1998, the MAH provided an updated expert report summarising the different specific obligations already submitted. The procedure started on 23 October 1998. During its December plenary CPMP meeting, the CPMP agreed with the Rapporteur's assessment report that the risk/benefit profile of Invirase remained favourable and that there was no remaining ground to keep the MA under exceptional circumstances since all the specific obligations have been fulfilled. The CPMP adopted on 16 December 1998 an Opinion on the annual re-assessment of the specific obligations and the risk/benefit ratio, stating that amendments of Annexes I, II and IIIB to the

Community Marketing Authorisation are necessary. Subsequent application for a Type II variation (update of the SPC) was submitted by the Marketing Authorisation Holder and the Opinion was adopted by the CPMP on 16 December 1998. Respective Commission Decision was issued on 8 April 1999.

- Pursuant to CPMP discussion on cases of lipodystrophy and other metabolic disorders as reported from HIV infected patients and treated with protease inhibitors (PIs), 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 25 February 1999.
- On 3 June 1999, the EMEA approved an application for a Type I variation related to a minor change of the manufacturing process of the active substance.
- 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 Summary of Product Characteristics 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.
- On 16 March 2000, the EMEA approved six applications for a Type I variation related to some minor changes of the manufacturing process of the active substance, changes in the suppliers of intermediate compounds used in manufacture of the active substance, a change in in-process controls applied during the manufacture of the product and an addition of a secondary packaging site.
- On 5 April 2000, the EMEA approved three applications for a Type I variation related to the addition of a manufacturing site of the medicinal product, some minor changes to the manufacturing process of the medicinal product and an alternative batch size of finished product.
- 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 20 October 2000.
- On 14 April 2000, the MAH applied for a Type II variation procedure related to the update of the Summary of Product Characteristics and Package Leaflet to include new safety information, particularly further to the evaluation of the Periodic Safety Update Reports and the review of specific safety issues by the CPMP and to harmonise with the product information of saquinavir soft capsules. On 21 September 2000, the CPMP adopted an Opinion on this variation and the respective Commission Decision was issued on 27 December 2000.

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
Minor change in labelling or package leaflet not connected with the SPC (Art. 10.3 Notification)	N/0028	N	20.06.00	27.07.00
Quality changes (to comply with the European TSE Directive and Guidance)	II/0029	II	25.04.01	04.05.01
Change in manufacturer(s) of the active substance	I/0030	I	04.05.01	10.05.01
Amendments of the Summary of Product Characteristics (SPC) and Package Leaflet (PL) following the revision of the Core Data sheet, the update of the class labelling on St. John's Wort, the evaluation of PSUR 11 and new information available on current treatment recommendation and clinical studies.	II-0032	II	30.05.02	10.09.02
The variation application relates to amendments of the SPC and PL following the revision of the Core Data sheet, the introduction of the class labelling on "antiretroviral therapy and lipodystrophy" and the update of the labelling on "Liver disease". It also seeks to modify section 5.1 of the SPC following CPMP assessment of the final study report on combination treatment with ritonavir (MaxCmin 1 study). Finally, section 4.8 of the SPC is re-arranged and minor amendments introduced in accordance with the QRD decisions.	II-0033	II	19.03.03	09.07.03
The variation application relates to amendments of the SPC and PL as a class labelling on liver impairment and anti-HIV products. A sentence on saquinavir target plasma concentrations has been added to section 5.2 of the SPC. Lipodystrophy harmonised wording is also implemented in section 2 and 4 of the PL. In addition, following CPMP assessment, a wording on the saquinavir- garlic interaction has been added to sections 4.3 and 4.5 of the SPC and point 2 of the PL. Minor revisions are made in the PL, updating contact addresses, also including Norway and Iceland.	II-0034	II	20.11.03	27.01.04

[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.

The MAH applied for F. Hoffmann- La Roche Ltd, Grenzacherst, 124. CH-4070 Basel Switzerland as an additional site for QC-testing and batch confirmation for capsules produced at F. Hoffmann-La Roche Lt d, Basel.	I/0035	I	06.10.03	06.10.03
The MAH applied to add a synthesis site for the intermediate chlorohydrin (steps 1 and 2 in the synthesis of saquinavir mesylate): Syntex SA de CV (Roche) - km 4.5 Carretera Federal Cuernavaca - Cuautla - 62500 CIVAC Jiutepec, Morelos - Mexico.	II/0040	II	22.04.04	-
Update of the SPC and PL to reflect the boosted dosing regimen more adequately. New pharmacokinetic findings on saquinavir interactions are added to SPC section 4.5, with consequential changes made in sections 4.2, 4.3, 4.4 and 5.2 and in the PL also reflecting the boosted dosing regimen. The SPC sections 4.2, 4.3, 4.4 and corresponding sections of the PL have been updated according to SPC Guidelines and "Note for Guidance " in the clinical development of HIV medicinal products. Main results of the MaxCmin 2 study have been added to SPC section 5.1. Section 4 of the PL has been brought in line with section 4.8 of SPC. Moreover, the SPC, PL and Annex II have been revised according to the latest Guidelines and QRD templates. The list of Local Representatives is updated in the PL.	II/0041	II	29.07.04	10.09.04
The MAH applied for a Notification in order to include the additional local representatives of the MAH for all 10 new European Member States and to present the list according to the latest EMEA/QRD Template.	N/0042	N	26.06.04	-