STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

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

- On 23 January 1998, the Marketing Authorisation Holder (MAH) submitted to the EMEA several applications for a Type I variation related to:
  - a change in the content of the manufacturing authorisation
  - a change in batch size of the finished product, deletion of a colorant in the tablets and to a change of the manufacturer of the active substance
  - minor modification of the manufacture of the active substance

  The EMEA issued the Notifications on these variation applications on 13 March 1998.
- On 23 January 1998, the MAH submitted to the EMEA two applications for a Type I variation related to the introduction of new manufacturing sites for the tablets and oral powder. The EMEA issued a notification on these two variations on 27 March 1998.
- Pursuant to CPMP discussion on cases of lipodystrophy and other metabolic disorders as 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. On 19 November 1998, the CPMP adopted an opinion on this variation and the respective Commission Decision was issued on 12 March 1999.
- On 4 December 1998 the MAH submitted an application for a Type II variation related to the implementation of additional information in the relevant parts of the Summary of Product Characteristics and Package leaflet with respect to an interaction with delavirdine and additional adverse reactions reported following post-marketing experience. The CPMP issued an Opinion on 22 April 1999 and the respective Commission Decision was issued on 30 July 1999.
- The MAH submitted to the EMEA on 8 February 1999 the documentation which formed the basis for the first annual re-assessment of the benefit/risk profile for Viracept pursuant to Article 13(2) of Council Regulation (EEC) No 2309/93 and Part 4 G of the annex to Council Directive 75/318/EEC. During its April 1999 plenary meeting, the CPMP adopted 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 European Commission amended the Decisions on 29 July 1999.
- On 11 February 1999, the MAH submitted several applications for a Type I variation related to the introduction of additional manufacturer of the finished product and the active substance, minor change in the manufacturing process of the active substance change in the test procedure of the medicinal product. The EMEA issued a notification on these variations on 8 April 1999.
- On 11 February 1999, the MAH submitted also two applications for a Type I variation related to a minor change in the manufacturing process of the active substance and change in the specifications of starting materials. The EMEA issued a notification on these variations on 5 May 1999.
- On 22 March 1999, the MAH submitted also an application for a Type I variation related to a change in the content of the manufacturing authorisation. The EMEA issued a notification on these variations on 22 June 1999.
- 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 16 November 1999.

- On 24 September 1999, the MAH submitted two applications for a Type I variation related to a change in the storage recommendations for the tablets and oral powder and the extension of the shelf life of the oral powder. The EMEA issued a notification on these variations on 26 November 1999.
- On 24 September 1999, the MAH submitted also two applications for a Type I variation related to an extension of the shelf life of the tablets and an addition of a large scoop to the existing dispensing scoop in the oral powder pack. The EMEA issued a notification on these variations on 23 December 1999.
- On 13 January 2000, the MAH submitted an application for a Type II variation for an update of the Summary of Product Characteristics and Package Leaflet following the availability of post authorisation data on interactions. The indication has also been updated to be in line with the general recommendation on antiretroviral products. In addition, the age of paediatric group has been amended from 2 years and over to 3 years and over. The CPMP issued an Opinion on 16 March 2000 and the respective Commission Decision was issued on 4 July 2000.
- On 17 January 2000, the MAH submitted two applications for a Type I variation related to a change in the manufacturer of the active substance and a change of the manufacturing site for part of the manufacturing process of the medicinal product. The EMEA issued a notification on these variations on 21 February 2000.
- On 17 January 2000, the MAH applied for an application for a Type I variation to change the manufacturing process for Viracept tablets to produce an improved tablet with higher tablet hardness. This change led to consequential changes in the in-process controls and tablet dimensions of Viracept tablets. The EMEA issued a notification on this variation on 23 February 2000.
- On 17 January 2000, the MAH submitted also an application for a Type I variation related to an extension of re-test period of the active substance. The EMEA issued a notification on these variations on 29 March 2000.
- The MAH submitted to the EMEA on 8 February 2000 the documentation which formed the basis for the second annual re-assessment of the benefit/risk profile for Viracept pursuant to Article 13(2) of Council Regulation (EEC) No 2309/93 and Part 4G of the annex to Council Directive 75/318/EEC. On 12 April 2000, the CPMP adopted 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 European Commission amended the Decisions on 13 July 2000.
- On 3 April 2000, the MAH applied for three applications for a Type I variation. The first application related to a change of the name of a manufacturer of medicinal product (secondary packaging site). The second application related to the addition of an additional site for the manufacture, primary packaging and secondary packaging/labelling of Viracept tablets. The third application related to the addition of a site for the spray drying of the active substance. This change led to a consequential variation to the description of this stage of the manufacturing process for the active substance. The EMEA issued a notification on these variations on 4 May 2000.
- On 7 September 2000, the MAH applied for five Type I variations. These variations related to a change in manufacturers of the active substance, a minor change in the manufacture of the medicinal product, a change in batch size of the finished product, a change of the manufacturing sites for part or all of medicinal product and a change in test procedures of the medicinal product. The EMEA issued a notification on these variations on 13 October 2000.
- 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 18 May 2000, the MAH submitted an application for a Type II variation to update the Summary of Product Characteristics and the Package Leaflet with respect to safety information following the assessment of the 4th Periodic Safety Update Report (PSUR). On 27 July 2000, the CPMP adopted an Opinion on this variation and the respective Commission Decision was issued on 16 November 2000.
- On 18 May 2000, the MAH submitted an application for a Type II variation to include in the Summary of Product Characteristics and the Package Leaflet an additional dosage recommendation for adult patients (i.e. twice daily dosage regimen). To support this change, the MAH provided supplementary information on 30 August 2000 and on 9 January 2001. On 1 March 2001, the CPMP adopted an Opinion on this variation and the respective Commission Decision was issued on 8 June 2001.
- *Viracept 250 mg film-coated tablets:*The MAH submitted on 19 July 2000 an application for a marketing authorisation for Viracept 250 mg film-coated tablets under Annex II to Commission Regulation (EC) No 542/95 as amended The procedure started on 16 August 2000. During its November 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 Viracept 250 mg film-coated tablets on 16 November 2000. The CPMP opinion was forwarded to the European Commission, which adopted the respective Decision on 5 March 2001.
- On 2 November 2000, the MAH submitted an application for a Type I variation related to a change in specification of the medicinal product. The EMEA issued a notification on this variation on 7 December 2000.
- On 3 November 2000, the MAH submitted an application for a Type II variation to demonstrate compliance with Commission Directive 1999/82/EC and the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products (CPMP/BWP/1230/98 rev.1). On 29 March 2001, the CPMP adopted an Opinion on this variation, which did not require any amendments to the Commission decision.
- On 7 December 2000, the MAH submitted an application for a Type II variation to update the Summary of Product Characteristics and subsequently the Package Leaflet further to the assessment of the 5th Periodic Safety Update Report and further to the availability of the results from the carcinogenicity studies. On 1 March 2001, the CPMP adopted an Opinion on this variation and the respective Commission Decision was issued on 8 June 2001.
- On 19 January 2001, the MAH submitted an application for a Type I variation to withdraw one manufacturing and primary packaging site of the finished product. The EMEA issued a notification on this variation on 14 February 2001.
- The MAH submitted to the EMEA on 20 February 2001 the documentation which formed the basis for the third annual re-assessment of the benefit/risk profile for Viracept pursuant to Article 13(2) of Council Regulation (EEC) No 2309/93 and Part 4G of the annex to Council Directive 75/318/EEC. On 25 April 2001, the CPMP adopted an opinion releasing Viracept from authorisation under exceptional circumstances. The European Commission amended the Decision on 1 August 2001.
- On 4 April 2001, the MAH submitted an application for a Type II variation to update the Summary of Product Characteristics and the Package Leaflet further for the film-coated tablet in line with the revisions adopted by the CPMP on 1 March 2001 related to adult twice daily dosing and safety revisions following CPMP assessment of the 5th PSUR. The respective Commission Decision was issued on 16 October 2001.
- On 4 May 2001, the MAH submitted three applications for a Type I variation to delete some manufacturing sites of the finished product, to withdraw some active substance manufacturing sites for all three pharmaceutical presentations and to revise test methods for the container for Viracept 250 mg film-coated tablet presentation. The EMEA issued notifications for these variations on 7 June 2001.

- On 4 May 2001, the MAH submitted one application for a Type I variation to add an additional pack size for the medicinal product (i.e the film-coated tablets). The EMEA issued a notification on this variation on 8 June 2001. The European Commission amended the Decision on 19 July 2001.

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
Article 10 (3) Notification to amend section 6 of Annex IIIB (Annexes included with EMEA notfication for I/77)	N/ 0074	N	29.10.01	05.02.02
Change in supplier of an intermediate compound used in manufacture of the active substance	I/0075	I	16.11.01	16.11.01
Replacement of an excipient with a comparable excipient (for 250 mg film-coated tablets)	I/0076	I	06.11.01	06.11.01
Change in the name of a manufacturer of the medicinal product	I/0077	I	29.10.01	05.02.02
Minor change of manufacturing process of the active substance	I/0078	I	16.11.01	16.11.01
Change in the address for Iceland included in section 6 of the Package Leaflet (Annex IIIB).	N/0079	N	04.02.02	04.02.02
To introduce changes in sections 4.2 (Posology and method of administration), 4.3 (Contraindications), 4.4. (Special warnings and special precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.8 (Undesirable effects) and Section 5.2 (Pharmacokinetic properties) of the Summary of Product Characteristics (SPC) following the CPMP assessment of the 6th PSUR and the third annual assessment (safety update). The Package Leaflet has been modified accordingly. In addition, Annex IIIA has been revised to be consistent with the latest EMEA QRD template.	II/0080	II	21.03.02	11 June 2002
The MAH applied to update the Summary of Product Characteristics (SPC) section 4.2 (posology and method of administration) (and the corresponding Patient Leaflet [PL] section) to include a twice daily (BID) dosing recommendation for children aged 3 to 13 years consistent with information in section 5.2 (pharmacokinetic properties) of the SPC approved in June 2001. Clinical pharmacodynamic data in SPC Section 5.1 (pharmacodynamic properties) has also been updated to reflect the clinical data on Viracept more accurately as it is currently used. In addition to the main revisions mentioned above, PL Section 6 (Other information) is also being updated to include changes to the address of the local representative in Ireland.	II/0081	II	26.07.02	10.09.02
Change in or addition of manufacturing site(s) for part or all of the manufacturing process	I/0082	I	06.09.02	16.09.02
Change in or addition of manufacturing site(s) for part or all of the manufacturing process.	I/0083	I	06.09.02	06.09.02
Change in test procedure of active substance.	I/0084	I	18.09.02	18.09.02
Change in test procedure of immediate packaging	I/0085	I	18.09.02	18.09.02
Change in test procedure of immediate packaging	I/0086	I	18.09.02	18.09.02

[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.

Pursuant to Article 13 of Council Regulation (EEC) No 2309/93 of 22 July 1993, as amended, Roche Registration Limited submitted to the EMEA on 9 September 2002 an application for a renewal of the Marketing Authorisation for Viracept oral powder, tablets and film-coated tablets (EU/1/97/054/001, 003 – 005).	R/0087	R	21.11.02	03.02.03
The MAH applied to update sections 4.4, 4.5, 4.6, 4.8 and 5.1 of the Summary of Product Characteristics (SPC) following conclusions made on the PSUR, covering the period 1 April 2001 to 31 March 2002. Relevant changes are also proposed for the Package Leaflet (PL).	II-0088	II	19.03.03	30.06.03
Pursuant to Article 2(1) of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended, and Annex II point 3(iii) thereof, MAH submitted to the EMEA on 07 May 2003 an Annex II application for the above mentioned medicinal product.	X-0089	X	21.01.04	28.04.04*
The variation concerns an update to sections 4.4 and 5.2 of the Summary of Product Characteristics (SPC) and section 2 of the Package Leaflet (PL) to implement the class labelling on liver impairment adopted by the CPMP for all anti-retroviral medicinal products on 25 April 2003. Lipodystrophy wording is also implemented in sections 2 and 4 of the PL as adopted by the CPMP on 19 March 2003. In addition, following CPMP assessment, a wording on the QT prolongation is proposed to sections 4.9 and 5.3 of the SPC. Minor revisions are made in the SPC and in the PL new contact information is provided for Norway and Netherlands.	II-0090	II	20.11.03	27.01.04
Addition of Basel as a site for QC testing for the oral powder presentation further to the Mutual Recognition agreement with Switzerland.	I-0091	I	24.09.03	-
Deletion of the site for spray drying of the active substance Atlantic Pharmaceuticals Services Inc., USA.	I-0092	I	24.09.03	-

* On 05 November 2004, the MAH notified the EMEA that the 625mg film-coated tablets will not be launched.