STEPS TAKEN AFTER THE MARKETING AUTHORISATION

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

- On 13 February 1997 the Marketing Authorisation Holder submitted to the EMEA two applications for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995. The scope of the first variation related to the extension of shelf life. The second variation related to the change of batch size of the active substance. On 10 April 1997, the EMEA approved these variations. Only the first variation required amendments to the Annex I (Summary of Product Characteristics) of the Commission Decision. The European Commission amended the Decision on 13 June 1997.
- On 8 April 1997 the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation in accordance with Commission Regulation No. 542/95. This application was related to the update of the Summary of Product Characteristics and of the Package Leaflet on the basis of the results of the evaluation of a previously submitted Periodic Safety Update Report and on results from interaction studies with rifabutin and rifampicin as required in the follow-up measures to which the Marketing Authorisation Holder is subject. The implementation of this variation was accelerated by the application of an urgent safety measure procedure (Art 1(2) of Commission Regulation (EC) No. 542/95). The EMEA agreed on 15 May 1997 on the urgent introduction of modifications in the Summary of Product Characteristics and in the Package Leaflet. The CPMP confirmed the acceptability of the corresponding Type II variation and issued a favourable opinion. This opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 27 August 1998.
- Pursuant to article 10(3) of Council Directive No. 92/27/EEC of 31 March 1992, the Marketing Authorisation Holder notified the EMEA on 14 July 1997 of their intention to introduce changes to the labelling. On 21 July 1997 the CPMP issued a favourable opinion, and the European Commission amended the Decision on 1 October 1997.
- On 4 July 1997, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation in accordance with Commission Regulation No. 542/95. This application was related to the update of the Summary of Product Characteristics and of the Package Leaflet on the basis of the results of the evaluation of a Periodic Safety Update Report covering the period from 13 September 1996 to 13 March 1997. The scope of the variation related to information on bioavailability, interaction with warfarin, hyperglycaemia/diabetes mellitus, alopecia and other adverse reactions. The CPMP issued a positive opinion on the Type II variation on 24 September 1997 and the European Commission amended the Decision on 22 January 1998.
- The Marketing Authorisation Holder submitted to the EMEA on 2 September 1997 the documentation which formed the basis for the annual re-assessment of the benefit/risk profile for Crixivan 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 December 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. Subsequent, simultaneous applications for a Type II variation (update of SPC and Package Leaflet) were submitted by the Marketing Authorisation Holder and respective opinions were adopted by the CPMP on 17 December 1997. The European Commission amended the Decisions on 8 and 29 April 1998 respectively.
- The Marketing Authorisation Holder submitted to the EMEA on 24 December 1997 eight Type I variations related to part II (chemical/pharmaceutical) of the dossier in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995. Only 2 variations related to changes in the SPC; one related to the colour of the capsules and the other to the extension of shelf life for the 400 mg capsule. The European Commission amended the Decision on 13 May 1998.

- On 6 February 1998 the Marketing Authorisation Holder submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 related to a change in the test procedure of the medicinal product. The EMEA approved the variation on 12 March 1998. This variation did not require any amendments to the Commission Decision.
- On 23 February 1998 the Marketing Authorisation Holder submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 related to a change in the test procedure of the active substance. The EMEA approved the variation on 24 March 1998. This variation did not require any amendments to the Commission Decision.
- On 27 January 1998 the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to the update of the SPC. The CPMP, during its February plenary meeting, considered the changes acceptable, and issued on 25 February 1998 a favourable opinion on the Type II variation. This opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 24 June 1998.
- On 15 April 1998 the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to the update of the SPC and the Package Leaflet. The CPMP, during its June plenary meeting, considered the changes acceptable, and issued on 24 June 1998 a favourable opinion on the Type II variation. This opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 29 October 1998.
- On 16 June 1998 the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation to introduce a new package size for the 400 mg capsules. The CPMP issued a favourable opinion 23 July 1998. This opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 6 November 1998.
- On 4 August 1998, the Marketing Authorisation Holder submitted to the EMEA an application for Crixivan 333 mg hard capsules, under Annex II to Commission Regulation (EC) 542/95 as amended. The CPMP recommended the approval for this additional strength and adopted an opinion on 17 December 1998. The respective Commission Decision was issued on 13 April 1999.
- On 8 October 1998, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to the update of the SPC and Package Leaflet. The CPMP, during its December plenary meeting, considered the changes acceptable, and adopted on 17 December 1998 a favourable opinion on the Type II variation. The corresponding Commission Decision was issued on 19 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, 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. On 19 November 1998, the CPMP adopted an opinion on this variation and the respective Commission Decision was issued on 12 March 1999.
- On 23 December 1998, the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation related to the addition of a manufacturing site for blister labelling. The EMEA approved this variation on 17 February 1999 which did not require any amendments to the Commission Decision.
- On 23 March 1999, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to the update of the SPC, and consequently the Package Leaflet following the availability of new interaction data with other medicinal products. At this occasion, the SPC, Labelling and Package Leaflet have been amended in line with the new EMEA/QRD Template. The CPMP, during its July plenary meeting, considered the changes acceptable, and adopted on 30 July 1999 a favourable opinion on the Type II variation. The corresponding Commission Decision was issued on 8 December 1999.

- On 7 June 1999, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to modifications in the in-process controls. The CPMP, during its July plenary meeting, considered the changes acceptable, and adopted on 30 July 1999 a favourable opinion on the Type II variation. This variation did not lead to any changes to Annexes to Commission Decision.

- 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 8 December 1999.

- On 9 July 1999, the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation related to the extension of the shelf life. The EMEA approved this variation on 25 August 1999, which required amendments to Annexes of the Commission Decision.

- On 3 August 1999, the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation related to a minor of the manufacturing process of the medicinal product with a minor consequential change of the manufacturing process of the active substance.

- On 21 September 1999, the Marketing Authorisation Holder submitted to the EMEA three applications for a Type I variation. The applications related to:

  - a new pack size (75 ml high-density polyethylene bottle containing 18 Crixivan 400 mg hard capsules).
  - change in the qualitative composition of immediate packaging material for Crixivan aluminium blister 400 mg, 42 hard capsules.
  - change in the shelf-life of Crixivan 400 mg, 42 hard capsules blister from 15 months to 24 months.

  The EMEA approved these variations on 27 October 1999, which required amendments to Annexes of the Commission Decision.

- On 4 November 1999, the Marketing Authorisation Holder submitted a Type II variation application related to the update of the Summary of Product Characteristics, and consequently Package Leaflet following the availability of new interaction data of indinavir with other medicinal products (sildenafil and saquinavir), new pharmacokinetics data in females and new safety data. The CPMP considered the changes acceptable, and adopted on 19 January 2000 a favourable opinion on the Type II variation. The subsequent Commission Decision was issued on 11 May 2000.

- On 7 January 2000, the Marketing Authorisation Holder submitted to the EMEA two applications for a Type I variation. The applications related;

  - The addition of a batch release site for blister packs of Crixivan 400 mg.
  - The addition of a pack size for Crixivan 400 mg hard capsules (blister pack containing 180 hard capsules).

  The EMEA approved these variations on 10 February 2000, which required amendments to Annexes of the Commission Decision.

- Pursuant to article 10(3) of Council Directive No. 92/27/EEC of 31 March 1992, Merck Sharp & Dohme Ltd notified the EMEA on 4 February 2000 of their intention to introduce changes to aspects of the Labelling not connected to the Summary of Product Characteristics.

  (Amendments of the name of the Marketing Authorisation Holder on the blister card to include the country of origin). The EMEA approved this notification on 10 February 2000.

- On 9 March 2000, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to the update of the Summary of Product Characteristics and Package Leaflet to include new information on interactions with *Hypericum perforatum* (St

John's wort) and pimozide. The CPMP considered the changes acceptable, and adopted on 16 March 2000 a favourable opinion on the Type II variation. The subsequent Commission Decision was issued on 5 July 2000.

- The MAH submitted on 6 January 2000 an application for a marketing authorisation for Crixivan 100 mg hard capsules under Annex II to Commission Regulation (EC) No 542/95 as amended. This low strength was intended to be indicated for children of 4 years of age and older who are able to swallow capsules. The procedure started on 21 January 2000 and the CPMP agreed on a consolidated list of questions on 25 May 2000. Additional data were submitted by the MAH on 5 June 2000. During its June meeting, the CPMP, in light of the overall data submitted and the scientific discussion within the Committee, issued by consensus a positive opinion for granting a Marketing Authorisation to Crixivan 100 mg hard capsules on 29 June 2000. The CPMP opinion was forwarded to the European Commission which adopted the respective Decision on 16 November 2000.On 17 October 2000, the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation related to a minor changes in manufacture of the medicinal product. The EMEA approved this variation on 20 November 2000.

- On 1 December 2000, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related to the update of the Summary of Product Characteristics and Package Leaflet to harmonise the information between the different strengths of Crixivan, to be in accordance with the current Guideline on Summary of Product Characteristics (December 1999) and to amend some wordings related to interaction data. The CPMP considered the changes acceptable, and adopted on 1 March 2001 a favourable opinion on the Type II variation. The subsequent Commission Decision was issued on 8 June 2001

- On 1 December 2000, the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation related changes to the manufacture of the active substance and control methods for the active substance, intermediates and starting material. The CPMP considered the changes acceptable, and adopted on 1 March 2001 a favourable opinion on the Type II variation, which did not lead to any amendments of the Annexes to the Commission Decision.

- On 4 December 2000, the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation related to a change of the imprint on the 100 mg hard capsules. The EMEA approved this variation on 20 December 2000.

- On 26 February 2001, the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation related to compliance with supplements to Pharmacopoeias. The EMEA approved this variation on 28 March 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
Change in weight of capsule shells	I/0046	I	01.06.01	-
Replacement of an excipient with a comparable excipient	I/0047	I	01.06.01	-
Change in test procedure of the medicinal product, with a consequential change in the specification of the medicinal product	I/0048	I	01.06.01	-
The Marketing Authorisation Holder (MAH) applied to update section 4.5 of the Summary of Product Characteristics (SPC) with respect to potential for drug interactions between indinavir and calcium channel blockers and to update section 4.8 of the SPC with references to anemia, cerebrovascular disorders, hypersensitivity vasculitis and thrombocytopenia based on post-marketing reports. Relevant sections of the Patient leaflet (PL) are updated accordingly.	II/0050	II	13.12.01	21.03.02
To update the analytical methods in the three higher strengths (200, 333 and 400 mg) in order to be in alignment with those approved for the 100 mg strength. The marketing authorisation holder takes the opportunity to correct typographical errors, to define the standard solution absorbance and to add information for analyst in all strengths. Moreover, the test method for assay of cis-aminoindanol in HPLC method is updated for the strength of 100mg.	II/0051	II	30.05.02	07.06.02
The (MAH) applied to update section 4.4 and section 4.5 of the Summary of Product Characteristics (SPC) further to the CPMP request to implement the class labeling adopted for protease inhibitors with regard to the risk of myopathy, including rhabdomyolysis, when co-administered with HMG-CoA reductase inhibitors. In addition to a request by the CPMP, section 5.2 of the SPC is updated with information on the circadian rhythm in the kinetics of indinavir.	II/0052	II	27.06.02	17.10.02
The (MAH) applied for the use of sodium hypochlorite in place of N-chlorosuccinimide for the formation of the iodohydrin intermediate (transition from Compound IVa to IVb) in Step 3 of the indinavir process, as an alternative process to the already approved one.	I/0053	I	12.07.02	15.07.02
Change of the address of the manufacturing site. The new address is South 2778 South East Highway, Elkton, Virginia. The manufacturing site will remain the same.	I/0054	I	10.09.02	17.09.02
Change of the amount of capsules used for manufacture due to revised individual capsule target weight. The new target weights are within 1-2 mg of the original values. The manufacturing formulas for Crixivan 100 mg, 200 mg, 333 mg and 400 mg are updated so that the weight of capsules used and total batch weight are calculated based on the new target capsule weight.	I/0055	I	10.09.02	17.09.02
Change in the 400 mg Crixivan hard capsules batch size from 1940 kg to either 1875 kg or 1834 kg. This change is due to the use of part of the total blended granulation for the manufacture of the 100 mg Crixivan hard capsules.	I/0056	I	10.09.02	17.09.02
The MAH applied to update section 4.4, section 4.5 and section 4.8 of the (SPC), with regard to the interstitial nephritis in patients with asymptomatic severe leukocyturia and with regard to indinavir/ritonavir drug interaction. In addition, a minor editorial amendment is proposed to the PL, clarifying the dosing regimen.	II/0057	II	20.02.03	08.05.03
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 and lipodystrophy" in the SPC.	II/0058	II	19.03.03	26.06.03
The MAH applied for a 2-year retest period for indinavir sulfate. In addition, the Marketing authorisation holder took the opportunity to correct an editorial error in the dossier	I/0059	I	26.06.03	-

[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

The MAH applied to update sections 4.2, 4.4, 5.2 of the SPC as a class labelling on liver impairment and anti-HIV products. Relevant changes are equally proposed for the Package Leaflet (PL), section 2. Lipodystrophy wording is also implemented in the PL, sections 2 and 4.	II/0060	II	20.11.03	30.01.04
Extension of the shelf life of Crixivan 100 mg hard capsules from 2 to 3 years.	I/0061	I	28.08.03	-
Change in batch size of the finished product - downscaling down to 10-fold	IA/0062	IA	25.03.04	-
To update of the Package Leaflet (PL) in order to include the additional local representatives of the MAH for all 10 new European Member States and to revise the format of the list in line with the latest EMEA/ QRD template.	N/0063	N	20.05.04	-
To update section 4.6 (Pregnancy and lactation) and 5.2 (Pharmacokinetic properties) of the Summary of Product Characteristics (SPC) with results of study PACTG358, concerning pharmacokinetics in pregnant women. In addition, the statements on lactose in section 4.4 (Special warnings and special precautions for use) of the SPC and section 2 of the Package leaflet (PL) were revised for consistency with the current Guideline on Excipients. Additional editorial changes were made throughout the SPC and the PL.	II/0064	II	29.07.04	09.09.04
Deletion of 42 and 180 hard capsule pack sizes for Crixivan 400 mg.	IA/0065	IA	20.08.04	-

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.