Steps taken after granting the Marketing Authorisation

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

- On 13 September 1996, the Marketing Authorisation Holder submitted two Type I Variations in accordance with Commission Regulation (EC) No. 542/95. These variations related to a new analytical method for assay and determination of related substances in the active substance and the medicinal product. On 23 October 1996, the EMEA approved these variations, which do not require an amendment to the Commission Decision.
- On 25 April 1997, the Marketing Authorisation Holder submitted a Type II Variation in accordance with Commission Regulation (EC) No. 542/95. This variation concerned amendments of sections 4.2, 4.4 and 5.2 of the SPC in accordance with the recommendation of the CPMP following evaluation of follow-up measures submitted by the Marketing Authorisation Holder in December 1996. On 18 June 1997, the CPMP adopted a positive opinion on this Type II variation, and the respective Commission Decision was issued on 8 October 1997. On 16 December 1997, the Marketing Authorisation Holder submitted a Type II Variation in accordance with Commission Regulation (EC) No. 542/95 as amended. This variation updated the SPC (sections 4.1, 4.2, 4.4, 4.5, 4.8, 8 and 9) and the PL as recommended by the CPMP following assessment of the PSUR and data submitted according to the obligations placed on the MAH. On 25 February 1998, the CPMP adopted a positive opinion on this Type II variation. The amendments included an additional paragraph on a Japanese clinical trial under the heading "Further information on Clinical Trials" in the SPC and the addition of "pancreatitis" as an undesirable effect. The respective Commission Decision was issued on 15 June 1998.
- On 5 July 1999, the Marketing Authorisation Holder submitted a Type II Variation in accordance with Commission Regulation (EC) No. 542/95 as amended. This variation updated the SPC with respect to information on overdose and the results of carcinogenicity studies. (sections 4.9 overdose and 5.3 preclinical safety) The procedure started on 30 July 1999. On 23 September 1999, the CPMP adopted a positive opinion on this Type II variation. The respective Commission Decision was issued on 31 January 2000.
- On 23 November 1999, the Marketing Authorisation Holder submitted 3 Type I Variations in accordance with Commission Regulation (EC) No. 542/95. These variations related to a Minor change of manufacturing process of the active substance with a subsequent change in specifications of starting material or intermediate used in the manufacture of the active substance; a change in test procedure for an intermediate used in the manufacture of the active substance; and an increase in the batch size of the active substance. On 20 December 1999, the EMEA approved these variations, which do not require an amendment to the Commission Decision.
- On 19 July 2000, the Marketing Authorisation Holder submitted 3 Type I Variations in accordance with Commission Regulation (EC) No. 542/95 to change the name of the Marketing Authorisation Holder from Rhône-Poulenc Rorer S.A. to Aventis Pharma S.A.; to change the name of the manufacturer of the finished medicinal product and the name of the active substance manufacturer from Rhône-Poulenc Rorer Pharmaceuticals Ltd to Aventis Pharma (Nenagh) Limited. The EMEA requested updated product literature from the applicant prior to validation and this was received on 17 August 2000. The EMEA issued a positive notification on 15 September 2000. The respective Commission Decision was issued on 29 December 2000.
- Pursuant to Article 13 of Council Regulation (EEC) No 2309/93 of 22 July 1993, as amended, Aventis Pharma S.A., France submitted to the EMEA on 14 February 2001 an application for a renewal of the Marketing Authorisation. The procedure started on 2 March 2001. On 25 April 2001, the CPMP adopted a positive opinion on the Renewal. The corresponding Commission Decision was issued on 11 July 2001.

- On 9 November 2001, the Marketing Authorisation Holder submitted a Type I Variation in accordance with Commission Regulation (EC) No. 542/95 as amended. The variation related to an extension of the shelf-life of the tablets from 2 to 3 years. The EMEA issued the Notification for this variation on 11 December 2001.
- On 10 January 2002, the Marketing Authorisation Holder submitted three Type I Variations in accordance with Commission Regulation (EC) No. 542/95 as amended. One variation related to an additional site of manufacturing, packaging and batch release site of the finished product. The EMEA issued a Notification for this variation on 12 February 2002. One variation related to a minor change in the manufacture of the finished product. The EMEA issued a Notification for this variation on 21 February 2002. One variation relates to a change in batch size of the finished product. The EMEA issued a Notification for this variation on 15 February 2002.
- On 17 June 2002, the Marketing Authorisation Holder submitted a Type II Variation in accordance with Commission Regulation (EC) No. 542/95, as amended. The Marketing Authorisation Holder applied for an update of section 5.2 and section 5.3 of the SPC following additional pharmacokinetics and toxicity studies. The company also used the opportunity to change the ATC code following the updated ATC classification, to update names/addresses of local representatives in the PL and to correct spelling mistakes in the German SPC and PL. The CPMP considered the variation acceptable and issued on 22 August 2002 a positive Opinion. The respective Commission Decision was issued on 20 November 2002.
- On 23 September 2002, the Marketing Authorisation Holder submitted a Type I Variation in accordance with Commission Regulation (EC) No. 542/95 as amended. The variation related to minor changes in manufacture of the medicinal product. The EMEA issued the Notification for this variation on 29 October 2002.
- On 8 January 2003, the Marketing Authorisation Holder submitted a Type II Variation in accordance with Commission Regulation (EC) No. 542/95, as amended. The Marketing Authorisation Holder applied for an update of the Summary of the Product Characteristics, Package Leaflet and labelling to comply with the current QRD template and to implement other linguistic improvements and correction of typographical errors. In addition the MAH took the opportunity to withdraw Aventis Pharma Nenagh Limited (Ireland) as manufacturing site for batch manufacture, testing, package and release for RILUTEK. The CPMP considered the variation acceptable and issued on 19 March 2003 a positive Opinion. The respective Commission Decision was issued on 22 June 2003