STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 1 October 2003 please refer to module 8B

- On 6 April 1999 the Marketing Authorisation Holder (MAH) submitted an application for a type II variation in connection with an extension of the indications to include treatment of postmenopausal osteoporosis. At the same time the MAH applied for an update of the Summary of Product Characteristics (SPC), Package Leaflet (PL) and labelling to take into account the latest Quality Review of Documents Group recommendations. The CPMP adopted a positive Opinion by a majority of 20 out of 26 votes with 2 abstentions on 18 November 1999. The respective Commission decision was issued on 24 March 2000.
- On 16 July 1999 the MAH submitted an application for a type II variation in connection with an update the undesirable effects section in the SPC and PL to include very rare cases of rash and gastrointestinal symptoms. This followed the submission of the first Periodic Safety Update Report (PSUR) (covering the period from 09 December 1997 to 08 December 1998) whereby the CPMP requested that this section be updated. The ATC code is now been assigned and has been included at the relevant section of the SPC. The CPMP adopted a positive Opinion 23 September 1999. The respective Commision Decision was issued on 31 January 2000.
- On 25 April 2000 the MAH submitted to the EMEA an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was to add new maximum batch size for the finished product. The procedure started on 27 April 2000. The EMEA notified the European Commission on 7 July 2000 that the variation was accepted and did not require any amendments to the Community Marketing Authorisation.
- On 20 December 2000 the MAH submitted to the EMEA an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was to change the address of the MAH. The procedure started on 5 January 2001. The EMEA notified the European Commission on 25 January 2001 that that the variation was accepted. Amendments to the Annexes I, IIIA and IIIB were required and the Commission Decision was issued on 6 March 2000.
- On 8 February 2001, the MAH submitted to the EMEA an application for a type II variation in accordance with Article 6 of Commission Regulation (EC) 542/95 as amended. The scope of this variation was to update the SPC and PL in order to reword and move the contraindication related to the use of Optruma in patients with signs and symptoms of breast cancer to section 4.4 of the SPC and to the warning section of the PL. In addition, to add a new warning in section 4.4 and the warning section of the PL for the use of Optruma women who have a history of marked elevations in triglycerides in response to oral oestrogen. Moreover, to add two undesirable effects to section 4.8 of the SPC and undesirable effects section of the PL based on the 4th PSUR covering the period 9 December 1999 to 8 June 2000. The CPMP adopted a positive Opinion for this variation on 27 June 2001. The respective Commission Decision was issued on 31 October 2001.
- On 20 April 2001 the MAH submitted to the EMEA an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was to change the currently registered specifications for purified water in order to comply with the requirements of the Ph. Eur. Monograph for purified water in bulk. The procedure started on 27 April 2001. The EMEA notified the European Commission on 18 May 2001 that that the variation was accepted and did not require any amendments to the Community Marketing Authorisation.
- On 12 June 2001 the MAH submitted to the EMEA an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was a minor change of manufacturing process of the active substance. The

procedure started on 19 June 2001. The EMEA notified the European Commission on 13 July 2001 that the variation was accepted and did not require any amendments to the Community Marketing Authorisation.

- Pursuant to article 61(3) of Council Directive No. 2001/83/EC of 6 November 2001, the MAH notified the EMEA on 7 February 2002 of their intention to introduce changes to an aspect of the Package Leaflet not connected to the Summary of Product Characteristics. On 5 March 2002, the EMEA notified the European Commission that the changes were accepted and the respective Commission Decision was issued on 19 April 2002.
- On 11 March 2002 the MAH submitted to the EMEA an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was to add a new packaging site and rename an authorised packaging site. The procedure started on 15 March 2002. The EMEA notified the European Commission on 15 April 2002 that the variation was accepted and did not require any amendments to the Community Marketing Authorisation.
- On 5 August 2002 the MAH submitted to the EMEA an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was to add a manufacturing site. The procedure started on 13 August 2002. The EMEA notified the European Commission on 11 September 2002 that the variation was accepted and did not require any amendments to the Community Marketing Authorisation.
- On 22 August 2002 the MAH submitted to the EMEA an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was a change to the qualitative composition of immediate packaging material. The procedure started on 23 August 2002. The EMEA notified the European Commission on 2 October 2002 that the variation was accepted and did not require any amendments to the Community Marketing Authorisation.
- Pursuant to article 61(3) of Council Directive No. 2001/83/EC of 6 November 2001, the MAH notified the EMEA on 4 October 2002 of their intention to introduce changes to an aspect of the Package Leaflet not connected to the Summary of Product Characteristics. On 11 October 2002, the EMEA notified the European Commission that the changes were accepted and the respective Commission Decision was issued on 7 November 2002.
- Pursuant to article 61(3) of Council Directive No. 2001/83/EC of 6 November 2001, the MAH notified the EMEA on 21 October 2002 of their intention to introduce changes to an aspect of the PL not connected to the SPC. On 31 October 2002, the EMEA notified the European Commission that the changes were accepted and the respective Commission Decision issued on 20 November 2002.
- Pursuant to article 61(3) of Council Directive No. 2001/83/EC of 6 November 2001, the Marketing Authorisation Holder notified the EMEA on 18 December 2002 of their intention to introduce changes to an aspect of the Package Leaflet not connected to the Summary of Product Characteristics. On 10 January 2003, the EMEA notified the European Commission that the changes were accepted. Amendments to the Annex III were required and the Commission Decision was issued on 31 January 2003.
- On 27 September 2002 the MAH submitted to the EMEA an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was to add an additional manufacturing site for control testing of bulk substance. The procedure started on 9 October 2002. The EMEA notified the European Commission on 9 November 2002 that the variation was accepted and did not require any amendments to the Community Marketing Authorisation.
- On 18 December 2002 the MAH submitted to the EMEA an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was to include an additional manufacturing facility for packaging and batch release. The procedure started on 20 December 2002. The EMEA notified the European

Commission on 14 January 2003 that the variation was accepted and the respective Commission Decision was issued on 14 February 2003.

- For the first renewal of Optruma, the CPMP was of the opinion that the quality, safety and efficacy of this medicinal product continued to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile continued to be favourable for the authorised indications and issued on 22 May 2003 a positive opinion for the renewal of the Community Marketing Authorisation. The respective Commission Decision was issued on 28 July 2003.
- On 30 April 2003 the MAH submitted to the EMEA an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was to replace an excipient with a comparable excipient. The procedure started on 5 May 2003. The EMEA notified the European Commission on 14 May 2003 that the variation was accepted and did not require any amendment to the Community Marketing Authorisation.
- On the 20 December 2002, the MAH submitted to the EMEA an application for a type II variation in accordance with Article 6 of Commission Regulation (EC) 542/95 as amended. The scope of this variation was to update the SPC sections 4.4, 4.8 and 5.1 on the basis of new clinical efficacy and safety data from the cumulative 4-year results from the osteoporosis treatment study. The EMEA notified the European Commission 19 March 2003 that the variation was accepted and the respective Commission Decision was issued on 26 June 2003.
- Pursuant to article 61(3) of Council Directive No. 2001/83/EC of 6 November 2001, the MAH notified the EMEA on 26 June 2003 of a change of the company labelling of the logo and branding design (colour, lay out). On 21 July 2003 the EMEA notified the MAH that the change was acceptable.