STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

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

- On 28 November 1996, the European Commission approved three Variations (Type I, 60 days procedure) for the following changes:
  - Manufacturer of active substance;
  - Batch size of active substance;
  - Test procedure of active substance.

- On 20 January 1997 (dated on notification 4 September 1996), the European Commission approved the transfer of the Marketing Authorisation Holder from Organon Ireland to N.V. Organon, The Netherlands. The relevant amendments have been incorporated in the relevant sections of the Commission Decision and of this EPAR.

- On 3 April 1997, the European Commission approved three Variations (Type I following type II) for the addition of new batch release sites. The relevant amendments have been incorporated in the relevant sections of the Commission Decision and of this EPAR.

- On 5 October 1998, the European Commission approved a Variation (Type II) for the following changes: amendments to the SPC and PL in order to give additional guidance to avoid injection of large volumes and to reduce pain at injection sites. Amendments have been incorporated in the relevant sections of the Commission Decision and of this EPAR.

- On 26 April 1999, the European Commission approved an Annex II application (Extension of the Marketing Authorisation) for 7 additional strengths/pharmaceutical forms. Amendments have been incorporated in the relevant sections of the Commission Decision and of this EPAR.

- Pursuant to article 10(3) of Council Directive No. 92/27/EEC of 31 March 1992, the Marketing Authorisation Holder notified the EMEA on 5 May 1999 of their intention to introduce changes to an aspect of the labelling not connected to the Summary of Product Characteristics. On 28 May 1999, the EMEA notified the European Commission that the changes were accepted. Amendments to Annex IIIA were required and the Commission Decision was issued on 8 July 1999.

- The CPMP issued on 23 September 1999 a positive Opinion on a Type II variation relating to a change in the release testing of the active substance. The Commission Decision was amended on 22 December 1999.

- The CPMP issued on 14 December 1999 a positive Notification on a Type I variation relating to a change in the release testing of the active substance. The Commission Decision was amended on 22 December 1999.

- The CPMP issued on 23 September 1999 a positive Opinion on an application in accordance with Annex II to Commission Regulation (EC) No. 542/95, as amended for 2 additional strengths (multidose preparations). The corresponding Commission Decision was issued on 10 February 2000.

- The CPMP issued on 23 September 1999 a positive Opinion on a Type II variation relating to amendments to the Summary of Product Characteristics and Package Leaflet to update the posology section. The Commission Decision was amended on 21 February 2000.

- Pursuant to article 10(3) of Council Directive No. 92/27/EEC of 31 March 1992, the Marketing Authorisation Holder notified the EMEA on 24 September 1999 of their intention to introduce changes to an aspect of the Labelling and Package Leaflet not connected to the Summary of
Product Characteristics. On 21 October 1999, the EMEA notified the European Commission that the changes were accepted. Amendments to Annex III were required and the Commission Decision was issued on 21 February 2000.

- Pursuant to article 10(3) of Council Directive No. 92/27/EEC of 31 March 1992, the Marketing Authorisation Holder notified the EMEA on 29 February 2000 of their intention to introduce changes to an aspect of the Labelling not connected to the Summary of Product Characteristics. On 7 April 2000, the EMEA notified the European Commission that the changes were accepted. Amendments to Annex IIIA were required and the Commission Decision was issued on 11 July 2000.

- The CPMP issued on 29 June 2000 a positive Opinion on a Type II variation to include an extra precaution regarding a possible increased risk for thrombosis in women with recognised risk factors in the Summary of Product Characteristics and Package Leaflet. Secondly, a sentence on possible interaction of Puregon and GnRH agonists was adapted to reflect the recent approval of GnRH antagonists. Thirdly, in the SPC for the powder and solvent for solution for injection, a warning on possible hypersensitivity and a statement on antibody formation were deleted. This was done to bring the text for the powder and solvent for solution for injection, in line with the recently approved text for the solution for injection. The Commission Decision was amended on 8 December 2000.

- The CPMP issued on 27 June 2000 a positive Opinion on a Type II variation to include a change in storage conditions for the Puregon solution for injection (vials and multidose cartridges) in the Summary of Product Characteristics, Labelling and Package Leaflet. Stability data were provided to justify that the product can be stored below 25°C for a maximum of 3 months. The Commission Decision was amended on 8 December 2000.

- The EMEA issued on 25 July 2000 a positive Notification on a Type I variation for the addition of a second manufacturing site for Puregon solution for injection. The Commission Decision was amended on 28 August 2000.

- The CPMP issued on 28 August 2000 a positive Opinion on a Type II variation concerning changes in test methods and release specifications for the active substance of Puregon solution for injection in cartridges. The Commission Decision was amended on 19 January 2001.

- The EMEA issued on 22 September 2000 a positive Notification on a Type I variation concerning a change in the in-process control for Puregon solution for injection in vials.

- The EMEA issued on 10 October 2000 a positive Notification on a Type I variation concerning the deletion of one of the manufacturing sites responsible for batch release. The Commission Decision was issued on 15 January 2001.

- The CPMP issued on 14 December 2000 a positive Opinion on a Type II variation concerning the addition of a new indication for Puregon (all strengths and presentations), namely treatment of male subjects who suffer from deficient spermatogenesis due to hypogonadotropic hypogonadism. Several sections of the Summary of Product Characteristics and Package Leaflet have been amended and the product information has been brought in line with the current QRD template. In addition, the instructions for ‘intramuscular administration’ in the Package Leaflet for the ‘Powder and solvent for solution for injection’ presentations, have been changed in accordance with the instructions in the approved Package Leaflet for the ‘Solution for injection’ presentations. The Commission Decision was amended on 10 April 2001.

- The CPMP issued on 29 March 2001 a positive Opinion on an application for a renewal of the Marketing Authorisation for Puregon. The Commission Decision was amended on 26 July 2001.
• The CPMP issued on 29 March 2001 a positive Opinion on a Type II variation concerning the demonstration of compliance with the 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). The Commission Decision was amended on 10 April 2001.

• On 28 March 2001, the Marketing Authorisation Holder submitted an application for a Type II variation in accordance with Article 6 of Commission Regulation (EC) 542/95 as amended. The MAH applied for modification of the Summary of product Characteristics and package leaflet following the first 5-year renewal of the marketing authorisation. The CPMP adopted a positive Opinion for this variation on 27 June 2001. The respective Commission Decision was issued on 5 February 2002.

• On 11 June 2001 the Marketing Authorisation Holder submitted to the EMEA an application for a Type I variation in accordance with Article 4 of European Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was to extend the shelf life as foreseen at the time of authorisation. The EMEA notified the European Commission on 13 July 2001 that the variation was accepted. Amendments to the Annex I was required and the Commission Decision was issued on 18 October 2001.


• On 12 November 2001 the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation in accordance with Article 6 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was a change of test methods and/or specifications for the active substance. The procedure started on 16 November 2001. The EMEA notified the European Commission on 21 February 2002 that the variation was accepted and did not require any amendment to the Community Marketing Authorisation. The respective Commission Decision was issued on 19 March 2002.

• On 2 January 2002 the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation in accordance with Article 6 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was a change in the test procedure of the active substance and/or specifications for the active substance. The procedure started on 18 January 2002. The EMEA notified the European Commission on 30 May 2002 that the variation was accepted and did not require any amendment to the Community Marketing Authorisation.

• On 12 February 2002 the Marketing Authorisation Holder 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 in the test procedure of the active substance. The procedure started on 22 February 2002. The EMEA notified the European Commission on 27 June 2002 that the variation was accepted and did not require any amendment to the Community Marketing Authorisation.

• On 27 February 2002 the Marketing Authorisation Holder 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 4 March 2002. The EMEA notified the European Commission on 30 May 2002 that the variation was accepted and did not require any amendment to the Community Marketing Authorisation.
On 19 April 2002 the Marketing Authorisation Holder submitted to the EMEA an application for a Type II variation in accordance with Article 6 of Commission Regulation (EC) No. 542/95, as amended. The scope of this variation was to update section 4.4 of the Summary of Product Characteristics (SPC) and section 2 of the Package Leaflet (PL) as requested by the CPMP following the assessment of a pharmaceutical Follow-up Measure related to the manufacturing process. Information regarding the possibility of Puregon to contain traces of streptomycin and/or neomycin that may cause hypersensitivity reactions was included in these sections. In addition, section 4.8 of the SPC and section 4 of the PL were updated to include information regarding the occurrence of rash and erythema based on data from post-marketing experience and assessment of the 6th PSUR. Moreover, other minor changes were introduced in the SPC and PL. The procedure started on 31 May 2002. The CPMP, on 25 July 2002, adopted a positive Opinion on this Type II variation. The Commission Decision amending Annex AI and IIIB was issued on 28 October 2002.