Steps taken after the Marketing Authorisation

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

- The CPMP during its meeting on 20-22 October 1998, concluded that the occurrence of hepatic abnormalities (hepatitis, jaundice, increased AST, ALT, alkaline phosphatase or bilirubin) must be closely reported in the forthcoming Periodic Safety Update Report.

- Following the recommendations made during the October CPMP meeting and given the suspension of the marketing authorisation of another COMT inhibitor, tolcapone (Tasmar) on 12 November 1998 due to increasing concerns over reports of severe hepatotoxicity (Press Release dated 15 October 1998 and 17 November 1988), and the common mechanism of action of entacapone and tolcapone, the Marketing Authorisation Holder (MAH) was invited by the EMEA to give an oral explanation on the safety data of entacapone. These data have been reviewed by the plenary CPMP meeting on 18 November 1998. The updated safety information indicates that entacapone does not appear to be hepatotoxic, although rare reports of clinically significant increases in liver enzymes have been reported. Nevertheless due to the awareness that abrupt withdrawal of COMT inhibition or dopaminergic containing medicinal products have resulted in Neuroleptic Malignant Syndrome (NMS) in a rare number of cases and knowing that rhabdomyolysis secondary to severe dyskinesia and NMS have also been rarely observed in patients with Parkinson's disease, the MAH considered it appropriate to introduce on 19 November 1998 provisional changes to prescribing and patient information through an urgent procedure, although these adverse events have not been reported with entacapone. The following changes were introduced through an Urgent Safety Restriction that has been finalised on 20 November 1998:

  a) amendment of section 4.3 of the SPC to include a contraindication in patients with a previous history of NMS and/or non-traumatic rhabdomyolysis.

  b) amendment of section 4.4 of the SPC to include the possibility of NMS, including rhabdomyolysis and hyperthermia.

  The Patient Information Leaflet has been amended accordingly. The plenary CPMP on 20 November 1998 adopted a revised provisional SPC, Package Information Leaflet and was informed on the information ("Dear Doctor letter") that the MAH will send out to health professionals in the European Union.

- In follow up to the USR, the MAH submitted a Type II variation in accordance with European Commission regulation (EC) No 542/95 on 24 November 1998. The CPMP adopted a positive opinion on the application on 17 December 1998 and the respective Commission decision was issued on 7 May 1999.

- On 29 January 1999, the MAH applied for a Type I variations, in accordance with Commission Regulation (EC) 542/95 as amended, to increase the batch size of entacapone and to amend the stages carried out by the manufacturers of the active substance. On 5 March 1999 the EMEA issued the corresponding notification.

- The MAH submitted on 18 March 1999 a Type I variation introducing an increase in the batch size of crude entacapone. The Marketing Authorisation Holder (MAH) received a positive notification from the EMEA on 17 May 1999.

- On 22 November 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 (sections 4.4 and 4.8) and the PL as recommended by the CPMP following assessment of the PSURs. Some minor administrative changes to the SPC. Labelling and PL were also introduced. On 11 April 2000, the CPMP adopted a positive opinion on this Type II variation. The amendments included an amendment to the wording in section 4.4 regarding Neuroleptic Malignant Syndrome and the addition of "confusion" and "hallucination" in section 4.8. The respective Commission Decision was issued on 27 July 2000.

- A Type I variation to change the manufacturing process of the active substance was submitted on 16 December 1999. The corresponding notification was issued by the EMEA on 20 January 2000.
- On 6 December 2000, the MAH applied for a Type II variation for Comtan, in accordance with Commission Regulation (EC) 542/95 as amended. The MAH applied to demonstrate 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). The CPMP considered this variation during its February 2001 plenary meeting and adopted a request for supplementary information on 27 February 2001. The MAH submitted the requested information on 7 March 2001. The CPMP, during its March 2001 plenary meeting, considered the variation acceptable and issued on 29 March 2001 an Opinion on the Type II variation.
- On 28 March 2001, 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 4.5, 4.8 and 5.2) as recommended by the CPMP following assessment of the third and fourth PSUR. On 27 June 2001, the CPMP adopted a positive opinion on this Type II variation. The corresponding Commission Decision was issued on 18 October 2001.
- An application for a Type I variation for a minor change to the manufacturing process of the active substance was submitted on 3 May 2001. The corresponding notification was issued by the EMEA on 13 July 2001.
- An application for a Type I variation for an extension of the retest period of the active substance was submitted on 20 June 2001. The corresponding notification was issued by the EMEA on 24 July 2001.
- The MAH submitted on 13 July 2001 a request to introduce changes to an aspect of the Labelling not connected to the SPC, in accordance with Article 10(3) of Council Directive No 92/27/EEC. This change concerned an update to the contact details of the local representatives. The MAH received a positive notification from the EMEA on 14 September 2001.
- The MAH submitted on 26 November 2001 applications for three Type I variations. One variation was for minor changes in the manufacture of the medicinal product and one was for a change in the specification of excipients in the medicinal product. The corresponding notifications for these two variations were issued by the EMEA on 21 December 2001. The third variation was for a minor change of manufacturing process of the active substance. The corresponding notification for this variation was issued by the EMEA on 21 January 2002.
- On 16 April 2002, the Marketing Authorisation Holder submitted an application for a Type II variation in accordance with Art. 6 of Commission Regulation (EC) No. 542/95, as amended. The Marketing Authorisation Holder applied for a variation to update the Summary of Product Characteristics (SPC) and Package Leaflet following the assessment of the 5th PSUR. The CPMP during its June 2002 plenary meeting considered the variation acceptable and issued on 27 June 2002 a positive Opinion on the Type II variation. The corresponding Commission Decision was issued on 30 September 2002.
- The MAH submitted on 27 February 2003 applications for three Type I variations. One variation was for a change in packaging site, one variation was for change in batch release site and the third variation was for a change in the name of the alternative packaging site. The corresponding notifications for these three variations were issued by the EMEA on 28 March 2003.
- The MAH submitted on 26 March 2003 applications for two Type I variations. One variation was for a change in test procedures for the medicinal product and the other variation was for changes to comply with supplements to the pharmacopoeias. The corresponding notifications for these two variations were issued by the EMEA on 2 May 2003.
- Pursuant to Article 13 of Council Regulation (EEC) No 2309/93, as amended, Novartis Europharm Ltd, submitted to the EMEA on 14 May 2003 an application for a renewal of the

Marketing Authorisation. The procedure started on 23 May 2003. On 24 July 2003, the CPMP adopted a positive Opinion on the Renewal. The corresponding Commission Decision was issued on 17 October 2003.