STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

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

- On 12 May 1997, the Marketing Authorisation Holder (MAH) notified the EMEA in accordance with Article 10(3) Council Directive 92/27/EEC of their intention to introduce a change to an aspect of the Package Leaflet (PL) not connected with the Summary of Product Characteristics (SPC). The scope of the variation concerned minor amendments to the PL for clarification and consistency with the SPC together with translation corrections. The procedure started on the 24 October 1997 and the EMEA notified the European Commission on 13 January 1998 that these changes were accepted.
- On 12 September 1997, the MAH submitted an application for a type II variation in accordance with Commission Regulation (EC) No 542/95. The scope of the variation concerned an update of the safety section of the SPC as a result of recommendations from the CPMP following assessment of the 1st PSUR and a clinical pharmacokinetics report in subjects with cirrhosis. On 19 November 1997 the CPMP adopted a positive opinion on the type II variation. The respective Commission Decision was issued on 26 March 1998.
- On 31 October 1997 the MAH submitted three parallel applications for type I variations in accordance with Commission regulation (EC) No 542/95. The MAH applied for a change in the name of one of the manufacturing sites, the address for a contract packaging site and a correction of an error in the specification of the first intermediate in the synthesis of the active substance olanzapine. The procedure started on 24 November 1997. The EMEA notified the European Commission on 18 December 1997 that the above variations were accepted.
- On 8 April 1998, the MAH submitted an application for a type II variation in accordance with Article 6 of Commission Regulation (EC) No 542/95. The scope of the variation concerned an update of the safety sections of the SPC and PL as a result of CPMP recommendations following the assessment of the 2nd PSUR and a review of available spontaneous reports for seizures in association with olanzapine. On 25 June 1998 the CPMP adopted a positive opinion on the type II variation. The respective Commission Decision was issued on 22 October 1998.
- On 29 July 1998, the MAH submitted two parallel applications for type I variations in accordance with Article 4 of Commission Regulation (EC) No 542/95. The MAH applied for an extension of retest period of the active substance from 18 to 36 months and an extension of shelf life from two to three years. The procedure started on 8 September 1998. The EMEA notified the European Commission that the variations were accepted on 1 October and 3 November 1998, respectively. The respective Commission Decision was issued on 17 December 1998.
- On 21 December 1998, the MAH submitted an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No 542/95. The MAH applied for an increase in the batch size of the finished product. The procedure started on 23 December 1998. The EMEA notified the European Commission on 17 February 1999 that the above mentioned variation was accepted.
- On 29 December 1998, the MAH submitted an application for a type II variation in accordance with Article 6 of Commission Regulation (EC) No 542/95. The MAH applied for an update of the safety sections of the SPC as a result of CPMP recommendations following the assessment of the 3rd PSUR. In accordance with the suggestions in the Rapporteur's assessment report on a previous type II variation, the MAH proposed to include a description on interactions with fluoxetine into the SPC. On 21 April 1999 the CPMP adopted a positive opinion on the type II variation. The respective Commission Decision was issued on 19 July 1999.
- On 4 May 1999, the MAH submitted an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No 542/95. The MAH applied for an increase in the batch size of the active substance olanzapine. The procedure started on 11 May 1999. The

EMEA notified the European Commission on 9 June 1999 that the variation was accepted and did not require any amendment to the Community Marketing Authorisation.

- On 1 July 1999, the MAH submitted an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No 542/95. The MAH applied for an increase in the batch size of the finished product. The procedure started on 6 July 1999. The EMEA notified the European Commission on 21 July 1999 that the variation was accepted. And did not require any amendment to the Community Marketing Authorisation.

- On 24 August 1999, the MAH submitted an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No 542/95. The MAH applied to delete one of the authorised assembly sites. The procedure started on 2 September 1999. The EMEA notified the European Commission on 24 September 1999 that the variation was accepted and did not require any amendment to the Community Marketing Authorisation.

- On 9 December 1999, the MAH submitted to the EMEA a line-extension application for the Marketing Authorisation for Zyprexa 15 and 20 mg coated tablets, under Annex II to Commission Regulation (EC) No. 542/95. On 21 September 2000 the CPMP adopted a positive opinion on the application. The respective Commission Decision to authorise the 15 and 20 mg strengths was issued on 27 December 2000.

- On 20 December 1999, the MAH submitted to the EMEA an application for a type II variation in accordance with Article 6 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The scope of the variation was to update the section 4.5 and 4.8 of the SPC to include potent inhibitors of P450-1A2 activity, bradycardia and abnormal gait in patients with Alzheimer's disease following the 5th PSUR. Some minor typographical corrections in the SPC and PL were also applied for. On 25 May 2000 the CPMP adopted a positive opinion.. The respective Commission Decision was issued on 25 September 2000.

- On 7 March 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 for a minor change in the manufacturing process of the active substance. The procedure started on 13 March 2000. The EMEA notified the European Commission on 10 April 2000 that the variation was accepted and did not require any amendment to the Community Marketing Authorisation. Pursuant to Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995 as amended, the MAH submitted to the EMEA on 4 April 2000 an application for a type I variation for Zyprexa. The scope of the variation was to add a contract packaging facility. The EMEA notified the European Commission on 4 May 2000 that the variation was accepted and did not require any amendment to the Community Marketing Authorisation.

- On 8 May 2000, the MAH submitted to the EMEA a line-extension application for the Marketing Authorisation for Zyprexa 10 mg Powder for Solution for Injection and Powder and Solvent for Solution for Injection, under Annex II to Commission Regulation (EC) No. 542/95. The procedure started on 23 May 2000. The Rapporteur's assessment report was circulated to CPMP members on 31 July 2000 and the final consolidated list of questions was sent to the MAH on 22 September 2000. The MAH submitted the responses to the CPMP consolidated list of questions on 21 November 2000. On 29 March 2001 the CPMP adopted a positive opinion on the application. The respective Commission Decision to authorise the Zyprexa 10 mg Powder for Solution for Injection and Powder and Solvent for Solution for Injection was issued on 2 July 2001.

- On 10 May 2000, the MAH submitted an application for a typ I varation in accordance with Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995 as amended. The scope of the variation was to to introduce an additional pack size being a blister pack of 28 tablets for Zyprexa 7.5 mg coated tablets. The EMEA notified the European Commission on 15 May 2000 that the variation was accepted. The respective Commission Decision was issued on 10 July 2000.

- On 21 June 2000, the MAH submitted an application for a type II variation in accordance with Article 6 of Commission Regulation (EC) 542/95 as amended. The scope of the variation was to

update the SPC and PL based on the 5th PSUR. The procedure started on 30 June 2000. The CPMP adopted a positive Opinion for this variation on 21 September 2000. The respective Commission Decision was issued on 27 December 2000.

- On 6 December 2000, the MAH submitted an application for a type II variation in accordance with Article 6 of Commission Regulation (EC) 542/95 as amended. The scope of the variation was to update of the section 4.8 of the SPC regarding information on hyperglycaemia, and the respective section of the PL to reflect this change. The procedure started on 15 December 2000. The CPMP adopted a positive Opinion for this variation on 1 March 2001. The respective Commission Decision was issued on 14 June 2001.
- On 13 December 2000, the MAH submitted an application for a type I variation in accordance with Article 4 of Commission Regulation (EC) No. 542/95 of 10 March 1995 as amended. The scope of the variation was to add alternative ink for the imprinting of the tablets. The EMEA notified the European Commission on 13 February 2001 that the variation was accepted and did not require any amendment to the Community Marketing Authorisation..
- On 11 January 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 of 10 March 1995 as amended. The scope of the variation was to add additional batch sizes for 5 mg and 10 mg tablets. The EMEA notified the European Commission on 20 February 2001 that the variation was accepted and did not require any amendment to the Community Marketing Authorisation.
- On 19 February 2001, the MAH 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 the variation was to change the address of the MAH. The procedure started on 23 February 2001. The EMEA notified the European Commission on 1 March 2001 that the variation was accepted. Amendments to the Annexes I, IIIA and IIIB were required and the Commission Decision was issued on 14 June 2001. On 14 March 2001, the MAH 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 an extension of the therapeutic indication to patients with bipolar disorder suffering from a manic episode. The CPMP adopted a positive Opinion for the indication "olanzapine is indicated for the treatment of a moderate to severe manic episode; olanzapine has not been demonstrated to prevent recurrence of manic or depressive episodes" on 21 February 2002. The respective Commission Decision was issued on 4 June 2002.
- On 23 July 2001, the MAH submitted to the EMEA an application for a type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of this variation was to add an alternative packaging and release site. The EMEA notified the European Commission on 24 August 2001 that the variation was accepted. The respective Commission Decision was issued on 19 October 2001.
- For the first renewal of Zyprexa, 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 26 July 2001 a positive opinion for the renewal of Community Marketing Authorisation. The respective Commission Decision of the renewal was issued on 20 November 2001.
- On 14 December 2001, the MAH submitted to the EMEA an application for a type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of this variation was a minor change to the coating weight of tablets. This variation was approved by the EMEA on 29 January 2002. The variation did not require any amendment to the Community Marketing Authorisation.
- On 12 February 2002, the MAH submitted an application for a type II variation in accordance with Article 6 of Commission Regulation (EC) 542/95 as amended. The procedure started on 22 February 2002. The MAH applied for an update of the SPC sections 4.8 and 4.5 and the corresponding sections of the PL following the 7th PSUR. The procedure started on 22 February 2002. The CPMP adopted a positive Opinion on 30 May 2002. The respective Commission Decision was issued on 9 September 2002.

- On 18 March 2002, the MAH submitted to the EMEA an application for a type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of this variation was to add a new packaging site and rename an authorised packaging site. This variation was accepted by the EMEA on 15 April 2002 and did not require any amendment to the Community Marketing Authorisation.
- On 18 May 2002, the MAH submitted an application for a type II variation in accordance with Article 6 of European Commission Regulation (EC) 542/95 as amended. The procedure started on 31 May 2002. The MAH applied for an update of the section 4.1 of the SPC to extend the therapeutic indication of Zyprexa Powder and Solvent for Solution for Injection to agitated patients with manic episode. The CPMP adopted a positive Opinion on 25 July 2002. The respective Commission Decision was issued on 18 October 2002.
- Pursuant to article 61(3) of Council Directive No. 2001/83/EC of 6 November 2001, the MAH notified the EMEA on 15 October 2002 of their intention to introduce changes to an aspect of the PL not connected to the SPC. On 25 October 2002, the EMEA notified the European Commission that the changes were accepted and did not require any amendment to the Community Marketing Authorisation.
- On 6 December 2002, the MAH submitted an application for a type II variation in accordance with Article 6 of Commission Regulation (EC) 542/95 as amended. The procedure started on 20 December 2002. The application related to an update in section 4.1 of the SPC to extend the therapeutic indication to include prevention of recurrence in patients with bipolar disorder. The CPMP adopted a positive Opinion on 27 July 2003 for the indication "olanzapine is indicated for the prevention of recurrence in patients with bipolar disorder". The respective Commission Decision was issued on 24 October 2003.
- On 4 February 2003, the MAH submitted an application for a type II variation in accordance with Article 6 of Commission Regulation (EC) 542/95 as amended. The procedure started on 24 February 2003. The application referred to an update to section 4.6 of the SPC regarding the levels of olanzapine found in breast milk, as well as section 4.8 regarding EPS following the review of the 9th PSUR. The CPMP adopted a positive Opinion on 26 June 2003. The respective Commission Decision was issued on 8 October 2003.
- On 5 March 2003, the MAH submitted to the EMEA an application for a type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of this variation was to change the qualitative composition of the immediate packaging material. This variation was accepted by the EMEA on 7 April 2003 and did not require any amendment to the Community Marketing Authorisation.
- On 5 September 2004, the MAH submitted to the EMEA an application for a type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of the variation was to add a new manufacturing site for part or all of the manufacturing process. The variation was accepted by the EMEA on 2 October 2003.
- On 5 February 2004, MAH submitted to the EMEA an application for a type I variation in accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of the variation was to add an additional manufacturing site and as a consequence increase the batch size. The variation was accepted by the EMEA on 2 October 2003.
- On 12 February 2004, the MAH submitted to the EMEA an application for a type I variationper Annex I (No. IA41a01) of Commission Regulation EC) No. 1085/2003. The scope of the variation was to add a new pack size containing 56 coated tablets packed in blister strips for the 2.5 mg, 5.0 mg, 15 mg and 20 mg strengths of Zyprexa coated tablets. The variation was accepted by the EMEA on 26 February 2004.
- On 11 February 2004, the MAH submitted to the EMEA an application for a type I variation as per Annex I (No IA47a) in accordance with Commission Regulation (EC) No. 1085/2003. The scope of this variation was to delete the bottle presentation for the 2.5 mg, 5 mg, 7.5 mg, 10 mg, 15 mg and 20 mg strengths of Zyprexa coated tablets. This variation was accepted by the EMEA on 7 April 2003.

- On 20 February 2004, the MAH submitted to the EMEA an application for a type I variation as per Annex I (No IA08a) of Commission Regulation (EC) No. 1085/2003. The scope of this variation was to add an additional facility for the control testing of Zyprexa coated tablets. This variation was accepted by the EMEA on 27 February 2004.
- On 1 March 2004, an Urgent Safety Restriction procedure was started at the request of the MAH to include information on cerebrovascular adverse events and increased mortality in elderly patients with dementia. The procedure was finalised on 2 March 2004.