STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

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

- On 5 August 1998, the Marketing Authorisation Holder (MAH) submitted an application for a marketing authorisation for Exelon 2 mg/ml oral solution, in accordance with Annex II to Commission Regulation (EC) No 542/95 as amended. The procedure started on 21 August 1998. The CPMP adopted a list of questions on 17 December 1998 to which the MAH responded on 14 January 1999. During its February meeting, the CPMP, in light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion (majority) for granting a Marketing Authorisation for Exelon 2 mg/ ml oral solution on 24 February 1999. The CPMP opinion was forwarded to the European Commission, which adopted the corresponding decision on 2 June 1999.
- On 4 February 1999, the MAH applied for 5 Type I variations for Exelon hard capsules, in accordance with Commission Regulation (EC) 542/95 as amended. The MAH applied for changes to the manufacturer of the finished product, the manufacturer responsible for batch release, the manufacturing process, the test procedures and the specification of the medicinal product. On 11 March 1999 the EMEA issued the corresponding notifications.
- On 18 March 1999, the MAH applied, in accordance with the Regulation, for a Type I variation to extend the shelf life of Exelon hard capsules from 2 years to 3 years. Additional minor typographical corrections were also implemented in the SPC, Labelling and Package Leaflet. The EMEA issued a notification on 19 April 1999. The respective Commission Decision was issued on 8 July 1999.
- The MAH submitted on 20 September 1999 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 the introduction of 'Instructions for Use' for the oral dosing syringe in the PL. The MAH received a positive notification from the EMEA on 16 December 1999. The respective Commission Decision was issued on 12 April 2000.On 20 September 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, 4.8, 4.9 and 5.1) and the Package leaflet as recommended by the CPMP following assessment of the PSURs. Some minor administrative changes to the SPC. Labelling and Package leaflet were also introduced. On 14 December 1999, the CPMP adopted a positive opinion on this Type II variation. The amendments included the addition of "gastric and duodenal ulcers", "bradycardia", "seizures" and "rashes" under undesirable effects. The respective Commission Decision was issued on 12 April 2000.
- On 22 September 2000, the MAH applied, in accordance with the Regulation, for 2 Type I variations to extend the shelf life of Exelon hard capsules from 3 years to 4 years, and the shelf life of Exelon oral solution from 2 to 3 years. The EMEA issued the notifications on 9 October 2000 and the corresponding Commission Decision was issued on 1 December 2000.
- On 22 September 2000, 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 (section *4.8)* and the Package leaflet as recommended by the CPMP following assessment of the fourth and fifth PSURs and the evaluation of a post marketing study investigating the effect of food on the bioavailability of the oral solution. Some minor administrative changes local representatives list on the Package leaflet were also introduced. On 14 December 2000, the CPMP adopted a positive opinion on this Type II variation. The amendments included the addition of "very rare cases of atrio-ventricular block" under undesirable effects. The respective Commission Decision was issued on 20 March 2001.
- On 26 January 2001, the MAH applied for a Type I variation for Exelon hard capsules, 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), and provided certificates of suitability issued by the European Pharmacopoeia.
The EMEA considered this variation to be acceptable and issued on 28 February 2001 a positive notification for the Type I variation application.

- On 2 February 2001, the MAH applied for a Type I variation for Exelon hard capsules, in accordance with Commission Regulation (EC) 542/95 as amended. The MAH applied to change the source of one of the excipients used in the formulation (magnesium stearate) from animal origin to vegetable origin. The EMEA considered this variation to be acceptable and issued on 28 February 2001 a positive notification for the Type I variation application.

- On 9 February 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 and the Package leaflet to include a recommendation on re-initiation of therapy following treatment interruption. On 25 April 2001, the CPMP adopted a positive opinion on this Type II variation. The corresponding Commission Decision was issued on 1 August 2001.

- On 28 August 2001, the MAH applied for a Type I variation for Exelon hard capsules, in accordance with Commission Regulation (EC) 542/95 as amended. The MAH applied to exend the shelf life as foreseen at time of authorisation from 4 years to 5 years. The EMEA considered this variation to be acceptable and issued on 3 October 2001 a positive Notification for the Type I variation application.

- The MAH submitted on 18 September 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 19 October 2001.

- On 27 December 2001, the MAH applied in accordance with Commission Regulation (EC) 542/95 as amended, for two Type I variations, one for Exelon hard capsules and one for Exelon oral solution. The MAH applied for an additional manufacturer, and a transfer of the manufacturer/importer for batch release in the EEA and of the site where the batch release takes place for the capsules. The Marketing Authorisation Holder also applied for a change in the name of the manufacturer of the finished product and site of manufacture, and in the name of the manufacturer/importer responsible for batch release in the EEA and site where the batch release takes place for the oral solution. The EMEA considered these variations to be acceptable and issued on 22 January 2002 a positive Notification for the each of the two Type I variations.

- On 6 February 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 to section 5.1 of the Summary of Product Characteristics and section 1 of the Package Leaflet to include new information on the pharmacodynamic properties of rivastigmine not only as an acetylcholinesterase inhibitor, but also as a butyrylcholinesterase inhibitor. On 27 June 2002, the CPMP adopted a positive opinion on this Type II variation. The corresponding Commission Decision was issued on 10 September 2002.

- On 20 May 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 to section 4.4, 4.9 and 4.8 of the Summary of Product Characteristics and section 4 and 5 of the Package Leaflet following the assessment of the sixth PSUR and the follow up to the sixth PSUR. Furthermore the Marketing Authorisation Holder applied for inclusion of the term ‘mild pancreatitis’ in section 4.8 of the SPC and section 5 of the Package Leaflet. On 19 September 2002, the CPMP adopted a positive opinion on this Type II variation. The corresponding Commission Decision was issued on 7 January 2003.

Scope	Application number	Type of modification[1]	Notification/ Opinion issued on[2]	Commission Decision Issued/amended on
Change in or addition of manufacturer(s) of active substance	I/23	I	20/12/02	-
Renewal of the Marketing Authorisation	R/24	R	19/03/03	30/06/03
New presentation(s)	II/25	II	17/12/03	04/03/04
Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	I/27	I	22/10/03	-
New presentation(s)	II/28	II	17/12/03	04/03/04
Change in batch size of the finished product - up to 10-fold	I/29	I	03/03/04	-
Replacement/add. of manufacturing site: Primary packaging site - Solid forms	I/30	I	23/03/04	-

[1] In accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended and after 1 October 2003 according to Commission Regulation (EC) No. 1085/03: **I** refers to a minor variation (Type I variation); **II** refers to a major variation (Type II variation); **I/II** refers to a minor variation following the procedure set out in Article 6, 7 and 8 of the Regulation; **X** refers to an Annex II application. **T** refers to a transfer of a Marketing Authorisation in accordance with Commission Regulation (EC) No 2141/96 of 7 November 1996. **N** refers to a notification in accordance with Article 61(3) of Council Directive 2001/83/EC.

[2] For Notifications and Type I variations, the date of entry into force of the change is the EMEA Notification date. The Commission Decision will be amended accordingly.