Steps taken after granting the Marketing Authorisation

For procedures finalised after 1 October 2002 please refer to module 8B.

- The Marketing Authorisation Holder submitted to the EMEA on 16 September 1997 applications for two type I variations falling within the scope of item No. 17 (Change in the specification of the medicinal product) and item No. 24 (Change in test procedure of active substance) of Annex I to Commission Regulation (EC) No 542/95. On 5 December 1997, the EMEA approved the variations (EMEA/H/C/125/I/01 and EMEA/H/C/125/I/02). These variations did not require amendments to the Commission Decision.

- The Marketing Authorisation Holder submitted on 22 December 1997 a request to change the Labelling and the Package Leaflet pursuant to Article 10(3) of Council Directive 92/27/EEC of 31 March 1992. The EMEA sent the notification to the European Commission on 12 January 1998 (EMEA/H/C/125/N/03). The Commission decision amending the Marketing Authorisation was issued on 3 March 1998.

- The Marketing Authorisation Holder submitted to the EMEA on 28 January 1998 an application for one type I variation falling within the scope of item No 17 of Annex I to Commission Regulation (EC) No 542/95. The Marketing Authorisation Holder applied for a change in specification of the medicinal product (inclusion of a specification for microbiological quality). On 4 March 1998, the EMEA approved the variation (EMEA/H/C/125/I/04). This variation did not require amendments to the Commission Decision.

- Pursuant to Article 13(2) of Council Regulation No. 2309/93 and Part 4G of the Annex to Council Directive 75/318/EEC, the Marketing Authorisation Holder provided throughout the year of the Marketing Authorisation additional efficacy and safety data as stated in Annex IIC to Commission Decision, which formed the basis of the annual re-assessment of the benefit/risk profile of Cystagon. Data were provided on 22 June 1998 and completed on 14 October 1998 following the CPMP's request during its plenary session on 15-17 September 1998. The Rapporteur's annual assessment report was circulated to all CPMP members on 7 December 1998. During its plenary meeting on 15-17 December 1998, the CPMP agreed with the Rapporteur's assessment report that the benefit/risk of mercaptamine bitartrate remained favourable and that the Marketing Authorisation remains under exceptional circumstances. The CPMP opinion included a revised list of specific obligations of Annex II.C. to the Community Marketing Authorisation (EMEA/H/C/125/S/05). The respective Commission Decision was issued on 19 April 1999.

- The Marketing Authorisation Holder submitted to the EMEA on 12 March 1999 an application for one type I variation falling within the scope of item No 1 of Annex I to Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder applied for a change in the manufacturing site for part of the manufacturing process of the medicinal product. On 23 April 1999, the EMEA issued the corresponding notification (EMEA/H/C/125/I/06). This variation required amendments to annex III of the Community Marketing Authorisation. The respective Commission Decision was issued on 01 July 1999.

- The Marketing Authorisation Holder submitted to the EMEA on 10 May 1999 an application for three type I variations falling within the scope of item No 8, 14 and 24 of Annex I to Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder applied for a change in the qualitative composition of the immediate packaging material, a change in test procedures of active substance and a change in specifications of the active substance. On 09 June 1999, the EMEA issued the corresponding notifications (EMEA/H/C/125/I/07, EMEA/H/C/125/I/08, EMEA/H/C/125/I/09). These variations did not required amendment to the Community Marketing Authorisation. The respective Commission Letter was issued on 18 June 1999.

- Pursuant to Article 13(2) of Council Regulation No. 2309/93 and Part 4G of the Annex to Council Directive 75/318/EEC, the Marketing Authorisation Holder provided throughout the second year of the Marketing Authorisation additional efficacy and safety data as stated in Annex IIC to Commission Decision, which formed the basis of the annual re-assessment of the benefit/risk profile of Cystagon. Data were provided on 20 July 1999. The Rapporteur's annual assessment

report was circulated to all CPMP members on 10 September 1999. During its plenary meeting on 19-21 October 1999, the CPMP agreed with the Rapporteur's assessment report that the benefit/risk of mercaptamine bitartrate remained favourable and that the Marketing Authorisation remains under exceptional circumstances. The CPMP opinion included a revised list of specific obligations of Annex II.C. to the Community Marketing Authorisation (EMEA/H/C/125/S/11). The respective Commission Decision was issued on 16 March 2000.

- On 09 September 1999, the Marketing Authorisation Holder submitted a Type II variation application in accordance with Article 6 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of the variation related to the update of sections 4.2 and 4.9 of the SPC following the CPMP's assessments of first annual re-assessment and 2nd PSUR, and in section 5.3 following the fulfilment of a specific obligation. At this occasion, Annexes I, IIIA and IIIB have been updated according to the latest EMEA/QRD template. On 18 November 1999 the CPMP approved the variation (EMEA/H/C/125/II/10). The variation required amendments in the relevant sections of the Commission Decision and the EPAR. The European Commission amended the Decision on 16 March 2000.

- The Marketing Authorisation Holder submitted on 12 January 2000 an application for a type I variation falling within the scope of item No 14 of Annex I to Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder applied for a change in specification for tartaric acid content in the active substance. On 10 February 2000, the EMEA issued the corresponding notification (EMEA/H/C/125/I/12). This variation did not require amendments to the Commission Decision.

- The Marketing Authorisation Holder submitted on 7 June 2000 an application for a type I variation falling within the scope of item No 15a of Annex I to Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder applied for a change in in-process controls applied during the manufacture of the product. On 14 July 2000, the EMEA issued the corresponding notification (EMEA/H/C/125/I/13). This variation did not require amendments to the Commission Decision.

- The Marketing Authorisation Holder submitted on 9 August 2000 an application for three type I variation falling within the scope of item No 1 (change in the premises of one of the manufacturing sites responsible for batch release), 8 (change in quantitative composition of immediate packaging material) and 32 (change of imprints) of Annex I to Commission Regulation (EC) No 542/95, as amended. On 21 September 2000, the EMEA issued the corresponding notification (EMEA/H/C/125/I/14, EMEA/H/C/125/I/15, EMEA/H/C/125/I/16). The variation No 1 requires amendments to Annexes II and IIIB of the Commission Decision.

- Pursuant to Article 13(2) of Council Regulation No. 2309/93 and Part 4G of the Annex to Council Directive 75/318/EEC, the Marketing Authorisation Holder provided throughout the third year of the Marketing Authorisation additional data as stated in Annex IIC to Commission Decision, which formed the basis of the annual re-assessment of the benefit/risk profile of Cystagon. On 21 September 2000, the CPMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, informed the European Commission that no updating of Annex I and III to the Community Marketing Authorisation for the medicinal product is required. The CPMP opinion included a revised list of specific obligations of Annex II.C. to the Community Marketing Authorisation (EMEA/H/C/125/S/17). The respective Commission Decision was issued on 29 January 2001.

- On 7 November 2000, the Marketing Authorisation Holder submitted a Type II variation application in accordance with Article 6 of Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended. The scope of the variation related to the update of sections 4.3, 4.4, 4.6, 5.1, 5.2 and 5.3 of the SPC in order to include new pharmacological data based on a recent clinical pharmacokinetic study and to revise the information on pregnancy based on new preclinical data on the reproduction toxicity of the active substance. The latest QRD template has also been taken into account and the imprint on the 50 mg capsule has been corrected in section 6.5. On 25 January 2001, the CPMP approved the variation (EMEA/H/C/125/II/18). The European Commission amended the Decision on 3 May 2001.

- On 23 February 2001, the Marketing Authorisation holder submitted an application for a type I variation in accordance with the Commission Regulation (EC) No 542/95, as amended. The Marketing Authorisation Holder 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 for the materials listed in Annex B. On 23 March 2001, the EMEA issued the corresponding notification (EMEA/H/C/125/I/19). This variation did not require amendments to the Commission Decision.
- Pursuant to Article 13(2) of Council Regulation No. 2309/93 and Part 4G of the Annex to Council Directive 75/318/EEC, the Marketing Authorisation Holder provided throughout the fourth year of the Marketing Authorisation additional data as stated in Annex IIC to Commission Decision, which formed the basis of the annual re-assessment of the benefit/risk profile of Cystagon. On 18 October 2001, the CPMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, informed the European Commission that no updating of Annex I and III to the Community Marketing Authorisation for the medicinal product is required. The CPMP opinion included a revised list of specific obligations of Annex II.C. to the Community Marketing Authorisation (EMEA/H/C/125/S/20).