STEPS TAKEN AFTER GRANTING THE MARKETING AUTHORISATION

For procedures finalised after 1 February 2005 please refer to module 8B

- On 4 April 1996 the Marketing Authorisation Holder submitted an application for a Type II variation to amend the section related to instruction for preparation of Taxotere and to update the safety information in the SPC, Labelling and Package Leaflet. The CPMP, during its May plenary meeting, adopted a list of questions. The company submitted the full responses to the CPMP list of questions on 6 June 1996. The CPMP, during its June plenary meeting, agreed on the amended text to be introduced into the SPC, Labelling and Package Leaflet and adopted a positive Opinion for the Type II variation. The Commission Decision for the Type II variation was issued on 7 October 1996.
- On 30 October 1996 the Marketing Authorisation Holder submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 relating to the addition of an alternative-manufacturing site of docetaxel bulk solution. The EMEA approved the variation on 6 December 1996. This variation did not require any amendments to the Commission Decision.
- According to the specific obligation (quality) set out in the CPMP Opinion dated 12 July 1995; the Marketing Authorisation Holder was requested to tighten the impurities specifications at shelf life. The proposed changes, including as a consequence the update of the test procedures of the finished medicinal product, agreed by the CPMP during its December plenary meeting were introduced through two Type I variations. These applications were submitted on 27 November 1996. The EMEA approved on 23 December 1996 both variations, which were considered as consequential. Both variations did not require any amendments to the Commission Decision.
- On 4 December 1996 the Marketing Authorisation Holder submitted two applications for a Type I variation in accordance with Commission Regulation (EC) No. 542/95. The scope of the first variation related to the change of the name of the manufacturer of the finished medicinal product and responsible for the batch release from May & Baker Ltd to Rhône-Poulenc Rorer. The second variation related to the change of the name of the manufacturer of the active substance, docetaxel, and docetaxel solution in polysorbate from Rhône-Poulenc Rorer S.A. to Rhône-Poulenc Rorer Principe Actifs. On 12 December 1996 the EMEA approved the variation. Only the first variation required amendments to be incorporated in the relevant sections of the Commission Decision. The European Commission amended the Decision on 3 March 1997.
- On 25 February 1997 the Marketing Authorisation Holder submitted an application for a Type I variation in accordance with Commission Regulation (EC) No. 542/95 relating to the modification in the SPC and Package Leaflet of the shelf life of the premix (i.e. 10-mg/ml docetaxel solutions) and of the medicinal product after reconstitution. The EMEA approved the variation on 2 April 1997, which required amendments to be incorporated in the relevant sections of the Commission Decision. The European Commission amended the Decision on 13 June 1997.
- Pursuant to Article 13(2) of Council Regulation (EEC) No 2309/93 and Part 4G of Annex to Council Directive 75/318/EEC, the Marketing Authorisation Holder provided throughout 1996 the preliminary reports of ongoing clinical studies which formed the basis of the annual re-assessment of the benefit/risk profile of Taxotere (e.g. clinical studies with Taxotere in monotherapy and in combination therapy, studies concerning the management of side-effects). On 8 November 1996 the Marketing Authorisation Holder provided an updated expert report summarising the different specific obligations already submitted within the period November 1995 - November 1996. The procedure started on 25 November 1996. During its December plenary meeting, the CPMP agreed with the Rapporteur's assessment report circulated on 3 December 1996 that the benefit/risk profile for Taxotere remained unchanged on the basis of the additional preliminary efficacy and safety data provided and that the Marketing Authorisation should therefore remain under exceptional circumstances. The CPMP agreed,

however, to revise the list of specific obligations and follow-up measures to be fulfilled. An Opinion on the annual re-assessment of the specific obligations and the benefit/risk profile of a medicinal product authorised under exceptional circumstances was adopted on 19 December 1996. The respective Commission Decision was issued on 22 May 1997.

- On 21 April 1997 the Marketing Authorisation Holder submitted an application for a Type II variation to update the safety section (addition of new undesirable effects) and the posology and method of administration section (fluid retention premedication regimen) of the Summary of Product Characteristics and consequently the Package Leaflet, based on post-marketing experience and new clinical data. The CPMP, during its July plenary meeting, considered the changes acceptable, and issued on 23 July 1997 a favourable Opinion on the Type II variation. This Opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 10 November 1997.

- On 24 October 1997 the Marketing Authorisation Holder submitted an application for a Type II variation for a change in the formulation of Taxotere. The CPMP, during its January plenary meeting, considered the changes acceptable, and issued on 28 January 1998 a favourable Opinion on the Type II variation. This Opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 9 June 1998.

- The Marketing Authorisation Holder submitted to the EMEA on 28 November 1997 the documentation that formed the basis for the annual re-assessment of the benefit/risk profile for Taxotere. During its March 1998 plenary meeting, the CPMP agreed with the Rapporteur's assessment report and adopted an Opinion on the annual re-assessment of the specific obligations and the benefit/risk ratio, stating that no amendments of Annexes I and III to the Community Marketing Authorisation are necessary as part of the annual re-assessment. Furthermore the CPMP agreed that the Marketing Authorisation Holder fulfilled all the specific obligations as listed in Annex II C to the original Commission Decision. The European Commission adopted the corresponding Decision on 7 July 1998. Therefore, the evaluation of the benefit/risk ratio has now been completed, and the conditional approval period has come to an end: the Annex II C has been modified accordingly.

- The Marketing Authorisation Holder submitted to the EMEA on 8 December 1997 an application for a Type II variation for a broadening of the indication. The CPMP, during its March plenary meeting, considered the changes acceptable and issued on 25 March 1998 a favourable Opinion on the Type II variation. This Opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 17 July 1998.

- On 12 March 1998 the Marketing Authorisation Holder submitted an application for a Type II variation in order to update the safety section of the SPC following a request of the CPMP after evaluation of Periodic Safety Update Report number 4 (addition of new undesirable effects and changes in the wording). The CPMP, during its May plenary meeting, considered the changes acceptable, and issued on 27 May 1998 a favourable Opinion on the Type II variation. This Opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 18 September 1998.

- Pursuant to article 10(3) of Council Directive No. 92/27/EEC of 31 March 1992, the Marketing Authorisation Holder notified the EMEA on 3 June 1998 of their intention to introduce a change to an aspect of the labelling not connected to the Summary of Product Characteristics (introduction of the text "New storage conditions"). On 12 June 1998 the EMEA has notified the European Commission that the changes were accepted. The European Commission amended the Decision on 5 August 1998.

- On 3 December 1998 the Marketing Authorisation Holder submitted an application for a Type II variation in order to update the safety section of the SPC following a request of the CPMP after evaluation of Periodic Safety Update Report number 5 (addition of new undesirable effects and changes in the wording). The CPMP, during its February 1999 plenary meeting, considered the changes acceptable, and issued on 25 February 1999 a favourable Opinion on the Type II

variation. This Opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 16 June 1999.

- Pursuant to Article 6 of Commission regulation (EC) No. 542/95 of 10 March 1995, the Marketing Authorisation Holder submitted to the EMEA on 3 December 1998 an application for a Type II variation for a for a new line extension i.e: locally advanced or metastatic non-small cell lung cancer after failure of prior chemotherapy. The CPMP, during its October 1999 plenary meeting, considered the changes acceptable and issued on 21 October 1999 a favourable Opinion on the Type II variation. This Opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 20 January 2000.
- Pursuant to Article 6 of Commission regulation (EC) No. 542/95 of 10 March 1995, the Marketing Authorisation Holder submitted to the EMEA on 20 December 1999 an application for a Type II variation for a new line extension i.e: the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition. The CPMP, during its May 2000 plenary meeting, considered the changes acceptable and issued on 25 May 2000 a favourable Opinion on the Type II variation. This Opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 29 January 2000.
- Pursuant to Article 6 of Commission regulation (EC) No. 542/95 of 10 March 1995, the Marketing Authorisation Holder submitted to the EMEA on 20 December 1999 an application for a Type II variation for a new line extension i.e: the treatment of patients with locally advanced or metastatic breast cancer who have not previously received cytotoxic therapy for this condition. The CPMP, during its May 2000 plenary meeting, considered the changes acceptable and issued on 25 May 2000 a favourable Opinion on the Type II variation. This Opinion was forwarded, in all official languages of the European Union, to the European Commission, which adopted the corresponding Decision on 28 August 2000.
- Pursuant to Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended, Rhône-Poulenc Rorer S.A. submitted to the EMEA on 8 May 2000 an application for a Type I variation to change the name of the MAH to Aventis Pharma S.A The corresponding Decision was adopted by the Commission on 15 September 2000.

Subsequent post Marketing Authorisation applications agreed upon are summarised in the table below:

Scope	Application number	Type of modification[1]	Notification/ Opinion issued on[2]	Commission Decision Issued/amended on
Change in the batch size of finished product	I/0017	I	23.02.99	11.03.99
Change in shelf-life after reconstitution	I/0018	I	05.07.99	05.10.99
Extension of shelf-life as foreseen at time of authorisation	I/0019	I	05.07.99	05.10.99
Extension of shelf-life as foreseen at time of authorisation	I/0020	I	05.07.99	05.10.99
Quality changes	II/0022	II	23.06.99	30.06.99
Update of Summary of Product Characteristics and Package Leaflet	II/0024	II	25.05.00	28.08.00
Change in the name and/or address of the marketing authorisation holder	I/0026	I	30.06.00	-
Quality change	II/0027	II	27.07.00	-
Change in the name of a manufacturer of the active substance	I/0028	I	19.07.00	-
Renewal	R/0029	R	20.09.00	28.12.00
Update of Summary of Product Characteristics	II/0030	II	25.01.01	03.05.01
Quality change	II/0031	II	25.07.01	N/A
Change following modification(s) of the manufacturing authorisation(s)	I/0032	I	05.07.01	13.08.01
Change in the name of a manufacturer of the active substance	I/0033	I	18.07.01	
Update of the SPC (point 4.8)	II/0034	II	13.12.01	16.04.02
New overfill values for the 20 mg concentrate and solvent vials	II/0035	II	17.01.02	23.04.02
Update of the SPC (point 4.8)	II/0037	II	21.11.02	24.01.03
Minor change in manufacture of the medicinal product	I/0038	I	14.06.02	21.06.02
Change in in-process controls applied during the manufacture of the product	I/0039	I	14.06.02	21.06.02
Additional indication (metastatic breast cancer)	II/0040	II	19.09.02	09.01.03
Change in the batch size of finished product	I/0041	I	05.09.02	16.09.02
Batch size of active substance	I/0042	I	16.04.03	23.04.03
Change in or addition of manufacturing site(s) for part or all of the manufacturing process	I/0043	I	08.05.03-	-
Update of Summary of Product Characteristics	II/0044	II	26.06.03	08.10.03
Replacement of an excipient with a comparable excipient	I/0045	I	23.05.03	26.05.03
Change in specification of excipients in the medicinal product (excluding adjuvants for vaccines)	I/0046	I	23.05.03	26.05.03
Change in specification of starting material/intermediate used in manuf. of the active substance	I/0047	I	15.07.03	23.07.03
Change in test procedure for starting material/intermediate used in manuf. of active substance	I/0048	I	30.07.03	05.09.03
Minor changes in manufacture of the medicinal product	I/0049	I	30.07.03	05.09.03
Change in test procedure for starting material/intermediate used in manuf. of active substance	I/0050	I	30.07.03	05.09.03
Change in or addition of manufacturing site(s) for part or all of the manufacturing process	I/0051	I	03.09.03	18.09.03

[1] In accordance with Commission Regulation (EC) No. 542/95 of 10 March 1995, as amended: **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 10(3) of Council Directive 92/27/EEC of 31 March 1992.

[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.

Extension of Indication	II/0052	II	16.09.04	20.10.04
Update of Summary of Product Characteristics	II/0053	II	24.03.04	26.05.04
Extension of Indication	II/0054	II	18.11.04	05.01.05
Change(s) to the manufacturing process for the active substance	II/0055	II	23.06.04	293.06.04
Change in shelf-life of finished product - as packaged for sale	IB/0056	IB	03.06.04	-
Change in shelf-life of finished product - as packaged for sale	IB/0057	IB	03.06.04	-
Extension of Indication	II/0058	II	18.11.04	22.12.04
Quality changes	II/0059	II	20.01.05	27.01.05
Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	IA/0060	IA	18.01.05	-