Steps taken after granting the Marketing Authorisation

For procedures finalised after 01 July 2004 please refer to module 8B.

- On 10 September 1999, the Marketing Authorisation Holder submitted to the EMEA one 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 move the site and responsibility for the final batch release in the European Union from Usiphar, Compiègne in France, to Hoechst Marion Roussel Deutschland GmbH, Frankfurt am Main, Germany. On 20 September 1999, the EMEA issued a positive notification for this Type I variation which required amendments to Annex II (General Conditions of the Marketing Authorisation) and Annex IIIB (Package Leaflet) of the Commission Decision. A Commission Decision was issued on 08 Dec 1999.

- On 20 October 1999, due to the reporting of 16 potential cases of pancytopenia and 9 cases of serious skin reactions, the Marketing Authorisation Holder requested an update of the Summary of Product Characteristics and Package Leaflet through an Urgent Safety Restriction (USR) procedure in accordance with article 1(2) of Commission Regulation (EC) No. 542/95 as amended. The scope of the procedure was to introduce new information regarding the association of leflunomide with other DMARDs, the monitoring of the patients being treated with leflunomide and the washout procedures to be performed in case of occurrence of serious hematological or cutaneous reactions. The changes were introduced in the Indications, Contra-indications, Special warnings and Precautions for use and Undesirable effects sections of the SPC. The Patient Leaflet was modified accordingly. The USR procedure was finalised on 21 October 1999. The EMEA issued a Public Statement to inform the health professionals and the patients of this new information

- In follow up to the USR, on 5 November 1999, the MAH submitted a Type II variation in accordance with European Commission regulation (EC) No 542/95 of 10 March 1995, as amended, to update the Summary of Product Characteristics and as a consequence the Package Leaflet to reflect the new information provisionally introduced through the USR. The CPMP adopted a positive opinion on the application on 18 November 1999. The respective Commission decision was issued on 24 March 2000.

- On 28 April 2000, the Marketing Authorisation Holder submitted to the EMEA one 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 introduce a change in the manufacturing process of the active substance. On 30 May 2000, the EMEA issued a positive notification for this Type I variation, which did not require any amendments to the Commission Decision.

- On 10 May 2000, the Marketing Authorisation Holder notified the EMEA of its intention to introduce changes to aspects of the Package Leaflet not connected to the Summary of the Product Characteristics, in accordance with Article 10(3) of Council Directive 92/27/EEC of 31 March 1992. On 17 May 2000, the EMEA issued a positive notification. The European Commission amended the Decision on 04 July 2000.

- On 16 June 2000, the Marketing Authorisation Holder submitted to the EMEA one 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 introduce a change in the manufacturing process of the active substance. On 19 July 2000, the EMEA issued a positive notification for this Type I variation, which did not require any amendments to the Commission Decision.

- On 20 July 2000, the Marketing Authorisation Holder submitted to the EMEA one 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 name of the Marketing Authorisation Holder from Hoechst Marion Roussel Deutschland GmbH to Aventis Pharma Deutschland GmbH (name change due to a merger with Rhone-Poulenc-Rorer). This change resulted in two consequential changes (in the name of the manufacturer of the active substance and of the manufacturer of the medicinal product). In addition the MAH took the opportunity to update the pharmacotherapeutic / ATC code to reflect the final WHO assignment and to amend minor linguistic errors within the product literature. On 25 August 2000, the EMEA issued a positive notification for this Type I variation which required amendments to Annex I (Summary of the Product Characteristics), Annex II (General Conditions of the Marketing Authorisation) and Annex III (Labelling and Package Leaflet) of the Commission Decision. A Commission Decision was issued on 15 Nov 2000.

- On 28 February 2001, due to the reporting of 296 cases with hepatic reactions including 129 serious cases (amongst these serious cases 2 cases of liver cirrhosis and 15 cases of liver failure, 9 with fatal outcome), the Marketing Authorisation Holder requested an update of the Summary of Product Characteristics and Package Leaflet through an Urgent Safety Restriction (USR) procedure pursuant to article 1(2) of Commission Regulation (EC) No. 542/95 as amended. The scope of the procedure was to strengthen the information regarding the liver monitoring of patients being treated with leflunomide, the association of leflunomide with other hepatotoxic medications and the washout procedures to be performed in case of occurrence of serious adverse reactions. The recommendations reinforce the fact that it is essential that monitoring recommendations should be strictly adhered to and that Arava should only be prescribed by specialists experienced in the treatment of rheumatoid arthritis. The changes were introduced to the Indications, Posology and method of administration, Contra-indications, Special warnings and Special Precautions for use and Undesirable effects sections of the SPC. The Patient Leaflet was modified accordingly. The USR procedure was finalised on 1 March 2001. The EMEA issued a Public Statement to inform the health professionals and the patients of this new information.

- On 28 February 2001, the Marketing Authorisation Holder 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 procedure started on 28 February 2001. The Marketing Authorisation Holder applied to demonstrate compliance with Commission Directive 1999/82/EC and the Note for Guidance on minimising the risk of transmitting animal spongiform Encephalopathy agents via medicinal products. On 28 March 2001 the EMEA approved this variation, which did not require any amendments to the Commission Decision.

- On 9 March 2001, the Marketing Authorisation Holder submitted to the EMEA one application for a Type II variation in accordance with Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The scope of this variation was to introduce changes in the Summary of Product Characteristics (SPC) and Package Leaflet (PL) in the following area, following the introduction of an Urgent Safety Restriction on 1 March 2001 to include new special warnings and special precaution for use with regard to serious liver injuries including fatal cases; to include additional undesirable effects related to serious liver injuries (hepatitis, jaundice/cholestasis and very rarely, severe liver injury such as hepatic failure and acute hepatic necrosis that may be fatal). The Commission Decision was issued 31 July 2001.

- On 8 August 2001, the Marketing Authorisation Holder submitted to the EMEA (in accordance with Council Directive No: 92/27/EEC of 31 March 1992), its intention to introduce changes to aspects of the Package Leaflet not connected to the Summary of Product Characteristics. The scope of this notification relates to a change of name and address of the Local Representative for Arava in France (Annex IIIB). The Commission Decision was issued on 27 November 2001.

- On 13 August 2001, the Marketing Authorisation Holder 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 Marketing Authorisation Holder applied to introduce an additional intermediate pack size of 50 film-coated tablets per bottle, intended for hospital use only. On 19 November 2001 the EMEA approved this variation, which required amendments to be incorporated into Annexes I, IIIA and IIIB of the Commission Decision.

- On 31 October 2001, the Marketing Authorisation Holder 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 Marketing Authorisation Holder applied to change one of the manufacturing sites for the manufacturing process for the medicinal product. On 19 November 2001 the EMEA approved this variation, which required amendments to be incorporated into Annexes II and IIIB of the Commission Decision. The Commission Decision was issued on 19 February 2002.

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 name of a manufacturer of the active substance.	I/0014	I	05/12/2001	07/01/2002
Replacement of an excipient with a comparable excipient.	I/0015	I	14/01/2002	06/03/2002
Changes to comply with supplements to pharmacopoeias.	I/0016	I	14/01/2002	06/03/2002
Extension of shelf-life as foreseen at time of authorisation.	I/0017	I	15/01/2002	22/03/2002
Update of Summary of Product Characteristics (SPC) following PSUR6 with regard to monitoring of liver function after therapy change (section 4.4 and 4.5) and addition of information on undesirable effects (section 4.8). The Package Leaflet (PL) is modified accordingly.	II/0018	II	25/04/2002	18/07/2002
Change in the qualitative composition of immediate packaging material	I/0019	I	16/01/2003	14/02/2003
Update of SPC and PL to amend section sections 4.2, 4.4 and 4.8 of the SPC based on PSUR 8 evaluation. The SPC update concerns increased frequency of liver function test monitoring and addition of information on undesirable effects. The PL is modified accordingly.	II/0020	II	24/07/2003	20/10/2003
Update of SPC sections 4.9 (Overdose) and 5.2 (Pharmacokinetic properties) in order to bring the SPC in line with the Corporate Data Sheet (CDS) (as requested in the assessment on PSUR 9), by including into section 4.9 post-marketing experience on overdose cases and into section 5.2 pharmacokinetic properties in renal failure.At the request of the CPMP, the MAH has also agreed to revise SPC section 4.2 (to improve the wording resulting from variation II/20).	II/0021	II	22/10/2003	27/01/2004
Update of the SPC sections 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.3 (Contraindications) and 5.1 (Pharmacodynamic properties) to extend the indication to psoriatic arthritis and include results from a multinational randomised, double-blind placebo controlled study in patients with psoriatic arthritis. The PL has been amended accordingly. In addition, the MAH took the opportunity to update the addresses of Aventis EU affiliates and to add the list of local representatives for the 10 accession countries in section 6 of the Package Leaflet in accordance with EMEA/QRD templates.	II/0022	II	24/03/2004	08/06/2004
Update of SPC sections 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects) to include a warning on interstitial pneumonia and to update the stated frequency for interstitial lung disease to "rare". Sections 2 and 4 of the PL are amended accordingly.	II/0023	II	22/04/2004	10/06/2004
Change in the name and/or address of a manufacturer of the finished product	IA/0025	IA	19/04/2004	-

[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.
S refers to an annual reassessment.

[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.