Steps taken after granting the Marketing Authorisation

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

- The MAH submitted to the EMEA on 13 August 1999 an application for a Type II variation, to add new indication for the reduction of signs and symptoms in Rheumatoid arthritis, pursuant to Article 6 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 27 August 1999. A positive opinion was adopted by the CPMP on 16 February 2000 and forwarded to the European Commission, which adopted a Decision on 27 June 2000.

- The MAH submitted to the EMEA on 11 October 1999 an application for a Type I variation, to extend of shelf life from 18 to 24 months, pursuant to Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started 15 October 1999. A positive notification was signed by the Head of Human Unit at the EMEA on 12 November 1999 and forwarded to the European Commission, which adopted a Decision on 8 February 2000.

- The MAH submitted to the EMEA on 11 October 1999 an application for a Type I variation, to change the manufacturing process of the active substance, pursuant to Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started 22 October 1999. A positive notification was signed by the Head of Human Unit at the EMEA on 16 December 1999 and forwarded to the European Commission.

- The MAH submitted to the EMEA on 17 January 2000 an application for a Type II variation to add to the indication section on Rheumatoid Arthritis the reduction in the rate of progression of joint damage, pursuant to Article 6 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started on 21 January 2000. A positive opinion was adopted by the CPMP on 21 September 2000 and forwarded to the European Commission that adopted a Decision on 29 January 2001.

- The MAH submitted to the EMEA on 13 July 2000 an application for a Type I Variation, to include 2 additional pack sizes, pursuant to Article 4 of Commission Regulation (EC) No 542/95 of 10 March 1995, as amended. The procedure started 9 August 2000. A positive notification was signed by the Head of Human Unit at the EMEA on 8 September 2000 and forwarded to the European Commission, which adopted a Decision on 16 November 2000.

- The MAH submitted to the EMEA on 13 December 2000 a request for an Urgent Safety Restriction, pursuant to Article 1 of Commission Regulation (EC) No 542/95 of 10 March 1995. The purpose of the Urgent Safety Restriction was to include information in the SPC and Package Leaflet on tuberculosis occurred during treatment with Remicade. The procedure started on 13 December 2000 and was finalised on 14 December 2000. The European Commission was notified on the USR on 14 December. Centocor B.V. submitted the corresponding type II variation application to the EMEA on 15 February 2001. A positive opinion was adopted by the CPMP on 29 March 2001 and forwarded to the European Commission which adopted a Decision on 31 July 2001.

- The MAH submitted to the EMEA on 19 February 2001 a Type II variation application, to introduce changes to the Summary of Product Characteristics (SPC) and Package Leaflet with regard to central nervous system disorders and anaphylactic/anaphylactoid reactions. In addition, in section 6.3 of SPC and in section 5 of the PL some changes were introduced to comply with the Note for Guidance on maximum shelf life for sterile products (CPMP/QWP/159/96 corr.). A positive opinion was adopted by the CPMP on 1 March 2001 and forwarded to the European Commission which adopted a Decision on 27 June 2001.

- Pursuant to Article 13(2) of Council Regulation (EEC) No. 2309/93 as amended and Part 4G of Annex to Council Directive 75/318/EEC, the MAH submitted to the EMEA on 31 October 2000 additional efficacy and safety data as stated in Annex IIC to Commission Decision, which formed the basis of the 1st annual re-assessment of the risk/benefit profile of Remicade (results from ACCENT I and ACCENT II clinical trials, new safety data). The procedure started on 26 January 2001. During the procedure, following the submission and the assessment of the second periodic safety update report (PSUR) for Remicade covering the period from 24 August 1998 to 23 August 2000, the CPMP decided during its February meeting to perform a full reassessment of the safety profile of Remicade in both indications in the framework of the annual reassessment procedure. On 29 March 2001, the CPMP agreed that the risk/benefit profile of Remicade remained favourable and that the MA should remain under exceptional circumstances until all the specific obligations are fulfilled. During this meeting the CPMP adopted an opinion on the annual re-assessment of the specific obligations and the risk/benefit ratio, stating that no amendments of Annexes I and III to the Community Marketing Authorisation were necessary. The Annex II has been updated. Corresponding Commission Decision was issued on 31 July 2001.

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
Minor change in labelling or Package Leaflet (PL) according to QRD template (Art. 10.3 Notification).	N/0007	N	12.01.01	-
Extension of shelf life to 36 months.	I/0008	I	07.02.01	
Update of or change(s) to the pharmaceutical documentation.	II-0011	II	25.04.02	30.04.02
Change following modification(s) of the manufacturing authorisation(s).	I/0013	I	02.10.01	-
Update of contact details of local representatives of the MAH in PL.	N/0014	N	10.09.01	-
Urgent Safety Restriction to restrict the indication for Crohn's Disease and to include safety information regarding heart failure, infections and tuberculosis.		USR	17.01.02	17.05.02
Adoption of Opinion on second Annual Reassessment, the Marketing Authorisation remains under exceptional circumstances.	S-0015	S	17.01.02	17.05.02
Update of the SPC sections: 4.8 (Undesirable effects) following PSUR 3 covering the period from 24.8.00 to 23.2.01 to incorporate new information regarding pancytopenia and listeriosis.	II-0016	II	17.01.02	17.05.02
Update of SPC section 4.8 (Undesirable effects) on congestive heart failure and section 5.3 (Preclinical safety data) with findings from 6 month toxicity study in mice.	II-0017	II	25.04.02	11.07.02
Minor change of manufacturing process of the active substance.	I-0019	I	30.05.02	03.06.02
Update of contact details of the local representatives of the Marketing Authorisation Holder in PL.	N-0020	N	03.06.02	-
Change(s) to the test method(s) and/or specifications for the finished product	II-0021	II	27.06.02	04.07.02
Change(s) to the manufacturing process for the finished product	II-0022	II	25.04.03	10.07.03
Update of SPC and PL following PSUR4 covering the period from 24.2.01 to 23.8.01: update of SPC section 4.4 (Special warnings and special precautions for use) regarding neurological events; update of section 4.8 (Undesirable effects) regarding infusion reactions, neurological and respiratory events ; minor corrections of section 5.1 (Pharmacodynamic Properties).	II-0023	II	25.07.02	14.10.02
Extension of the therapeutic indications to include Ankylosing Spondylitis. Section 4.1 (Therapeutic Indications), 4.2 (Posology and method of administration), 5.1 (Pharmacodynamic Properties) and section 4.8 (Undesirable effects) of the SPC were updated.	II-0024	II	20.02.03	15.05.03
Update of the SPC to reflect clinical experience with repeated administration in severe active Crohn's disease.	II-0025	II	20.02.03	15.05.03
Minor change of manufacturing process of the active substance	I-0026	I	21.11.02	09.12.02
Replacement of an excipient with a comparable excipient	I-0027	I	07.01.03	-
Third Annual Reassessment. Remicade remains authorised under exceptional circumstances.	S-0028	S	20.02.03	15.05.03
Update of the SPC section 4.8 (Undesirable effects) following CPMP assessment of 5th PSUR covering the period from 24.08.2001 to 23.02.2002.	II-0029	II	20.02.03	15.05.03
Minor change of manufacturing process of the active substance	I-0030	I	25.04.03	02.05.03
Extension of shelf-life or retest period of the active substance	I-0031	I	12.03.03	-
Update to the SPC Section 4.1 (Therapeutic Indications), 4.2 (Posology and method of administration), 5.1 (Pharmacodynamic Properties), 4.4 (Special warnings and special precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), and section 4.8 (Undesirable effects) of the SPC were updated together with the PL to include data from the ACCENT II trial with regard to the long	II-0032	II	24.07.03	20.10.03

[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.
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.

Scope	Application number	Type of modification[1]	Notification/ Opinion issued on[2]	Commission Decision Issued/amended on
term treatment (46 weeks) of Crohn's disease patients.				
Change in specification of starting material/intermediate used in manuf. of the active substance	I-0034	I	16.04.03	-
Minor changes in manufacture of the medicinal product	I-0035	I	24.07.03	29.07.03
Change to the test method and/or specifications for the active substance	II-0038	II	25.09.03	30.09.03
Minor change of manufacturing process of the active substance	I-0039	I	25.09.03	30.09.03
Change in test procedure of active substance	I-0040	I	25.09.03	30.09.03
Change in supplier of an intermediate compound used in manufacture of the active substance	I-0041	I	29.08.03	-
Change in in-process controls applied during the manufacture of the product	I-0042	I	03.10.03	-
Change(s) to the manufacturing process for the finished product	II-0043	II	17.12.03	22.12.03
Update of the Summary of Product Characteristics (SPC) sections 4.2 (Posology and method of administration), 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects).Based on the CPMP assessment of PSUR6 (covering the timeperiod 24/02/2002-23/08/2002) and PSUR7 (24/08/2002-23/02/2003): changes for infusion rate/infusion related reactions and vasculitis; inclusion of a warning regarding stricturing C.D. Further to the CPMP evaluation of the fourth annual reassessment, a sentence is reworded in section 4.2 regarding continuation of therapy in patients who show no evidence of therapeutic benefit. The Package Leaflet has been amended accordingly	II-0044	II	17.12.03	09.03.04
Update of the SPC, based on the ASPIRE study: update of section 4.1(Therapeutic Indications) to add treatment of methotrexate -naive subjects with early rheumatoid arthritis, of section 4.4 (Special warnings and special precautions for use) to add information about use of infliximab concurrently with live vaccines and of section 5.1 (Pharmacodynamic Properties) to add information about the ASPIRE trial. The MAH took this opportunity to also introduce minor spelling changes in the SPC. The PL is changed accordingly. In addition the MAH has completed the list of local representatives to include the 10 new EU member states in accordance with EMEA/QRD templates.	II-0045	II	22.04.04	08.06.04
Extension of the therapeutic indication to include patients with active psoriatic arthritis in SPC section 4.1 (Therapeutic Indications). The SPC sections 4.2 (Posology and method of administration) and 5.1 (Pharmacodynamic Properties) were updated with respectively the posology for the treatment of active psoriatic arthritis, and with information about the IMPACT trial. The Package Leaflet has been revised accordingly.	II-46	II	29.07.04	24.09.04
Change(s) to the test method(s) and/or specifications for the active substance	II-0047	II	26.02.04	05.03.04
Update of SPC section 4.8 (Undesirable effects) to include pancreatitis as requested by CPMP following assessment of PSUR8 (24.02.03 to 23.08.03); in addition the MAH proposes to add agranulocytosis.	II-0049	II	22.04.04	08.06.04
Renewal. Based on the review of the available information, the CPMP was of the opinion that the quality, safety and efficacy of Remicade continued to be adequately and sufficiently demonstrated and therefore considered that the benefit/risk profile of Remicade continued to be favourable.	R-50	R	23.06.04	20.09.04
Minor change in labeling or package leaflet not connected with the SPC (Art. 61.3 Notification)	N/0051	N	28.05.04	-