Enbrel

Procedural steps taken and scientific information after the authorisation
Changes made after 01/10/2004

For procedures finalised before 01/10/2004, please refer to module 8b

MAJOR CHANGES[1]

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
II/0111	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.8 of the Summary of product characteristics relating to uveitis. The PL is updated accordingly.This variation application is submitted further to the request of the CHMP following assessment of PSUR 16, covering the period 03 February 2008 to 02 February 2009.	24/09/2009	26/11/2009	SPC, PL	On the basis of the number of events of uveal inflammation that occurred coincident to etanercept use, the number of reports in etanercept patients with RA, published literature, and the reports of positive dechallenge and rechallenge, the proposal for addition of this event to Section 4.8 of the SPC as an uncommon adverse drug reaction is considered appropriate. The change made to the Package Leaflet is consistent with the SPC change, and is appropriate.
R/0110	Renewal of the marketing authorisation	24/09/2009	26/11/2009	SPC, Annex II, Labelling, PL	Based on the CHMP review of the available information and on the basis of a re-evaluation of the benefit risk balance, the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and therefore considered that that the benefit risk profile of Enbrel continues to be favorable. The CHMP recommends the renewal of the Marketing Authorisation for Enbrel with unlimited validity.
II/0113	Quality changes The MAH applied to register a new storage site of Enbrel cell banks.	19/11/2009	26/11/2009		
II/0112	Quality changes	22/10/2009	29/10/2009		

[1] Major changes e.g. Type II variations, Annex II applications, Renewals and Annual Reassessments
[2] SPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet)

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
	The MAH applied to tighten some in-process control during the manufacturing process of the drug substance.				
II/0109	Quality changes The MAH applied to revise his method for detection of adventitious virus during manufacture of the drug substance.	24/09/2009	01/10/2009		
II/0108	Changes to QPPV Update of DDPS (Pharmacovigilance) Update of the Detailed Description of the Pharmacovigilance System (DDPS). Consequently, Annex II has been updated to reflect the latest version of the DDPS. The MAH has also taken the opportunity to correct the contact detail of the UK local representative.	29/05/2009	16/07/2009	Annex II, PL	Update of the Detailed Description of the Pharmacovigilance System (DDPS) [Module 1.8.1] to reflect a change in the Qualified Person in the EEA for Pharmacovigilance (QPPV). Other administrative and editorial changed are incorporated in this revised DDPS (version 2.1)
II/0102	Quality changes The MAH has applied for the approval of a new 50 mg solution for injection in pre-filled pen presentation for Enbrel.	29/05/2009	16/07/2009	SPC, Labelling, PL	
II/0101	Update of Summary of Product Characteristics	29/05/2009	16/07/2009	SPC	Results from 5 clinical studies demonstrate that the long-term use of etanercept in the treatment of plaque psoriasis provides sustained efficacy and safety in the treatment of psoriasis with no evidence of increased toxicity. Thus, treatment beyond the current restriction of 24 weeks is supported, and provides a useful alternative to meeting the needs of patients. The removal of a time restriction for treatment courses in adult psoriasis is in line with other biological immunosuppressive therapies, many of which have a smaller safety database. No reliable predictive factors were identified, which would provide guidance to clinicians regarding those subjects who would be most appropriate for continuous therapy. Therefore, the decision to use intermittent or continuous therapy should be based on the physician's judgment in consultation with the patient, as specified in the CHMP psoriasis guidelines

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
II/0105	Change(s) to the test method(s) and/or specifications for the active substance Changes in drug substance specifications.	29/05/2009	04/06/2009		
II/0107	Update of Summary of Product Characteristics and Package Leaflet Updates to section 4.4 of the SPC with consequential changes to the PL regarding use of etanercept in patients with alcoholic hepatitis, based on a review of data from a pooled analysis of clinical trials, findings from published epidemiologic studies, and information from the MAH's pharmacovigilance database. The MAH has also taken this opportunity to make linguistic improvements and corrections to the product information based on a quality review of all translations of Product Information (PI) annexes for Enbrel.	23/04/2009	29/05/2009	SPC, PL	A review of data from a pooled analysis of clinical trials, findings from published epidemiologic studies, and information from the MAH's pharmacovigilance database shows that etanercept is ineffective in the treatment of alcoholic hepatitis. Furthermore in one study, the outcome of subjects receiving etanercept therapy included significantly higher rates of mortality (at 6 months) and serious infections than subjects receiving placebo. The use of etanercept's product information in the treatment of patients with alcoholic hepatitis is therefore not recommended. The product information has been updated accordingly.
II/0106	Update of Summary of Product Characteristics and Package Leaflet Update to section 4.4 and 4.8 of the SPC relating to Non-melanoma skin cancer. Consequential changes have been made to the Package Leaflet. The MAH has also taken this opportunity to make other minor changes to bring clarity and consistency in the SPC and PL. A change has also been made in the PL's list of local representatives. Relevant information relating to use of Enbrel in children (already present in the PL for the 25mg presentations) has now also been added to the PL for the 50mg presentations.	23/04/2009	29/05/2009	SPC, PL	Following a review of data from pooled analysis of psoriasis clinical trials, the United BioSource Corporation (UBC) meta-analysis of malignancy clinical trial data, findings from published epidemiologic studies, and post-marketing reports there is a risk that the occurrence of non melanoma skin cancer may be causally related to etanercept therapy. The Enbrel's product information has been updated accordingly.

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
II/0103	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.4 and 4.8 of the SPC relating to opportunistic infections. The PL is updated accordingly. The MAH also took the opportunity to update the Enbrel's 50mg presentations PL by deleting the sentence "Enbrel 50 mg should only be used by adults (aged 18 and over)". Enbrel 50 mg presentations were authorised for use in the paediatric population, therefore the sentence is no longer applicable.	19/02/2009	25/03/2009	SPC, PL	Opportunistic infections have been reported in association with etanercept (including invasive fungal, protozoal, bacterial and atypical mycobacterial infections). The most commonly reported invasive fungal infection was Pneumocystis; the second most commonly reported infection was Aspergillus. The MAH has investigated the opportunistic infections reported in completed clinical trials involving the administration of etanercept in all authorised indications. The MAH has also retrieved relevant case reports committed to the etanercept safety database up to 30 October 2008. The data suggest an increased risk of opportunistic infections associated with etanercept. The comparative clinical trial data set suggests an approximately threefold excess risk compared to controls. Opportunistic infections in the postmarketing setting appear to be associated with an appreciable mortality which may have been preventable if the nature of the infection had been correctly recognised and treated at an earlier stage in the illness. The SPC has previously noted a risk of opportunistic infection. Additional information to include these findings has been added to the relevant sections of the product information.
II/0104	Change(s) to the manufacturing process for the active substance Chenges in manufacturing process for active substance.	19/03/2009	23/03/2009		
II/0100	Quality changes The MAH proposes to reduce limits for endotoxines and bioburden of the harvest filtrate in-process control . In addition the MAH seeks to register a name change to a contract manufacturere.	18/12/2008	23/12/2008		
II/0099	Quality changes As a consequence of FUM 117, the MAH proposes to tighten some in-process controls for the drug substance.	18/12/2008	23/12/2008		

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
II/0096	Change(s) to the test method(s) and/or specifications for the finished product Change(s) to the test methods of the finished product.	18/12/2008	23/12/2008		
II/0095	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test methods for the active substance.	18/12/2008	23/12/2008		
II/0094	Extension of Indication Extension of therapeutic indications. To extend the therapeutic indications to include the treatment of chronic severe plaque psoriasis in children and adolescents from the age of 8 years who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies. The MAH also took the opportunity to make a correction in the preparation instructions in section 7 of the PL for Paediatric use. The MAH also made a correction in section 4.8 of the 50 mg presentations' Summary of Product Characteristics.	20/11/2008	22/12/2008	SPC, Annex II, PL	Please refer to the Scientific Discussion "Enbrel/H/C/000262/II/0094" for further information.
II/0097	Update of Summary of Product Characteristics and Package Leaflet To update section 4.8 of the Summary Product Characteristics (SPC) regarding skin and subcutaneous tissue and immune system disorders, based on information from spontaneous adverse reaction reports, published literature and clinical trials. The Package Leaflet (PL) was updated accordingly.	24/07/2008	29/08/2008	SPC, PL	On the basis of the number of reports received, several of which had a temporal relationship to the use of etanercept, the undesirable effect section (4.8) of the SPC was updated regarding skin and subcutaneous tissue disorders and the following adverse events added: psoriasis (including new onset and pustular, primarily palms and soles) and psoriasiform rash; Stevens-Johnson syndrome; erythema multiforme; Toxic epidermal necrolysis. Section 4.8 was also updated regarding immune system disorders to include: Macrophage activation syndrome (MAS, which is an excessive activation of white blood cells associated with inflammation), based on published and post-marketing experience reports of MAS occurring in temporal association with

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
	Section 4.4 of the SPC was also updated to reflect the occurrence of demyelination disorders in paediatric patients, as reported in PSUR 15 covering the period 03 February 2007 to 02 February 2008. In addition, the marketing authorisation holder (MAH) took the opportunity to make other changes to sections 6.3 of the SPC and 7 of the PL to improve clarity of the prescribing information. Furthermore, the MAH updated the contact details for some of its local representative (UK, Ireland and Germany).				etanercept therapy; and anti-neutrophilic cytoplasmic antibody (ANCA) positive vasculitis based on the review of the cases observed in patients which provide a suspicion that the occurrence of ANCA positive vasculitis is causally related to etanercept. The PL was updated accordingly. The warnings section was also revised to reflect the occurrence of demyelination in paediatric patients as reported in the 15th PSUR. Finally the MAH took the opportunity to update sections 6.3 of the SPC and 7 (user instructions) of the PL to improve clarity and to minimise potential damage to the needle whilst removing the needle cap.
II/0093	Update of Summary of Product Characteristics and Package Leaflet Section 4.2 of the SPC was updated to include a 50 mg once-weekly dosage regimen in the treatment of plaque psoriasis. Consequential changes were implemented in sections 4.8 and 5.1 of the SPC, and section 3 of the PL. In addition, the MAH took the opportunity to update section 2 of the PL on coadministration with anakinra or abatacept in line with information in the SPC. Furthermore, the ATC classification in section 5.1 was updated in accordance with the updated version of the World's Health Organisation ATC classification.	30/05/2008	07/07/2008	SPC, PL	Based on the data from clinical trial, the posology for plaque psoriasis was updated to include the possibility of administration of 50 g once weekly. The data showed that the 50 mg weekly regimen can be used as an alternative to 25 mg twice weekly. There were no new safety signals from the data presented nor would this be expected in view of the limited change in posology. Sections 4.2, 4.8 and 5.1 of the SPC were updated. Section 3 of the PL was updated accordingly. In addition the MAH took the opportunity to add a statement "You or the child should not use Enbrel with medicines that contain the active ingredient anakinra or abatacept" which was originally intended to be added with variation EMEA/H/C/262/II/87. Furthermore the MAH took the opportunity to amend the etanercept's ATC code in accordance with the updated version of the World's Health Organisation ATC classification.
II/0092	Change(s) to the test method(s) and/or specifications for the finished product Quality changes	26/06/2008	02/07/2008		
II/0091	Change(s) to the test method(s) and/or specifications for the active substance Quality	26/06/2008	02/07/2008		

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
II/0083	Quality changes Change(s) to the manufacturing process of the active substance. The MAH has further applied to add Wyeth Biotech Andover, MA, USA as an alternative site for creation of the Working Cell Bank (WCB).	21/02/2008	28/02/2008		
II/0090	Quality changes Change(s) to the test method of the finished product	13/12/2007	21/12/2007		
II/0088	Update of Summary of Product Characteristics and Package Leaflet To update section 4.8 of the SPC to include the new adverse event "interstitial lung disease (including pneumonitis and pulmonary fibrosis)" following a review of reports of interstitial lung disease presented in PSUR n. 14. The PL has been updated accordingly. Furthermore, the Marketing Authorisation Holder took the opportunity to amend some inconsistencies in the PL.	18/10/2007	19/11/2007	SPC, PL	In the 14th PSUR (covering the period from 3 August 2006 to 2 February 2007), the Marketing Authorisation Holder provided a cumulative review of reports of interstitial lung disease (ILD) from clinical studies, spontaneous ADR reports and from the published literature. A total of 252 medically confirmed reports of ILD (including pulmonary fibrosis and pneumonitis), which were reported in association with etanercept therapy have been reviewed. Many of the reports described a similar presentation of flu-like symptoms or respiratory symptoms and negative lung cultures. Many of the patients responded to steroid treatment; however some were associated with a fatal outcome. Although many of the reports were confounded by past medical history of respiratory disorders and use of concomitant medications, there were spontaneous reports which suggested a causal association with etanercept therapy. The estimated frequency of ILD was determined to be uncommon. Thus, section 4.8 of the SPC was updated to include the new adverse event "interstitial lung disease (including pneumonitis and pulmonary fibrosis)" under the new category "Respiratory, thoracic and mediastinal disorders".
II/0087	Update of Summary of Product Characteristics To include in sections 4.4 and 4.5 of the SPC data from two published studies on concomitant use of abatacept and etanercept which showed a higher frequency of serious	18/10/2007	19/11/2007	SPC	The Marketing Authorisation Holder provided data from two published studies which showed that there was a higher frequency of adverse events in rheumatoid arthritis patients when abatacept was used concomitantly with biological therapies, including etanercept. Furthermore, patients did not derive any extra benefits from this combined treatment. Thus, the CHMP concluded that the combination of abatacept and etanercept is not recommended.

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
	adverse events without clinical benefit. Thus, the combination of abatacept and etanercept is not recommended.				
II/0077	Update of Summary of Product Characteristics To update the sub-section "Antibodies to Enbrel" of section 5.1 of the SPC with information on the percentage of patients in whom antibodies to etanercept have been detected.	18/10/2007	19/11/2007	SPC	Following a post-approval commitment from the line extension EMEA/H/C/262/X/65 (Enbrel solution for injection in pre-filled syringes), the MAH presented data on anti-etanercept antibodies from 5 long-term studies in subjects with rheumatoid arthritis, psoriasis, and psoriatic arthritis. This analysis showed that antibodies to etanercept have been detected in the sera of some subjects treated with etanercept. These antibodies have all been non-neutralising and were generally transient and there appeared to be no correlation between antibody development and clinical response or adverse events. In subjects treated with approved doses of etanercept in clinical trials for up to 12 months, cumulative rates of anti-etanercept antibodies were approximately 6% of subjects with rheumatoid arthritis, 7.5% of subjects with psoriatic arthritis, 2.0% of subjects with ankylosing spondylitis, 7% of subjects with psoriasis, and 3% of subjects with juvenile idiopathic arthritis. The proportion of subjects who developed antibodies to etanercept in longer-term trials (of up to 3.5 years) increases over time, as expected. However, due to their transient nature, the incidence of antibodies detected at each assessment point was typically less than 7% in rheumatoid arthritis subjects and psoriasis subjects. In a long-term psoriasis study in which patients received 50 mg twice weekly for 96 weeks, the incidence of antibodies observed at each assessment point was up to approximately 9%.
II/0085	Quality changes Extension of Shelf life for Enbrel 25 mg pre-filled syringes.	20/09/2007	15/10/2007	SPC, Labelling, PL	
II/0082	Update of Summary of Product Characteristics Following the assessment of PSUR No. 13	19/07/2007	29/08/2007	SPC, Annex II	From the results of a study on the interaction between etanercept and digoxin, it emerged that the co-administration of etanercept and digoxin did not significantly affect the plasma concentration of either digoxin or etanercept. Thus, section 4.5 was updated to include

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
	(covering the period from 3 February 2006 to 2 August 2006), to update section 4.5 of the SPC to include a statement that no clinically significant pharmacokinetic interactions were observed in studies with digoxin or warfarin and to update Annex II to reflect that PSURs should be submitted annually. The MAH also took the opportunity to re-organise section 4.5 of the SPC to improve clarity.				information that no clinically significant pharmacokinetic interactions were observed in studies with digoxin. From the results of the study on the interaction between etanercept and warfarin, it emerged that no significant change in etanercept pharmacokinetics was observed after etanercept and warfarin combination therapy. Thus, section 4.5 was updated to include a statement that no clinically significant pharmacokinetic interactions were observed in studies with warfarin. Following the assessment of PSUR n. 13, the CHMP concluded that based on the safety profile for Enbrel in the currently authorised therapeutic indications the PSUR cycle should revert to yearly reporting instead of the current 6-monthly cycle. Thus, Annex II was updated to reflect that PSURs should be submitted annually.
II/0079	Update of Summary of Product Characteristics and Package Leaflet To update section 4.4 of the SPC to include precautions relating to the reactivation of hepatitis B virus and worsening of hepatitis C in patients receiving Enbrel. To include in section 4.4 of the SPC recommendations that patients should be evaluated for infections and for tuberculosis. Furthermore, to re-organise sections 4.4. and 4.8 of the SPC. To update the PL in order to reflect the changes implemented in the SPC. Finally, a Patient Alert Card has been included in the Product Information.	19/07/2007	29/08/2007	SPC, PL	The MAH conducted a cumulative review of safety data to identify reports on reactivation of viral hepatitis in etanercept-treated patients who had chronic viral hepatitis prior to the Enbrel therapy. This review identified reports on reactivation of hepatitis B virus (HBV), in patients who were chronic carriers of this virus, and reports of worsening of hepatitis C in patients receiving Enbrel. Patients at risk for HBV infection should be evaluated for prior evidence of HBV infection before initiating Enbrel therapy. Caution should also be exercised when administering Enbrel to patients identified as carriers of HBV. Since serious infections and cases of active tuberculosis have been reported in patients treated with Enbrel, recommendations, regarding the evaluation of patients for infections before, during and after Enbrel use, including screening and appropriate treatment for tuberculosis in all patients prior to initiating Enbrel therapy, have been added to the Enbrel SPC. The text in section 4.4 of the SPC has been re-organised under two paragraphs, "Immunosuppression" and "Malignancies and lymphoproliferative disorders", and section 4.8 of the SPC has been revised to focus on serious infections.

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
					A Patient Alert Card has been included in the Product Information. This Patient Alert Card should be given to patients treated with Enbrel. It provides important safety information relating to infections and congestive heart failure (consistent with the Package Leaflet) for patients and physicians. Finally, the MAH took the opportunity to improve the instruction for use of Enbrel in section 7 of the PL to provide a clearer diagram showing the recommended injection sites.
II/0081	Quality changes	24/05/2007	23/07/2007		
II/0080	Change(s) to the manufacturing process for the active substance	24/05/2007	30/05/2007		
II/0076	Change(s) to the manufacturing process for the finished product Changes to the manufacturing process for the finished product. Additionally the Marketing Authorisation Holder (MAH) took the opportunity to update the Product Information according to the latest EMEA/QRD template.	22/02/2007	02/04/2007	SPC, Annex II, Labelling, PL	The MAH applied for the use of dihydrate forms of sodium phosphate for the pre-filled syringes. Therefore, section 6.1 "List of excipients" of the SPC, the labelling and section 6 "Further information. What Enbrel contains" have been updated to include the two new excipients "sodium phosphate monobasic dihydrate" and "sodium phosphate dibasic dihydrate". Additionally, the product information has been updated in accordance with the latest QRD template version 7.2.
II/0072	Extension of Indication To update sections 4.1, 4.8 and 5.1 of the SPC to reflect 2 year data of a placebo-controlled clinical study in the treatment of psoriatic arthritis. Section 1 of the PL has been updated accordingly. Furthermore, the MAH took the opportunity to complete the list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania) and to amend the name and contact details of the Icelandic local representative	14/12/2006	18/01/2007	SPC, PL	Clinical and radiographic results from a 2 year clinical study in patients with active psoriatic arthritis were assessed. The study began with a 6-month double blind, placebo-controlled period where patients were randomised to receive subcutaneous injections of 25 mg etanercept or placebo twice weekly. Patients could then continue in a blinded maintenance period of up to 6 months, until all patients had completed the initial 6-month period. After the maintenance period, all subjects received open-label 25 mg etanercept twice-weekly for 1 year. Radiographs of hands and wrists were obtained at baseline and months 6, 12, and 24. In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression at 12 months was higher in the Enbrel group compared with the placebo group (73% vs. 47%, respectively). The effect of Enbrel on radiographic progression was maintained in patients who continued on treatment during the second

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
					year. The slowing of peripheral joint damage was observed in patients with polyarticular symmetrical joint involvement. Enbrel treatment resulted in improvement in physical function during the double blind period, and this benefit was maintained during the longer term exposure of up to 2 years. Therefore section 4.1 "Therapeutic indications" of the SPC was updated to include that Enbrel has been shown to improve physical function in patients with psoriatic arthritis, and to reduce the rate of progression of peripheral joint damage as measured by X ray in patients with polyarticular symmetrical subtypes of the disease. Additionally, section 5.1 "Pharmacodynamic properties" of the SPC was updated to include the radiographic results observed in this clinical study in patients with active psoriatic arthritis. As during the open-label period of the study 1 patient reported a serious infection (pneumonia), section 4.8 "Undesirable effects" of the SPC was updated accordingly. The PL, section 1 "What Enbrel is and what it is used for" was amended to reflect the update of the SPC.
II/0075	Update of Summary of Product Characteristics and Package Leaflet To update section 4.8 of the SPC in paediatric patients with juvenile idiopathic arthritis" to include "appendicitis" as a severe event observed in clinical trials in children and to indicate that infections seen in this population were generally mild to moderate in severity. Additionally to improve consistency in section 7 "Instructions for preparing and giving an injection of Enbrel" across all the PLs.	18/10/2006	29/11/2006	SPC, PL	Following the assessment of safety data concerning the severity and localisation of infections observed in clinical studies in children with juvenile idiopathic arthritis, the CHMP concluded that a number of infections were mild to moderate in severity and that appendicitis needed to be included in section 4.8 of the SPC. Therefore the MAH amended section 4.8 of the SPC "Undesirable effects in paediatric patients with juvenile idiopathic arthritis" to include "appendicitis" as a severe event observed in clinical trials in children and to indicate that infections seen in this population were generally mild to moderate in severity.
II/0074	Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	20/10/2006	SPC, PL	The MAH conducted a pharmacokinetic study in which a single subcutaneous dose (3 mg/kg) of 125I-radiolabelled Enbrel was administered to lactating rats.

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
	To update section 4.6 of the SPC to include the information that etanercept was excreted in the milk of rats and detected in the serum of the pups as shown in a pre-clinical study. To implement a minor change in section 7 (point h) of the PL for Enbrel 50 mg "powder and solvent for solution for injection".				This study showed that etanercept and its breakdown products are transferred to pups from maternal rats. Pups were exposed to significant amounts of Enbrel, and to greater amounts of breakdown products, after administration of Enbrel to maternal rats. The CHMP agreed with the MAH to include in section 4.6 "Pregnancy and Lactation" of the SPC information that etanercept was excreted in the milk of rats and detected in the serum of the pups as shown in a pre-clinical study.
II/0073	Change(s) to the manufacturing process for the finished product	21/09/2006	28/09/2006		
X/0065	02_iv_Change or addition of a new pharmaceutical form The Marketing Authorisation Holder applied to extend the range of 25mg and 50mg presentations to include a liquid formulation in pre-filled syringes.	27/07/2006	26/09/2006	SPC, Labelling, PL	The Marketing Authorisation Holder applied to extend the range of 25mg and 50mg presentations to include a liquid formulation (solution for injection) in pre-filled syringes. The new formulation has a modified formulation compared to the Enbrel presentations already approved (powder for solution for injection). The main advantage with the pre-filled syringe presentations is the elimination of the reconstitution step, facilitating administration of the product.
X/0063	02_iii_Change or addition of a new strength/potency The Marketing Authorisation Holder applied to add a new paediatric 25 mg multidose strength to the product range.	01/06/2006	04/08/2006	SPC, Labelling, PL	The Marketing Authorisation Holder applied to extend the range of 25mg and 50mg presentations to include a 25mg formulation (powder for solution for injection) which is reconstituted with a bacteriostatic solvent for multidose administration. The new formulation uses bacteriostatic solvent (benzyl alcohol) for reconstiution compared to the Enbrel presentations already approved (powder for solution for injection) which are reconstituted with water for injections. The main advantage with the preserved paediatric presentation is the ability to use up to two doses of the product from the vial, thereby, reducing wastage.
II/0069	Update of Summary of Product Characteristics and Package Leaflet As requested by the CHMP following the assessment of PSUR n. 10 (covering the period from 20 July 2004 to 2 February 2005), the MAH updated section 4.8 of the	27/04/2006	31/05/2006	SPC, PL	In the reporting period of the PSUR n. 10 (from 20 July 2004 to 2 February 2005) the MAH received a total of 38 reports covering 49 medically confirmed suspected adverse reactions relating to abnormal liver function tests. The reports were similar to those discussed in the cumulative review of hepatic disorders that the MAH has provided along with PSUR n. 10.

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
	SPC to include a new "rare" undesirable effect (Elevated liver enzymes) under a new body system (Hepatobiliary disorders). As requested by the CHMP following the outcome of an Ad Hoc Expert Group meeting on TNF-antagonists, the MAH updated section 4.4 of the SPC to include a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist. Section 4. of the PL has been amended to reflect the new undesirable effect. In addition, the MAH took the opportunity to improve the clarity of the instructions provided in the section "Instructions for preparing and giving an injection of Enbrel" in the PL. Additionally, following a request from the CHMP the wording of the indication 'polyarticular-course juvenile chronic arthritis' has been modified to reflect the currently valid definition 'polyarticular juvenile idiopathic arthritis'.				The CHMP concluded that a large number of reports of hepatobiliary disorders have been presented in the PSUR n.10, some of which provided reasonable information on positive dechallenge and rechallenge. Therefore, the CHMP concluded that the MAH should provide a further review of hepatobiliary disorders in the next PSUR with a view to updating the Product Information with a statement regarding this issue. Therefore, the MAH has examined his database with a focus on case reports containing at least one event coded to MedDRA terms consistent with elevation of liver enzymes, without a reasonable alternative explanation for the event, and which showed evidence of a positive rechallenge or dechallenge. The MAH concluded on the basis of this analysis that there are reasonable grounds to suspect a causal association between etanercept administration and the occurrence of elevations of serum concentrations of hepatic enzymes. The MAH estimated the frequency of elevation of liver enzymes in association with etanercept to be less than 1/1000 patients exposed, based on an analysis of the incidence of adverse events in placebo-controlled clinical trials in which methotrexate was not allowed to be administered. Therefore section 4.8 "Undesirable effects" of the SPC has been updated to include "Hepatobiliary disorders: Rare: Elevated liver enzymes" and section 4 "Possible side effects" of the PL has been updated to include "Liver disorders: Rare: Elevated liver blood tests". Following the review of the available data on malignancies and lymphoproliferative disorders in patients treated with TNF Alpha Blockers, the CHMP concluded that section 4.4 "Special warnings and special precautions for use" should be updated to include the information that more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients in the controlled portions of clinical trials of TNF-antagonists, . However, the incidence was rare, and the follow-up period of placebo patients was shorter than for patients receiving TNF-antagonist therapy. Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. With the

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
					current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded. The section "Instructions for preparing and giving an injection of enbrel" has been updated to improve clarity in the instructions for preparing and giving Enbrel. The current wording 'polyarticular-course juvenile chronic arthritis' has been changed to reflect the currently valid definition 'polyarticular juvenile idiopathic arthritis' throughout the entire Product Information.
II/0070	Change(s) to the test method(s) and/or specifications for the active substance	27/04/2006	03/05/2006		
II/0066	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.2 of the SPC for Enbrel 25 mg and 50 mg to include an alternative 50 mg once weekly dosing regimen for the treatment of ankylosing spondylitis and psoriatic arthritis. Consequentially changes to sections 4.8, 5.1 and 5.2 of the SPC for Enbrel 25 mg and 50 mg have also been introduced to reflect the submitted supporting data. Since this variation is for an alternative 50 mg dosage regimen for ankylosing spondylitis and psoriatic arthritis, these two indications have been added to Section 4.1 of the SPC for Enbrel 50 mg. The package leaflets have been amended to reflect the changes implemented in the SPC.	23/02/2006	03/04/2006	SPC, PL	The recommended posology for Enbrel in psoriatic arthritis and ankylosing spondylitis is 25 mg Enbrel administered twice weekly. The objective of this type II variation is to amend the dose regimen for etanercept to include 50 mg once per week in the treatment of psoriatic arthritis and ankylosing spondylitis in adults in order to increase patient convenience and enhance compliance. The safety and efficacy of 50 mg Enbrel administered once weekly versus 25 mg Enbrel administered twice weekly were evaluated in a double-blind, placebo-controlled study of 356 patients with active ankylosing spondylitis. The primary objective of this study was to assess the efficacy and safety of etanercept 50 mg once weekly. The secondary objective was to evaluate the quality of life and pharmacokinetics of etanercept 50 mg once weekly. Subjects were randomly assigned to receive either subcutaneous injections of etanercept 50 mg once weekly, etanercept 25 mg twice weekly or placebo. The results from this study indicate that the safety and efficacy profiles of the 50 mg once weekly and 25 mg twice weekly regimens were similar. In addition the two etanercept dosing regimens produce equivalent AUC exposure as demonstrated by a population pharmacokinetics analysis which found that in these ankylosing spondylitis patients, the etanercept steady state AUCs were 466 ug*hr/mL and 474 ug*h/mL for 50 mg Enbrel once weekly (N= 154)

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
					and 25 mg twice weekly (N = 148), respectively. The CHMP concluded that the results from this study can be extrapolated to patients with psoriatic arthritis given that etanercept is equally effective in this population.
II/0060	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.1, 4.4, 4.8 and 5.1 of the SPC to reflect 2-year data from a controlled clinical study comparing Enbrel alone, methotrexate alone, and combination therapy with Enbrel and methotrexate, in adults with rheumatoid arthritis. Sections 1 and 4 of the PL were updated in accordance.	26/01/2006	13/03/2006	SPC, PL	Clinical and radiographic results from a 2-year clinical study comparing Enbrel alone, methotrexate alone, and combination therapy with Enbrel and methotrexate have been assessed in adults with reumathoid arthritis. In this clinical study, structural joint damage was assessed radiographically and expressed as change in Total Sharp Score (TSS) and its components, the erosion score and joint space narrowing score (JSN). Radiographs of hands/wrists and feet were read at baseline, 12, and 24 months. The results of this 2-year study showed that the mean changes from the baseline in TSS were lower for patients in combination therapy with Enbrel and methotrexate and the etanercept group compared with the methotrexate group and this was confirmed over 24 months. In an analysis in which all patients who dropped out of the study for any reason were considered to have progressed, the percentage of patients without progression (TSS change = 0.5) at 24 months was higher in the Enbrel in combination with methotrexate group compared with the Enbrel alone and methotrexate alone groups (62%, 50%, and 36%, respectively; $p<0.05$). The difference between Enbrel alone and methotrexate alone was also significant ($p<0.05$). Among patients who completed a full 24 months of therapy in the study, the non-progression rates were 78%, 70%, and 61%, respectively. The mean changes from baseline in erosion scores for the combination treatment group and the etanercept group were significantly lower compared with the methotrexate group. At 24 months the combination-treated patients had significantly lower erosion change scores than patients treated with etanercept alone. The mean changes from baseline to 12 and 24 months in joint space narrowing were significantly lower for patients in the combination group compared with the methotrexate group . In conclusion significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy were observed after 24 months in adults

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
					with rheumatoid arthritis. The clinical results showed significant advantages for Enbrel in combination with methotrexate compared with Enbrel monotherapy and methotrexate monotherapy after 24 months in respect of ACR(American College of Rheumatology response criteria), HAQ (Health Assessment Questionnaire), and DAS (Disease activity score) Therefore the therapeutic indications were revised in order to reflect that the the combination of Enbrel with methotrexate has been shown to be superior to Enbrel monotherapy in the treatment of moderate to severe active rheumatoid arthritis. The package leaflet has been updated to reflect the changes to the SPC.
II/0067	Change(s) to the manufacturing process for the active substance	23/02/2006	03/03/2006		
II/0054	Update of Summary of Product Characteristics and Package Leaflet This variation relates to an update of section 4.4 and section 4.8 of the SPC to include new clinical information from a study in Wegener's granulomatosis. The list of local representatives (Norway and Finland) in the PL has been updated.	23/06/2005	01/08/2005	SPC, PL	This variation relates to data submitted by the MAH concerning a trial in which patients with Wegener's granulomatosis were treated with etanercept or placebo (the Wegener's granulomatosis etanercept trial - WGET). WGET was a placebo-controlled trial, in which 89 patients were treated with Enbrel in addition to standard therapy (including cyclophosphamide or methotrexate, and glucocorticoids) for a median duration of 25 months. The results of WGET have not shown Enbrel to be an effective treatment for Wegener's granulomatosis. The incidence of non-cutaneous malignancies of various types was significantly higher in patients treated with Enbrel than in the control group. Since the results of WGET suggest that Enbrel is not recommended for the treatment of Wegener's granulomatosis, the MAH proposed to update section 4.4 "Special warnings and special precautions for use" and section 4.8 "Undesirable effects" of the SPC to include these new clinical data from WGET.
II/0057	Change(s) to the manufacturing process for the active substance Change(s) to the manufacturing process for the finished product The Marketing Authorisation Holder applied to add Wyeth Grange Castle as an additional site for the manufacture of etanercept active	23/06/2005	22/07/2005	Annex II	

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
	substance.				
X/0047	02_iii_Change or addition of a new strength/potency Extension of the Marketing Authorisation for Enbrel 50 mg.	20/01/2005	28/04/2005	SPC, Annex II, Labelling, PL	Following the assessment of data on quality, safety and efficacy the CHMP concluded that that the benefit/risk profile for Enbrel 50 mg for the treatment of active rheumatoid arthritis and plaque psoriasis, was favourable and therefore recommended the granting of the marketing authorisation for Enbrel 50 mg. "Click here for further information".
II/0056	Change(s) to the manufacturing process for the active substance	16/03/2005	22/03/2005		
II/0055	Change(s) to the test method(s) and/or specifications for the finished product	16/03/2005	22/03/2005		
R/0053	Renewal of the marketing authorisation	16/12/2004	10/03/2005	SPC, Annex II, Labelling, PL	
II/0048	Update of Summary of Product Characteristics and Package Leaflet Update of section 4.5 in the SPC to add information regarding the interaction between sulfasalazine and Enbrel in accordance with the CPMP recommendations dated 3 May 2004, following the assessment of the 7th Enbrel PSUR. Update of the information concerning vaccination in section 4.4 and section 4.5 in the SPC in line with the company reference safety information (Core Data Sheet version 10.0). Amendment of the order of instructions for preparing and giving an injection of Enbrel in the PL for greater clarity. Minor change to the list of local representative (France) in the PL.	15/12/2004	10/03/2005	SPC, PL	The results of a clinical study showed that patients who were receiving sulfasalazine and Enbrel experienced a statistically significant decrease in mean white blood cell counts in comparison to groups treated with Enbrel or sulfasalazine alone. Therefore section 4.5 "Interaction with other medicinal products and other forms of interaction" in the SPC was updated to add these information on the interaction between sulfasalazine and Enbrel. In line with the company reference safety information, the data on a clinical study in patients with psoriatic arthritis receiving Enbrel and a vaccine were added in section 4.4 "Special warnings and special precautions for use" in the SPC: most psoriatic arthritis patients receiving Enbrel were able to mount effective B-cell immune response to pneumococcal polysaccharide vaccine, but titers in aggregate were moderately lower and few patients had two-fold rises in titers compared to patients not receiving Enbrel. Section 4.5 "Interaction with other medicinal products and other forms of interaction" in the SPC was amended as well (deletion of statement "No data are available on the effects of vaccination in patients receiving Enbrel"). The order of instructions for preparing and giving an injection of Enbrel in the PL was amended for greater clarity.

No	Scope	Opinion issued on	Commission Decision Issued/ amended on	Product Information affected[2]	Summary
					The name of the French local representative in the PL was amended.
II/0050	Quality changes	21/10/2004	05/11/2004		
II/0046	Change(s) to the manufacturing process for the active substance	21/10/2004	05/11/2004		
II/0045	Change(s) to the manufacturing process for the finished product	21/10/2004	05/11/2004		

MINOR CHANGES[3]

No	Scope	Product Information affected[2]	Date[4]
IA/0115	09_Deletion of manufacturing site		11/11/2009
IA/0114	25_b_02_Change to comply with Ph. - compliance with EU Ph. update - excipient		22/09/2009
IA/0098	09_Deletion of manufacturing site		21/08/2008
IA/0089	05_Change in the name and/or address of a manufacturer of the finished product		08/10/2007
N/0086	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	Labelling, PL	24/08/2007
IA/0078	28_Change in any part of primary packaging material not in contact with finished product 30_a_Change in supplier of packaging components - deletion of supplier		15/12/2006
IA/0071	09_Deletion of manufacturing site		12/04/2006
IA/0068	37_a_Change in the specification of the finished product - tightening of specification limits		09/01/2006
IB/0064	12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening		25/10/2005
IA/0062	09_Deletion of manufacturing site		11/07/2005
IA/0061	05_Change in the name and/or address of a manufacturer of the finished product	Annex II, PL	21/06/2005
IA/0059	09_Deletion of manufacturing site	Annex II, PL	02/05/2005
IB/0058	30_b_Change in supplier of packaging components - replacement/addition		29/03/2005
IB/0052	41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	SPC, Labelling, PL	08/10/2004

[3] Minor changes e.g. Type I variations and Notifications
[4] Date of entry into force of the change