Enbrel

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification[1] issued on	Commission Decision Issued[2] / amended on	Product Information affected[3]	Summary
II/0254	Update of section 4.8 of the SmPC in order to update the frequency of Adverse Drug Reaction (ADR) `Glomerulonephritis' from `Not Known' to `Rare' following PSUSA/00010795/202302 procedure, based on available evidence from clinical trials, literature, and post-marketing data. The Package	11/04/2024		SmPC and PL	For more information, please refer to the Summary of Product Characteristics.

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	Leaflet is updated accordingly. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				
PSUSA/10795 /202302	Periodic Safety Update EU Single assessment - etanercept	12/10/2023	14/12/2023		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10795/202302.
IB/0253	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/10/2023	14/12/2023	SmPC, Annex II, Labelling and PL	
II/0249	Update of section 4.6 of the SmPC in order to update information on breast feeding exposure based on the cumulative review of etanercept specific pharmacology, safety database and published medical literature. The Package Leaflet is updated accordingly. In addition, the MAH is taking this opportunity to correct minor administrative and typographical changes to the SmPC, Labelling and Package Leaflet. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	06/07/2023	14/12/2023	SmPC, Labelling and PL	SmPC new text Limited information from the published literature indicates etanercept has been detected at low levels in human milk. Etanercept could be considered for use during breast feeding taking into account the benefit of breast feeding for the child and the benefit of therapy for the woman. While systemic exposure in a breastfed infant is expected to be low because etanercept is largely degraded in the gastrointestinal tract, limited data regarding systemic exposure in the breastfed infant are available. Therefore, the administration of live vaccines (e.g., BCG) to a breastfed infant when the mother is receiving etanercept could be considered 16 weeks after stopping breast-feeding (or at an earlier timepoint if the infant etanercept serum levels are undetectable).

					For more information, please refer to the Summary of Product Characteristics.
II/0251	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	02/02/2023	n/a		
IB/0250	B.II.z - Quality change - Finished product - Other variation	12/12/2022	20/03/2023	SmPC	Product information updated to implement editorial updates impacting SmPC Section 6.5 "Nature and contents of container".
IB/0248	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	17/11/2022	n/a		
II/0246	Update of section 5.1 of the Summary of product characteristics (SmPC) in order to update clinical information based on final results obtained from the clinical paediatric study B1801023 (CLIPPER 2). Also, the Risk management plan (RMP) was brought up to date with version 7.6. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	05/05/2022	20/03/2023	SmPC	Of the 127 patients in the parent study (Study B1801014) 109 participated in the open-label extension study (Study B1801023 – CLIPPER 2) and were followed for 8 years. The extension study was designed to further characterise the long-term safety profile, including malignancy and other safety adverse events (SAEs), and clinical benefit for those paediatric subjects who received at least 1 dose of etanercept and completed approximately 96 weeks of etanercept treatment in the parent study. At the end of the extension study 84/109 (77%) patients had completed the study; 27 (25%) while actively taking Enbrel, 7 (6%) had withdrawn from treatment due to low/inactive disease; 5 (5%) had re-started Enbrel following an earlier withdrawal from treatment, and 45 (41%) had stopped Enbrel (but remained under observation); 25/109 (23%) patients permanently discontinued from the study. Improvements in clinical status achieved in the parent study were generally maintained for all efficacy endpoints during the entire

					follow-up period. Patients actively taking Enbrel could enter an optional withdrawal-retreatment period once during the extension study based on investigator's judgment of clinical response. 30 patients entered the withdrawal period. 17 patients were reported to have a flare (defined as ≥ 30% worsening in at least 3 of the 6 ACR Pedi components with ≥ 30% improvement in not more than 1 of the remaining 6 components and a minimum of 2 active joints); median time to flare after Enbrel withdrawal was 190 days. 13 patients were re-treated and the median time to re-treatment from withdrawal was estimated as 274 days. Due to the small number of data points, these results should be interpreted with caution. The safety profile of the extension study (Study B1801023 – CLIPPER 2) was consistent with that observed in the parent study (Study B1801014). For more information, please refer to the Summary of Product Characteristics.
II/0244	C.I.13: Submission of the final report from study B1801310 (BIKER), listed as a category 3 study in the RMP. This is an observational Post-Authorisation Safety Study (PASS) of Etanercept and Methotrexate in the treatment of Juvenile Idiopathic Arthritis (JIA) using data obtained from participants in the German Biologics JIA Registry (BIKER) to monitor long-term safety and effectiveness of etanercept in the treatment of JIA in regular clinical practice. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	05/05/2022	n/a		

II/0243/G	This was an application for a group of variations. B.II.e.z - Change in container closure system of the Finished Product - Other variation B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	24/03/2022	20/03/2023	SmPC, Labelling and PL	The SmPC sections 1, 2, 4.2, 4.4, 6.4, 6.5, 6.6, 8 (in the presentation of the solutions for injection in dose-dispenser cartridges) have been updated to include the information related to the dose-dispenser cartridge and SMARTCLIC injection device. The Labelling, PL have been updated accordingly. In addition, the list of local representatives in the PL is being revised, correcting the details for Belgien/Luxemburg and the information on the UK Local Representative is updated to include Northern Ireland.
N/0247	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/11/2021	20/03/2023	PL	
IA/0245	A.7 - Administrative change - Deletion of manufacturing sites	08/06/2021	n/a		

IB/0242	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/05/2021	17/06/2021	SmPC	
WS/1653	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the second 5-year report from the British Society for Rheumatology Biologics Register (BSRBR, also referred as study B1801309) listed as a category 3 study in the RMP. This is a prospective observational cohort study which investigates the long-term outcomes of patients with rheumatoid arthritis treated with etanercept with particular reference to safety. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	06/05/2021	n/a		The final study report from the BSRBR (listed as a category 3 study in Enbrel RMP) addressed the following safety concerns: malignancy; serious and opportunistic infections; central demyelinating disorders; aplastic anaemia; congestive heart failure; acute ischemic cardiovascular events. The review showed that the results are consistent with the current overall safety profile of etanercept in the approved indications for adult patients. A review of cervical cancer risk was also performed by the MAH including data from other registries. A total of 102 cases of cervical cancer (20 from BSRBR, 2 from RABBIT and 76 from ARTIS registries) were retrieved in the etanercept exposed cohorts. The results of the analyses showed that the incidence rate in the Enbrel-exposed group was not significantly higher than the comparator group (csDMARD). PRAC agreed that no causal association could be established between cervical cancer and etanercept. The MAH should continue to monitor cervical cancer events using routine pharmacovigilance activities. Overall, no new safety concerns were identified and no amendments to the product information are warranted in this variation.
II/0234	Update of section 5.1 of the SmPC in order to update the efficacy and safety information based on the final results from study (B1801381); this is a multicenter open-label study which evaluated withdrawal and retreatment of etanercept in subjects with non-	04/02/2021	17/06/2021	SmPC, Annex II and PL	Study B1801381 was a multi-center, open-label, phase 4, 3-period study which evaluated the withdrawal and retreatment of Enbrel in patients with active non-radiographic axial spondyloarthritis (nr-AxSpa) who achieved an adequate response following 24 weeks of

	radiographic axial spondyloarthritis who achieved an adequate response following 24 weeks of treatment. In addition, the MAH took the opportunity to make some editorial changes and bring the PI in line with the latest QRD template version 10.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				treatment. At week 24, 119 (57%) patients achieved inactive disease and entered into the Period 2 40-week withdrawal phase where subjects discontinued etanercept, yet maintained the background NSAID. The primary measure of efficacy was the occurrence of flare (defined as an ASDAS erythrocyte sedimentation rate (ESR) greater than or equal to 2.1) within 40 weeks following withdrawal of Enbrel. Patients who flared were retreated with Enbrel 50 mg weekly for 12 weeks (Period 3). In Period 2, the proportion of patients experiencing ≥1 flare increased from 22% (25/112) at week 4 to 67% (77/115) at week 40. Overall, 75% (86/115) patients experienced a flare at any time point within 40 weeks following withdrawal of Enbrel. The key secondary objective of Study 2 was to estimate time to flare after withdrawal of Enbrel and additionally compare the time to flare to patients from Study 1 who met the Study 2 withdrawal phase entry requirements and continued Enbrel therapy. The median time to flare following withdrawal of Enbrel was 16 weeks (95% CI: 13-24 weeks). Less than 25% of patients in Study 1 who did not have treatment withdrawn experienced a flare over the equivalent 40-weeks as in Period 2 Study 2. The time to flare was statistically significantly shorter in subjects who discontinued Enbrel treatment (Study 2) compared to subjects who received continuous etanercept treatment (Study 1), $p < 0.0001$. Of the 87 patients who entered Period 3 and were retreated with Enbrel 50 mg weekly for 12 weeks, 62% (54/87) reachieved inactive disease, with 50% of them reachieving it within 5 weeks (95% CI: 4 8 weeks, KM analysis).

					The trend of clinical improvement in Period 1, worsening in Period 2, and improvement in Period 3 was observed across clinical measures. For more information, please refer to the Summary of Product Characteristics.
II/0238	Update of section 4.8 of the SmPC to add headache to the list of adverse drug reactions with a frequency very common; the package leaflet is updated accordingly. In addition, the MAH took the opportunity to remove text for inflammatory bowel disease and uveitis specific to the paediatric population from section 4.4 and 4.8 of the SmPC and the package leaflet for consistency as requested by PRAC in the latest PSUSA (PSUSA/00010795/202002). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	14/01/2021	17/06/2021	SmPC and PL	In clinical trials (including all indications for Enbrel), 10,7% (826 /7722) of the patients included in the etanercept arm developed headache, this corresponds to a frequency 'very common' as per the SmPC guideline. Therefore, based on clinical trials data and post-marketing experience, the adverse drug reaction 'headache' is added to the tabulated list of adverse reactions in section 4.8 of the SmPC with a frequency 'very common'. The package leaflet is updated accordingly.
IA/0241	A.7 - Administrative change - Deletion of manufacturing sites	11/01/2021	17/06/2021	Annex II and PL	
N/0239	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	30/11/2020	17/06/2021	PL	
IAIN/0237	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/10/2020	17/06/2021	SmPC and PL	
IB/0235/G	This was an application for a group of variations.	23/09/2020	n/a		

	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation				
PSUSA/10795 /202002	Periodic Safety Update EU Single assessment - etanercept	03/09/2020	n/a		PRAC Recommendation - maintenance
WS/1747	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of an updated RMP (version 7.4) in line with the latest GVP Module V RMP template (rev. 2) and revision of the list of safety concerns. In addition, the MAH took the opportunity to implement outcomes of previous procedures (type II variation EMEA/H/C/WS/1270 and PSUR EMEA/H/C/PSUSA/001295/201902) to remove or consolidate risks. The MAH is also removing the addendum to RMP version 6.3., making clinical and post-marketing data updates in the RMP and reflecting the completion of post-authorisation studies. Furthermore, the 'patient alert card' is renamed 'patient card' throughout the SmPC, package leaflet and Annex IID and the additional risk minimisation measures are updated in the Annex IID of the product information. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	11/06/2020	17/06/2021	SmPC, Annex II and PL	Within this variation the list of safety concerns for Enbrel has been updated as follows: Important identified risks: Malignancy (including lymphoma and leukemia); Serious and opportunistic infections (including tuberculosis, Legionella, Listeria, parasitic infection); Demyelinating disorders; Aplastic anemia and pancytopenia; CHF in adult subjects. Important potential risks: Encephalitis/leukoencephalomyelitis; Progressive multifocal leukoencephalopathy; Impaired growth and development in juvenile subjects; Acute ischemic CV events in adult subjects. Missing information: Immunogenicity profile and related clinical outcomes of etanercept manufactured using the SFPHC process in a real-life post-marketing setting. The educational material for Enbrel consists of a patient card which is provided to etanercept prescribing physicians for distribution to patients receiving etanercept. The healthcare professional guide and needle free demonstration device are no longer needed as educational materials.

	authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
IB/0233	B.II.z - Quality change - Finished product - Other variation	08/06/2020	n/a		
PSUSA/1295/ 201902	Periodic Safety Update EU Single assessment - etanercept (except for biosimilars)	19/09/2019	14/11/2019	SmPC and PL	Please refer to Enbrel EMEA/H/C/PSUSA/00001295/201902 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
WS/1654	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from study (B1801311 - BADBIR) listed as a category 3 study in the RMP. This is a prospective cohort study that compared patients treated with biologic interventions (etanercept, adalimumab, and ustekinumab) and patients with similar disease characteristics but exposed only to conventional non-biologic systemic therapies. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/10/2019	n/a		The primary objective of this British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) was to investigate the long-term safety outcomes of psoriasis patients treated with biologic therapy. The data were collected during the observation of psoriasis patients treated with etanercept and conventional therapy who were registered in the BADBIR register between 01 September 2007 and 31 July 2018. As of the 31st of July 2018, 1811 patients were registered with the etanercept cohort (n=1379, 76%) or have switched to etanercept from another biologic therapy (n=432, 24%), and 5346 patients were registered for the conventional cohort. Patients were recruited into the etanercept cohort from 123 centres across the UK and the Republic of Ireland. The analyses indicated a significantly increased risk of serious infection (aHR 1.79; 95% CI 1.37,2.33), respiratory (aHR 2.42; 95% CI 1.18, 4.95), cardiac (aHR 1.63; 95% CI 1.04, 2.57), nervous system (aHR 2.18; 95% CI 1.32, 3.61), skin (non-cancer; aHR 1.55; 95% CI 1.07, 2.24) and

					malignant events (aHR 1.49; 95% CI 1.13, 1.95) for those psoriasis patients currently or previously receiving etanercept. Within these categories, psoriasis patients currently or previously receiving etanercept had a significantly increased risk of pneumonia (aHR 1.68; 95% CI 1.02, 2.77), septicaemia (aHR 2.78; 95% CI 1.21, 6.39), cellulitis (aHR 2.28; 95% CI 1.19, 4.37), other serious infection (aHR 1.93; 95% CI 1.33, 2.79), other cardiac (aHR 1.79; 95% CI 1.06, 3.04), other nervous system (aHR 1.92; 95% CI 1.12, 3.30), skin cancer (aHR 1.75; 95% CI 1.15, 2.66) and solid tumours (aHR 1.52; 95% CI 1.06, 2.19). A greater incidence of pregnancies was reported for female patients receiving etanercept during follow-up when compared to those receiving conventional therapy (aHR 1.93; 95% CI 1.14, 3.26). No other events differed significantly between those receiving conventional therapy and those receiving etanercept. The findings of the analyses suggest that patients exposed to etanercept have an increased risk of developing serious infections, respiratory, cardiac, nervous system and skin (non-cancer) serious adverse events (SAEs), and malignancies as compared with those exposed to conventional treatment after adjusting for potential confounders. The generalisation and external validity of this study results are limited due to the presence of potential bias, notably confounding by indication. Overall, these findings are consistent with the known safety profile of etanercept in the treatment of adult psoriasis. These reported risks have been well characterised through the risk management plan and are listed in the product information. No new safety concerns were identified. Overall, the results presented in this application are

					consistent with previous reported data and do not warrant amendment to the product information.
WS/1614	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report for the PURPOSE study, a category 3 study in the RMP. PURPOSE was a non-interventional, multi-centre, prospective, observational, cohort study to evaluate the long-term safety and effectiveness of etanercept prescribed by dermatologists to paediatric patients for the treatment of plaque psoriasis. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	03/10/2019	n/a		Out of the 72 patients enrolled in the PURPOSE study, 29 patients (40.4%) patients completed the 5-year follow up period. The main reasons for not completing the follow-up were early discontinuation due to the study ending prior to patient completing 5-year follow-up (27.8%, 20/72) and patients lost to follow-up (15.3%, 11/72). No serious or opportunistic infections, or malignancies were reported. There were 25 treatment-emergent SAEs, including 7 considered possibly related to etanercept. The most frequent reported SAEs were under the SOC "Skin and subcutaneous tissue disorders". No deaths were reported. The safety data are in line with the known safety profile for etanercept. Effectiveness of etanercept was evaluated in 32 patients, of whom (87.5%, 28/32) completed a 24-week course of therapy. The reasons for not completing a course of therapy were treatment being ineffective (3 patients) and lost to follow-up (1 patient). Of these 32 patients, 16 required more than one treatment period with other systemic therapies, mostly with other systemic biologics. Decrease in severity of plaque psoriasis after treatment with etanercept based on the judgment of the investigator was observed in 30/32 patients. The effectiveness data were too limited to draw conclusions.
IG/1139	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	20/09/2019	n/a		

IG/1087	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	15/04/2019	n/a		
IG/1082	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/04/2019	14/11/2019	SmPC and PL	
WS/1526	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from study (RABBIT register Cohort 2) listed as a category 3 study in the RMP. This is a prospective, non-interventional, observational, long-term cohort Germanic biologics register to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis factor (TNF)-inhibitor therapies in the treatment of rheumatoid arthritis (RA) in comparison to cohorts of RA patients treated with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologic (b)DMARDs. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/03/2019	n/a		The RABBIT register is an on-going long-term observational cohort study initiated in Germany in 2001. A total of 10,919 patients with RA were considered for the analyses. At enrolment, patients of the three exposure groups (Enbrel (n=1,537), other bDMARDs (n=6,030), csDMARDs (n=3,349)) had a mean age of 57 - 59 years, and 73 - 75% of the patients were female. Patients treated with Enbrel were comparable to patients treated with other bDMARDs in terms of some disease characteristics. The fully adjusted analysis of the complete cohort of the RABBIT register did not reveal a negative impact of Enbrel on the outcomes of hospitalisations due to infection and pneumonia. After adjustment for available confounders, hazard ratios (HR) for stroke were significantly lower in patients treated with Enbrel compared to csDMARDs (on drug: HR=0.5 (95% CI 0.3; 0.9)). No effect of Enbrel on the outcomes of myocardial infarction, coronary artery disease and incident heart failure was observed. There was no significant association between patients currently exposed (on drug + 3 months risk window) or ever exposed to Enbrel and the risk for overall and first malignancies, lung cancer, lymphoma, malignant melanoma and NMSC. Thus, a reduced risk was seen for breast cancer in the group of Enbrel in the ever exposed

					analysis HR=0.5 (95% CI 0.2; 0.97)). Furthermore, a non-significantly elevated risk of leukaemia was revealed for Enbrel users relative to csDMARD treated patients (ever exposed: HR 1.9 (95% CI 0.7; 5.3)). Mortality risk was significantly reduced in patients currently receiving Enbrel (on-drug plus 3-months risk window: HR=0.6 (95%CI 0.4; 0.8)), but the result did not persist in the ever exposed approach. The spectrum of adverse pregnancy in patients receiving Enbrel did not differ from the other treatment groups. There were low numbers of tuberculosis, opportunistic infections, worsening of heart failure, glioblastoma, cervical cancer and central demyelination, and therefore no adjusted risks for these events were analysed. Results showed a reduced risk for stroke, breast cancer and mortality relative to csDMARD users. In this analysis no association with other safety events, including infections, cardiovascular outcomes and malignancy, were identified. Overall the results of this study do no suggest any new safety concerns for etanercept and are in line with the known safety profile for etanercept. No changes to the product information are deemed necessary as a consequence of the findings of this study.
WS/1270	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.6 of the SmPC in order to update the current safety information on pregnancy based on the final results from study B1801396, a non-interventional PASS listed as a category 3 study in	17/01/2019	14/11/2019	SmPC and PL	The final report for study B1801396, a non-interventional, population-based, multi-country, observational cohort register study using merged data from Sweden, Denmark and Finland, was submitted as part of this variation application. In this observational multi country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept during the first 90 days of pregnancy (n=425) to those exposed to non-biologic drugs

	the RMP. This is a non-interventional, population-based, multi-country, observational cohort register study to evaluate the risk of adverse pregnancy outcomes in patients with rheumatoid arthritis and related inflammatory diseases, who were treated with etanercept compared to patients with the same diseases of interest who were treated with non-biologic systemic drugs, but without etanercept or other biologics during pregnancy, using merged data from Sweden, Denmark and Finland. The Package Leaflet is updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				(n=3497), there was no observed increased risk of major birth defects (crude odds ratio [OR]= 1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.58-1.60 after adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth, or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. In total the effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. Based on all available data, etanercept should only be used during pregnancy if clearly needed. Section 4.6 of the SmPC and section 2 of the PL have been updated accordingly.
PSUSA/1295/201802	Periodic Safety Update EU Single assessment - etanercept (except for biosimilars)	06/09/2018	n/a		PRAC Recommendation - maintenance
T/0222	Transfer of Marketing Authorisation	11/07/2018	30/07/2018	SmPC, Labelling and PL	
WS/1408	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	26/07/2018	n/a		

WS/1362	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from the study 20050111 listed as category 3 study in the RMP, in order to fulfil Enbrel P46 0134.2. This is a multicentre, open-label extension study to evaluate the long-term safety and efficacy of etanercept in paediatric subjects with moderate to severe plaque psoriasis for up to 264 weeks (or until the quarterly visit after the subject's 18th birthday, whichever comes last) who participated in controlled study 20030211. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/05/2018	n/a		Please refer to Scientific Discussion Enbrel & Lifmior-H-C-WS-1362.
N/0219	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/05/2018	30/07/2018	Labelling	
IAIN/0218/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	12/04/2018	30/07/2018	Annex II and PL	

	site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing				
IAIN/0215	B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	16/02/2018	30/07/2018	SmPC, Labelling and PL	
IB/0214	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/02/2018	n/a		
WS/1190/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No	25/01/2018	30/07/2018	SmPC and PL	

	1234/2008. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test				

	B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process				

	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits				
II/0213	Update of section 4.8 of the SmPC to update the frequency category of 7 ADRs currently listed and to split one ADR into 2, following a re-analysis of the frequencies of all listed ADRs based on clinical trial experience in controlled clinical studies as proposed by the MAH in LEG 0168 in follow-up to a PRAC request in etanercept PSUSA/00001295/201602. The description of the ADRs 'interstitial lung disease and 'autoimmune hepatitis' has also been amended as a consequence. The Marketing authorisation holder (MAH) also took the opportunity to reformat the ADR listing in section 4.8 of the SmPC. Section 4.4 of the SmPC and the Package Leaflet are updated accordingly. In addition, the MAH took the opportunity to combine the 25 mg and 50 mg pre-filled syringe (PFS) SmPCs and Package Leaflets. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/10/2017	18/12/2017	SmPC and PL	Based on the re-analysis of the frequencies of all listed adverse drug reactions, the frequency category of the following ADRs was changed as follows: for 'rash' from 'uncommon' to 'common', for 'leukopenia', 'anaemia', 'neutropenia' and from 'rare' to 'uncommon', for 'interstitial lung disease (including pneumonitis and pulmonary fibrosis)' from 'uncommon' to 'rare', for 'peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy' from 'very rare' to 'rare' and for 'leukaemia' from 'unknown' to 'rare'. In addition 'congestive heart failure' has been split into 'worsening of cardiac failure congestive' with a frequency' uncommon' and 'new cardiac onset cardiac failure congestive' with a frequency 'rare'. In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of interstitial lung disease in patients receiving etanercept without concomitant methotrexate was 0.06% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of interstitial lung disease was 0.47% (frequency uncommon). There have been post-marketing reports of interstitial lung disease

					(including pneumonitis and pulmonary fibrosis), some of which had fatal outcomes. In controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of autoimmune hepatitis in patients receiving etanercept without concomitant methotrexate was 0.02% (frequency rare). In the controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of autoimmune hepatitis was 0.24% (frequency uncommon).
WS/1261	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report for the Anti-Rheumatic Treatment in Sweden Registry-Etanercept Cohort Study listed as a category 3 study in the RMP. This non-interventional PASS aimed at providing an assessment of a number of pre-specified safety outcomes for Enbrel as used in the treatment of RA in Sweden, using data from the ARTIS system, in total and from 2006. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/10/2017	n/a		The final study report of the Anti-Rheumatic Treatment in Sweden Registry-Etanercept Cohort Study (ARTIS-ETN) Registry provides information on a number of measured outcomes (e.g. primary invasive cancers excluding non-melanoma skin cancers, melanoma, leukaemia, cervical cancer, stroke, fatal cardiovascular event, demyelinating event /MS and all-cause mortality). The results from the ARTIS registry are consistent with the current overall safety profile of etanercept in in the treatment of rheumatoid arthritis. No new safety concerns were identified. Overall, the results presented in this application are consistent with previous reported data and did not warrant amendment to the product information.
PSUSA/1295/ 201702	Periodic Safety Update EU Single assessment - etanercept (except for biosimilars)	01/09/2017	n/a		PRAC Recommendation - maintenance
IB/0208	C.I.11.z - Introduction of, or change(s) to, the	09/06/2017	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
II/0207/G	This was an application for a group of variations. B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	05/05/2017	18/12/2017	SmPC, Labelling and PL	
II/0204	Update of section 4.8 of the SmPC in order to change the frequency category of the adverse drug reaction (ADR) 'elevated liver enzymes' from 'rare' to 'uncommon' and to add some further details on the frequency of elevated liver enzymes reported ADRs with etanercept in double-blind controlled trials with or without concomitant methotrexate use, following the assessment of Enbrel (etanercept) PSUSA/00001295/201602. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update section 4.4 of the SmPC on traceability of biological medicinal products as requested by the CHMP, to make a small correction in section 6 of the	23/03/2017	18/12/2017	SmPC, Labelling and PL	Following a request from the PRAC as part of Enbrel (etanercept) PSUSA/00001295/201602, the MAH conducted a review of the adverse event 'elevated liver enzymes' across etanercept clinical trials. In the double-blind periods of controlled clinical trials of etanercept across all indications, the frequency (incidence proportion) of adverse events of elevated liver enzymes in patients receiving etanercept without concomitant methotrexate was 0.54% (frequency uncommon). In the double-blind periods of controlled clinical trials that allowed concomitant treatment with etanercept and methotrexate, the frequency (incidence proportion) of adverse events of elevated liver enzymes was 4.18% (frequency common). Therefore the frequency of the adverse drug reaction 'elevated liver

	50 mg solution for injection in a pre-filled pen Package Leaflet and to bring the Product Information in line with the latest QRD template version 10. C.I.3.b - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Change(s) with new additional data submitted by the MAH				enzymes' from 'rare' to 'uncommon'. In addition, as requested by the CHMP, in order to improve the traceability of biological medicinal products, the trademark and the batch number of the administered product should be clearly recorded (or stated) in the patient file.
IB/0206	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	27/02/2017	n/a		
IB/0205/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of	08/02/2017	n/a		

	the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.f.1.e - Stability of FP - Change to an approved stability protocol				

II/0198	Submission of the final clinical study report for the BSPAR (British society for paediatric and adolescent rheumatology) etanercept registry, a cohort study (category 3 study in the RMP) C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/01/2017	n/a		The final study report submitted for the British Society for Paediatric and Adolescent Rheumatology-Etanercept Cohort Study provides information on safety from a prospective cohort study which included data from over 1,000 JIA patients exposed to etanercept, and over 400 JIA patients exposed to methotrexate. The results from the BSPAR registry are consistent with the current overall safety profile of etanercept in the paediatric population and in line with the results from a previous paediatric registry study in patients with juvenile idiopathic arthritis (JIA). No new safety concerns were identified. Overall, the results presented in this application are consistent with previous reported data and did not warrant amendment to the product information.
IA/0203	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	05/01/2017	18/12/2017	SmPC, Labelling and PL	
IA/0202/G	This was an application for a group of variations. B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	16/12/2016	n/a		
IB/0200/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	30/11/2016	n/a		

	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
IB/0201/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	20/10/2016	n/a		
II/0199	Submission of a revised RMP (version 6.1) in order to remove 'injection site reactions' as an important potential risk and 'use in pregnant women' , 'use in hepatic and renal impaired subjects' and 'use in	13/10/2016	n/a		

	different ethnic origins' as missing information. In addition the MAH has taken the opportunity to amend the due dates of several category 3 studies, to align the RMP with GVP module V on Risk Management Systems (revision 1), to review the list of studies included in the Pharmacovigilance plan and to update the clinical trials and post-marketing experience. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
PSUSA/1295/ 201602	Periodic Safety Update EU Single assessment - etanercept (except for biosimilars)	02/09/2016	n/a		PRAC Recommendation - maintenance
IB/0196	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	04/04/2016	n/a		
II/0194	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	19/09/2016	SmPC and PL	
II/0190	Update of section 5.1 of the SmPC in order to reflect the final 2-year data from study B181031 (non-radiographic axial spondyloarthritis study); the Package Leaflet and Labelling are updated accordingly. In addition, the Marketing authorisation	01/04/2016	19/09/2016	SmPC, Annex II, Labelling and PL	Section 5.1 of the SmPC is being updated to reflect the final 2-year data from study B181031. "Improvements in health-related quality of life and physical function were also maintained through 2 years of therapy…The 2 year data did not reveal any new safety findings. MRIs of the sacroiliac

	holder (MAH) took the opportunity to bring the Product information in line with the latest QRD template version 9.1. Changes are also introduced in the local representatives for Czech Republic, Norway and Sweden in section 6 of the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				joint and spine were obtained to assess inflammation at baseline, week 12 and 104.”
IB/0195/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	17/02/2016	n/a		
IB/0193	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	17/02/2016	n/a		
II/0184	Update of section 4.6 of the SmPC in order to update the information on the effects of etanercept on pregnancy and lactation. The Package Leaflet and	19/11/2015	19/09/2016	SmPC and PL	A higher rate of major birth defects was observed in an observational study comparing pregnancies exposed to etanercept during the first trimester, with pregnancies not

	the RMP are updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the RMP in reference to past approved variations. The RMP version 5.4 was agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				exposed to etanercept or other TNF-antagonists (adjusted odds ratio 2.4, 95% CI: 1.0 – 5.5). The types of major birth defects were consistent with those most commonly reported in the general population and no particular pattern of abnormalities was identified. No change in the rate of spontaneous abortion, stillbirth, or minor malformations was observed. Enbrel is not recommended during pregnancy.
II/0189/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	05/11/2015	n/a		

	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.4.c - Change in the batch size (including batch size ranges) of the finished product - The change requires assessment of the comparability of a biological/immunological medicinal product or a new bioequivalence study B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits				
IB/0191	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	29/09/2015	n/a		
II/0188/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.II.e.4.b - Change in shape or dimensions of the container or closure (immediate packaging) - The change in shape or dimensions concerns a fundamental part, which may have a significant impact on the delivery, use, safety or stability of the FP B.II.e.7.a - Change in supplier of packaging	24/09/2015	19/09/2016	PL	

	components or devices (when mentioned in the dossier) - Deletion of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.f.1.e - Stability of FP - Change to an approved stability protocol B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test				
II/0182	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	24/09/2015	n/a		
PSUSA/1295/ 201502	Periodic Safety Update EU Single assessment - etanercept (except for biosimilars)	10/09/2015	n/a		PRAC Recommendation - maintenance
II/0179	Submission of the final report from the Organization of Teratology Information Specialists (OTIS) registry, as listed in Part III of the Risk Management Plan C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/07/2015	n/a		
II/0187/G	This was an application for a group of variations. B.II.b.1.c - Replacement or addition of a	16/07/2015	n/a		

	manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method B.II.b.4.c - Change in the batch size (including batch size ranges) of the finished product - The change requires assessment of the comparability of a biological/immunological medicinal product or a new bioequivalence study B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.f.1.e - Stability of FP - Change to an approved stability protocol				

N/0183	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	08/09/2015	PL	
IB/0185/G	This was an application for a group of variations. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	20/04/2015	08/09/2015	SmPC	
II/0180	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/03/2015	n/a		
II/0174	Update of section 5.1 of the SmPC in order to include long-term data obtained from two open-label studies: 20021618 and 20021623. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/03/2015	08/09/2015	SmPC	The availability of long-term data has been reflected in section 5.1 of the SmPC, under clinical efficacy and safety, as follows: "Continued durable responses have been seen for up to 10 years in open label extension treatment trials when patients received Enbrel without interruption"
IB/0178	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	05/03/2015	n/a		

IA/0181	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	26/02/2015	n/a		
II/0177	Submission of the final report for study B1801130 as listed in Part III of the Risk Management Plan. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		No changes to the product information are necessary as a result of the study.
II/0176	Submission of the 5-year Clinical Study Report for the AntiRheumatic Therapies In Sweden (ARTIS) registry study, as listed in Part III of the Risk Management Plan. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/02/2015	n/a		Overall the results for the 5-year Clinical Study Report for the ARTIS registry do not raise any new safety signals for etanercept. No changes to the RMP or product information are required as a consequence of the results from the ARTIS registry study.
II/0175	B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation	18/12/2014	08/09/2015	SmPC	
II/0173	Update of section 4.8 of the SmPC to align with the etanercept Core Data Sheet to introduce viral infections in the list of the opportunistic infections and to reflect it in the discussion on opportunistic infections and to update the sentence on the most commonly reported invasive fungal infections.	25/09/2014	08/09/2015	SmPC	TNF inhibitors such as Etanercept and Infliximab are known to supress the immune system – hence serious, life-threatening, opportunistic infection involving multiple organ systems and sites have been reported rarely in patients taking TNF inhibitors. The proposed updates are acceptable and in line with information from the MAH safety database, as well as current knowledge on

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				immunosuppressants/Tumour Necrosis Factor alpha (TNF-α) inhibitors. It is noted that the information is already included in the product information for Remicade (Infliximab), a product which belongs to the same therapeutic group as Etanercept.
PSUV/0172	Periodic Safety Update	11/09/2014	n/a		PRAC Recommendation - maintenance
II/0167	Extension of Indication to include the treatment of adults with severe non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) evidence, who have had an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs). As a consequence, sections 4.1, 4.2 and 5.1 of the SmPC are updated. The package leaflet is updated in accordance. In addition, the MAH took this opportunity to include minor administrative changes in the section 4.2 of the SmPC of 50 mg formulation product information. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/06/2014	28/07/2014	SmPC and PL	Please refer to the scientific discussion Enbrel EMEA/H/C/00262/II/167 for further information.
II/0170	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	26/06/2014	n/a		
IB/0169	C.I.7.b - Deletion of - a strength	09/01/2014	28/07/2014	SmPC, Labelling and	

				PL	
IA/0168	A.7 - Administrative change - Deletion of manufacturing sites	25/11/2013	n/a		
IA/0166/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites	16/10/2013	n/a		
IB/0165	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/10/2013	13/11/2013	SmPC and PL	
II/0163	Update of section 4.4 of the SmPC in order to update the safety information regarding Hepatitis B reactivation in patients treated with Enbrel. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to update the pre-filled pen Package Leaflet in accordance with recently completed user consultation testing. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/09/2013	13/11/2013	SmPC and PL	The literature review has revealed cases of Hepatitis B reactivation in patients treated with TNF-α inhibitors, including etanercept, who were anti-HBc+ (but HBsAg negative). Although the precise explanation for this reactivation is not clear it could be explained by the presence of HBV DNA in the blood or liver in the absence of detectable serum HBsAg (occult HBV infection). The review of the pharmacovigilance database provided support for hepatitis B reactivation in patients with a history of hepatitis B as out of the 141 cases identified in which a history of viral hepatitis was reported, 36 reported a history of hepatitis B. In these 36 patients, time to onset of the hepatic events varied from 2 weeks to 18 months. Where laboratory tests were reported, most showed elevations of

					liver enzymes and some reported increased HBV DNA. Ten patients were reported to have a positive dechallenge to etanercept therapy, and 5 had a negative dechallenge. Anti-viral therapy was reported in 6 of the 10 patients with a positive dechallenge, with 3 patients receiving lamivudine and 3 patients receiving entecavir. Of the 36 patients with hepatitis B, 20 were treated with immunosuppressants or agents which could have had an impact on liver function. Section 4.4 of the SmPC has been expanded to include all patients previously infected with HBV in light of the anti-HBc+ patients treated with etanercept in which there was a reactivation of hepatitis B.
II/0164	Update of section 4.6 of the SmPC to add information regarding the placental transfer of etanercept. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template. Finally the MAH proposed to enhance part of the instructions for preparing for an injection using the pre-filled syringe presentations following the introduction of a new packaging design, referred to as a slim-pack design. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/07/2013	13/11/2013	SmPC and PL	The MAH has made the proposal to amend the Enbrel's PI to mention that etanercept crosses the placenta and has been detected in the serum of infants born to female patients treated with Enbrel during pregnancy based on two literature reviews indicating that Etanercept concentrations are found in maternal serum, cord blood and breast milk. No key safety information has been found in the Pfizer database and no safety signal was identified. The MAH's proposal is based on published data and one report of a medically important adverse event (AE) of neonatal asphyxia. Therefore there is evidence in the scientific literature of transplacental transmission of etanercept. The MAH's proposal to amend the PI is endorsed by the CHMP. Information relating to live vaccination is already included in section 4.4 of the Enbrel's SmPC. This inclusion of this information in section 4.6 of the SmPC strengthens this warning and is therefore also endorsed by the CHMP.
II/0162	Changes in the product information wording, in	30/05/2013	13/11/2013	SmPC and PL	The revised wording of the product information aims to

	particular the sections 6.6 of the Summary of Product Characteristics (SmPC) and the 5 and 7 of the Package Leaflet (PL), to address the existence of particulates in the pre-filled syringe (PFS) and pre-filled pen (PFP) presentations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				enhance the patients and healthcare professionals understanding and judgement on the appearance description of Enbrel solution in the pre-filled syringe (PFS) and pre-filled pen (PFP) presentations when inspecting the solution prior its use.
II/0161	Update of section 4.6 of the SmPC in order to mention that etanercept has been reported to be excreted in human milk following subcutaneous administration. The Package Leaflet is updated accordingly. Furthermore the Annex II is being brought in line with the latest QRD template. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/02/2013	13/11/2013	SmPC, Annex II and PL	There is evidence in the scientific literature that etanercept is excreted and can be measured in human breast milk. The data for these cases show there were very low levels of etanercept in infant serum suggesting that absorption of etanercept present in breast milk by the infant's gastrointestinal system is possible. Thus, the proposed amendments to the product information are endorsed. Based on an analysis of the MAH's global safety database of all lactation cases, the evidence does not suggest that infants exposed to etanercept through breast milk are at an increased risk for infections or other adverse outcomes. Nevertheless women using Enbrel should not breast-feed.
IB/0160/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.3.z - Change in the manufacturing process of the finished product - Other variation	20/12/2012	n/a		
IB/0157	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing	12/12/2012	n/a		

	takes place				
IB/0158	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	10/12/2012	n/a		
IG/0235/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
II/0156	Update of section 4.8 of the SmPC in order to include the term hepatitis B reactivation as an undesirable effect of treatment with etanercept. The Package Leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/11/2012	13/11/2013	SmPC and PL	The MAH cumulatively reviewed the evidence of the association between etanercept treatment and viral hepatitis. While the post-marketing data is not compelling, taken with the literature available for HBV reactivation in association with TNF inhibitors indicative of an increased risk the MAH proposed including hepatitis B reactivation in section 4.8 of the SmPC. The CHMP agreed with the MAH's proposal for amendment of the product information. The available evidence implies that there is an increased risk of hepatitis B reactivation, which may be attributable to treatment with etanercept. The CHMP was also of the opinion that the majority of the criteria that are conventionally considered in the assessment of causality support the likelihood of a causal relationship.
II/0154	Update of section 4.8 of the SmPC in order to add scleritis as an adverse reaction.	20/09/2012	24/10/2012	SmPC	The MAH has conducted a comprehensive and competent review of the evidence concerning the association between

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				administration of etanercept and the development of scleritis. Based upon the reports of positive dechallenge and rechallenge identified in the MAH's pharmacovigilance database and the literature, and the fact that other forms of ocular inflammation, namely uveitis, are included in the current product information for etanercept, the inclusion of scleritis in the SmPC is considered justified. This is supported by the analysis of MarketScan data, in which prevalence estimates of scleritis for patients with inflammatory disease receiving etanercept are higher (with non-overlapping confidence intervals) than patients with inflammatory disease alone. Although it is possible that reports of scleritis could have been associated with greater disease severity in etanercept-treated patients, a causal association could not be ruled out. From the estimated exposure in double-blind and open label etanercept clinical trials scleritis falls under the CIOMS frequency category of "uncommon".
II/0151	to add a single period of storage at an alternative storage condition for the 10 mg/vial presentation. B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	20/09/2012	24/10/2012	SmPC, Labelling and PL	
II/0152	Update of sections 4.4 and 4.8 of the SmPC in order to provide supplementary information regarding the risk of opportunistic infections including specific pathogens Listeria, Legionella and parasitic infections in patients treated with Enbrel.	19/07/2012	30/08/2012	SmPC	The MAH has conducted a comprehensive review of the evidence concerning the association between administration of etanercept and the development of Legionella, Listeria, and parasitic infection/infestation. These complications are uncommon occurrences and the

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				estimates of risk are correspondingly imprecise, but the available data suggests that there may be an increased risk attributable to treatment with etanercept. The risk is also biologically plausible given the clinical pharmacology of TNF-inhibitors. The estimated frequency of Legionella infections was determined to be "rare", for parasitic infections "uncommon" and for Listeria infections "not known".
II/0145	Extension to the JIA indication to include the: - Treatment of polyarthritis (rheumatoid factor positive or negative) and extended oligoarthritis in children and adolescents from the age of 2 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. - Treatment of psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, methotrexate. - Treatment of enthesitis-related arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, conventional therapy. together with reclassification of the licensed indication of polyarticular JIA into the ILAR classification of polyarthritis (rheumatoid factor positive) and polyarthritis (rheumatoid factor negative). Furthermore, an additional etanercept dosage regimen of 0.8 mg/kg (up to a maximum of 50 mg per dose) once weekly (QW) is proposed in addition to the current approved JIA dosage of 0.4 mg/kg (up to a maximum of 25 mg per dose) BIW	21/06/2012	31/07/2012	SmPC and PL	Please refer to the Scientific Discussion "Enbrel/H/C/262/II/145" for further information.

	for the treatment of JIA. Consequential changes have been made to section 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC and the package leaflet. The product information has been brought in line with the latest QRD templates. In addition the list of the local representatives in the PL has been updated. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/0169/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	08/06/2012	n/a		
IB/0150	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	23/03/2012	n/a		

IA/0149	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	14/02/2012	n/a		
IA/0148	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	09/02/2012	n/a		
IB/0147	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	23/01/2012	n/a		
IB/0146/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	23/01/2012	n/a		
IAIN/0144	B.IV.1.b - Change of a measuring or administration device - Deletion of a device	28/12/2011	31/07/2012	SmPC, Labelling and PL	
IA/0142	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	05/10/2011	n/a		

IB/0141	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	04/10/2011	n/a		
II/0139	to include a single period of storage at alternative storage conditions of 25 degree C for up to 4 weeks. B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	21/07/2011	24/08/2011	SmPC, Labelling and PL	
II/0134	Extension of the lower age range for the approved therapeutic indication for paediatric plaque psoriasis from "from the age of 8 years" to "from the age of 6 years". Consequential changes have been made to section 4.1, 4.2 and 5.1 of the SmPC and the package leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/07/2011	24/08/2011	SmPC and PL	Please refer to the Scientific Discussion "Enbrel/H/C/262/II/134" for further information.
II/0126	Extension of the lower age range for the approved therapeutic indication for polyarticular juvenile idiopathic arthritis (JIA) "from the age of 4 years" to "from the age of 2 years". Consequential changes have been made to section 4.1, 4.2 and 5.1 of the SmPC and the package leaflet. In addition the list of the local representatives in the PL has been updated. C.I.4 - Variations related to significant modifications	21/07/2011	24/08/2011	SmPC and PL	Please refer to the Scientific Discussion "Enbrel/H/C/262/II/126" for further information.

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
T/0140	Transfer of Marketing Authorisation from Wyeth Europa Limited to Pfizer Limited. Transfer of Marketing Authorisation	11/07/2011	08/08/2011	SmPC, Labelling and PL	n/a
X/0127	Annex I_2.(c) Change or addition of a new strength/potency	14/04/2011	29/06/2011	SmPC, Annex II, Labelling and PL	Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of this new paediatric presentation: Enbrel 10 mg powder and solvent for solution for injection in the treatment of Polyarticular juvenile idiopathic arthritis and Paediatric plaque psoriasis was favourable and therefore recommended the granting of the extension to the marketing authorisation. Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.
II/0136	Update of section 4.8 of the SPC to add "systemic vasculitis" as an undesirable effect. The package leaflet is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/05/2011	29/06/2011	SmPC and PL	The MAH has examined the medical literature, its clinical trial database, and its adverse drug reaction database for evidence of an association between administration of etanercept and the occurrence of systemic vasculitis. The MAH's pharmacovigilance database contains 634 reported cases of vasculitis in of which 77 were medically-confirmed cases consistent with systemic vasculitis. A reporting rate of 35 events per 1 million patient-years can be estimated from these data, which is more than 1.7 fold higher than the background incidence. Data from 42 etanercept trials

					were searched in the MAH's clinical trials' databases for cases of vasculitis and reported 42 cases of systemic vasculitis, from which an exposure adjusted event rate of 2.3 events per 1000 patient-years was estimated. Based on this data, the addition of "systemic vasculitis" with an "Uncommon" frequency in the etanercept product information is considered appropriate.
WS/0117	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.8.b - Introduction of a new Pharmacovigilance system - which has been assessed by the relevant NCA/EMA for another product of the same MAH	14/04/2011	27/05/2011	Annex II	
II/0135	Update of section 4.8 of the SmPC to add "autoimmune hepatitis" following a request from the CHMP. The PL is updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	27/05/2011	SmPC and PL	The MAH has examined the medical literature, its clinical trial database, and its adverse drug reaction database for evidence of an association between administration of etanercept and the occurrence of autoimmune hepatitis (AIH). The MAH's pharmacovigilance database contains 6 reports of serious adverse events of AIH from clinical trials (3 of which were considered possibly related to etanercept). A cumulative review of adverse event reports in the MAH's pharmacovigilance database also identified 26 medically-confirmed spontaneous reports of AIH. Available reports in medical literature (2) were covered by the above reports from the MAH database. Based on these data, a causal association to etanercept cannot be excluded. The cumulative clinical trial exposure for etanercept exceeds 22600 individuals, and therefore, the estimated frequency of the adverse drug reaction of "autoimmune hepatitis"

					(0.027%) has been determined to fall within the CIOMS frequency category of "rare".
IB/0137	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	13/05/2011	n/a	SmPC and PL	Update of Section 4.8 of the SmPC to include the term 'sarcoidosis' as an undesirable effect. The Package Leaflet is updated accordingly. The MAH also took the opportunity to amend the contact details of some local representatives in the Package Leaflet.
IA/0138/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	13/05/2011	n/a	Annex II	
II/0129	Update of section 4.8 of the SmPC to delete the sub-section "serious adverse events reported in clinical trials" in accordance with the SmPC guideline. The section has also been updated in accordance with the latest QRD template. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/01/2011	21/02/2011	SmPC	The MAH's approach to describe the adverse events from clinical trials in section 4.8 of the SmPC is acceptable. The exclusion of the terms deep vein thrombosis membranous glomerulonephropathy and polymyositis from section 4.8 of the SmPC has been adequately justified either by the lack of reasonable grounds to suspect a causal association with the etanercept administration in the isolated cases observed, or because no differences between etanercept-treated patients and control in the overall small number of these events were identified. The MAH has conducted an extensive investigation of the association between hypertension and administration of etanercept. Given the

					small number of observations of serious hypertensive events in the spontaneous reporting data set, the clinical trial data set, and the degree of uncertainty attached to the causality of this event, no changes to the SmPC with respect to this type of reaction are currently required.
II/0120	Update of sections 4.4 and 4.8 of the SmPC with information regarding reports of inflammatory bowel disease in JIA patients treated with Enbrel. The PL is updated accordingly. The MAH is also proposing some additional changes to the SmPC and PL for the pre-filled syringe and pen presentations to improve information regarding which presentations are most appropriate for use in paediatric population. Other editorial changes are made to section 4.2 of the SmPC. The MAH has also taken the opportunity to correct the contact detail of the French local representative. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/12/2010	21/01/2011	SmPC and PL	The evidence for a potential association between etanercept treatment and IBD in JIA patients derives predominantly from spontaneous reports and case reports from the literature. In a search in patients with the diagnosis of JIA and/or age under 18 years of age and/or age group of neonate, infant, child or adolescent, the MAH has identified 29 case reports in its database with features consistent with inflammatory bowel disease. Treatment indications were predominantly JIA (22 case reports). The data provided by the MAH imply that that there could be increased risk of IBD associated with administration of etanercept to young patients for treatment of JIA. An estimate of the incidence of IBD in patients treated with Enbrel for JIA suggests that this may be considerably higher than the incidence in young people in the general population. The statements included in section 4.4 and 4.8 of the SmPC to describe this risk are therefore considered appropriate.
IB/0133	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	10/12/2010	n/a		
II/0130	To update sections 4.4 and 4.8 of the SmPC with information regarding reports of melanoma, Merkel cell carcinoma and peripheral demyelinating polyneuropathy. The PL is updated accordingly.	21/10/2010	26/11/2010	SmPC and PL	The MAH conducted a cumulative review of the occurrence of melanoma in patients who have received etanercept. Based on the information from clinical trials there were a total of 9 melanomas in etanercept clinical trials. The MAH

	Changes have also been made to the instructions for use in the Package Leaflets for the prefilled pen presentations, in order to improve comprehension and minimise the risk for error. This variation application is submitted further to the request of the CHMP following assessment of PSUR Nr. 17, covering the period 3 February 2009 - 2 February 2010. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				pharmacovigilance database has identified 243 case reports of melanoma occurring in temporal association with etanercept therapy. Based on this information the MAH agreed to include "melanoma" is section 4.4 of the SmPC and in section 4.8 with a frequency category of "rare". Cumulatively, the MAH has received a total of 15 reports (14 incident and 1 prevalent) of neuroendocrine carcinoma of the skin (Merkel cell carcinoma) occurring in temporal association with etanercept therapy. Based on this information, the reports from the spontaneous environment and recent published literature, the MAH agreed to add "merkel cell carcinoma" to section 4.4 of the SmPC and to section 4.8 with frequency category "not known". The MAH identified one report of chronic inflammatory demyelinating polyradiculopathy in a subject who received etanercept for the treatment of rheumatoid arthritis in an etanercept clinical trial programme and 71 reports from the pharmacovigilance database including reports of peripheral demyelinating polyneuropathy (including Guillain-Barré syndrome), chronic inflammatory demyelinating polyneuropathy and multifocal motor neuropathy. The review of the literature identified 5 reports of Guillain-Barré syndrome. Based on this information the MAH agreed to add Peripheral demyelinating events, including Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, demyelinating polyneuropathy, and multifocal motor neuropathy to section 4.4 of the SmPC and to section 4.8 with frequency category of "very rare".
IB/0132	C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46,	17/11/2010	n/a	SmPC	Update of Section 4.4 of the Enbrel's SmPC regarding 'Use in Elderly Patients' in fulfillement of FUM FU2 146.1.

	or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH				
IB/0131	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol	08/10/2010	n/a	SmPC	
IB/0128/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	12/08/2010	n/a		
II/0117	Update of section 4.4 of the Summary of Product Characteristics (SmPC) to include leukaemia and paediatric malignancy in the existing warning on malignancies and lymphoproliferative disorders, and of section 4.8 to include lymphoma and leukaemia. The package leaflet (PL) is updated accordingly. In addition, the following changes were introduced: - Change in SmPC section 4.8 to add "worsening" to the adverse reaction psoriasis with corresponding changes to the PL; - Correction in SmPC section 5.1 for all 50 mg formulations to delete reference to juvenile idiopathic	20/05/2010	01/07/2010	SmPC, Annex II and PL	From the data presented by the MAH on lymphomas, leukaemias and paediatric malignancies, it is agreed that there are a number of uncertainties regarding whether there is or not a causal association between the use of etanercept and the development of lymphomas, leukaemias or paediatric malignancies. Nevertheless, given the mechanism of action of TNF blocker agents, the risks for the development of such malignancies cannot be excluded. Therefore it has been included in the SmPC that, in the post-marketing setting, cases of leukaemia and malignancies in children, adolescents and young adults (up to 22 years of age) have been reported in patients treated

	arthritis; - Update of SmPC section 4.4 for some presentations to align the advice with regard to vaccinations; - Editorial changes to section 4.8 of the SmPC. Furthermore, Annex II has been corrected with regard to manufacturing sites and the list of the local representatives in the PL has been updated. Update of Summary of Product Characteristics and Package Leaflet				with a TNF-antagonist, including etanercept. In paediatric patients approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. Overall, a risk for the development of malignancies in children and adolescents treated with TNF-blockers cannot be excluded. As there is a risk for lymphoma and leukaemia attributable to treatment with all TNF inhibitors, and that the risk applies equally to all authorised TNF inhibitors, section 4.8 of the SmPC has been updated to include "lymphoma" and "leukaemia". Finally the ADR psoriasisis in section 4.8 has been expanded to include "worsening" of psoriasis.
II/0119	Update of section 4.4 of the SmPC with information regarding reports of hypoglycaemia following initiation of Enbrel in patients receiving medication for diabetes. The PL is updated accordingly. Some additional changes have been made to the package leaflets for the pre-filled syringe and pre-filled pen presentations of Enbrel to improve clarity and understanding. Update of Summary of Product Characteristics and Package Leaflet	18/03/2010	05/05/2010	SmPC and PL	There have been spontaneous reports of hypoglycaemia following initiation of etanercept therapy in patients receiving medication for diabetes, necessitating a reduction in anti-diabetic medication in some of these patients. This is supported by further evidence from the medical literature which suggested that impaired glucose tolerance had improved in some patients treated with tumour necrosis factor inhibitors including etanercept. The Enbrel's product information has therefore been updated accordingly.
II/0116	To introduce changes to the etanercept downstream manufacturing process. Quality changes	22/04/2010	27/04/2010		

IA/0125	C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	13/04/2010	n/a	Annex II	
IA/0124	C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities	13/04/2010	n/a	Annex II	
IA/0123	C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD	13/04/2010	n/a	Annex II	
IA/0122	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	13/04/2010	n/a	Annex II	
IA/0121	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	13/04/2010	n/a	Annex II	
N/0118	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/02/2010	n/a	PL	
R/0110	Renewal of the marketing authorisation.	24/09/2009	26/11/2009	SmPC, Annex II, Labelling and 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	The MAH applied to register a new storage site of Enbrel cell banks. Quality changes	19/11/2009	26/11/2009		
II/0111	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. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	26/11/2009	SmPC and 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.
IA/0115	IA_09_Deletion of manufacturing site	11/11/2009	n/a		
II/0112	The MAH applied to tighten some in-process control during the manufacturing process of the drug substance. Quality changes	22/10/2009	29/10/2009		
II/0109	Quality changes	24/09/2009	01/10/2009		
IA/0114	IA_25_b_02_Change to comply with Ph. - compliance with EU Ph. update - excipient	22/09/2009	n/a		

II/0108	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. Changes to QPPV Update of DDPS (Pharmacovigilance)	29/05/2009	16/07/2009	Annex II and 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	The MAH has applied for the approval of a new 50 mg solution for injection in pre-filled pen presentation for Enbrel. Quality changes	29/05/2009	16/07/2009	SmPC, Labelling and PL	
II/0101	Update of Summary of Product Characteristics	29/05/2009	16/07/2009	SmPC	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
II/0105	Changes in drug substance specifications. Change(s) to the test method(s) and/or specifications for the active substance	29/05/2009	04/06/2009		
II/0107	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. Update of Summary of Product Characteristics and Package Leaflet	23/04/2009	29/05/2009	SmPC and 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 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	23/04/2009	29/05/2009	SmPC and 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.

	presentations) has now also been added to the PL for the 50mg presentations. Update of Summary of Product Characteristics and Package Leaflet				
II/0103	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. Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	25/03/2009	SmPC and 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	Chenges in manufacturing process for active substance.	19/03/2009	23/03/2009		

	Change(s) to the manufacturing process for the active substance				
II/0100	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. Quality changes	18/12/2008	23/12/2008		
II/0099	As a consequence of FUM 117, the MAH proposes to tighten some in-process controls for the drug substance. Quality changes	18/12/2008	23/12/2008		
II/0096	Change(s) to the test methods of the finished product. Change(s) to the test method(s) and/or specifications for the finished product	18/12/2008	23/12/2008		
II/0095	Change(s) to the test methods for the active substance. Change(s) to the test method(s) and/or specifications for the active substance	18/12/2008	23/12/2008		
II/0094	Extension of therapeutic indications. To extend the therapeutic indications to include the treatment of chronic severe plaque psoriasis in	20/11/2008	22/12/2008	SmPC, Annex II and PL	Please refer to the Scientific Discussion "Enbrel/H/C/000262/II/0094" for further information.

	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. Extension of Indication				
II/0097	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. 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). Update of Summary of Product Characteristics and	24/07/2008	29/08/2008	SmPC and 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 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

	Package Leaflet				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.
IA/0098	IA_09_Deletion of manufacturing site	21/08/2008	n/a		
II/0093	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. Update of Summary of Product Characteristics and Package Leaflet	30/05/2008	07/07/2008	SmPC and 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	Quality changes Change(s) to the test method(s) and/or specifications for the finished product	26/06/2008	02/07/2008		

II/0091	Quality Change(s) to the test method(s) and/or specifications for the active substance	26/06/2008	02/07/2008		
II/0083	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). Quality changes	21/02/2008	28/02/2008		
II/0090	Change(s) to the test method of the finished product Quality changes	13/12/2007	21/12/2007		
II/0088	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. Update of Summary of Product Characteristics and Package Leaflet	18/10/2007	19/11/2007	SmPC and 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	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 adverse events without clinical benefit. Thus, the combination of abatacept and etanercept is not recommended. Update of Summary of Product Characteristics	18/10/2007	19/11/2007	SmPC	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.
II/0077	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. Update of Summary of Product Characteristics	18/10/2007	19/11/2007	SmPC	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	Extension of Shelf life for Enbrel 25 mg pre-filled syringes. Quality changes	20/09/2007	15/10/2007	SmPC, Labelling and PL	
IA/0089	IA_05_Change in the name and/or address of a manufacturer of the finished product	08/10/2007	n/a		
II/0082	Following the assessment of PSUR No. 13 (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-	19/07/2007	29/08/2007	SmPC and 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 information that no clinically significant pharmacokinetic interactions were observed in studies with digoxin.

	organise section 4.5 of the SPC to improve clarity. Update of Summary of Product Characteristics				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	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. Update of Summary of Product Characteristics and Package Leaflet	19/07/2007	29/08/2007	SmPC and 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. 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.
N/0086	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/08/2007	n/a	Labelling and PL	
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	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	22/02/2007	02/04/2007	SmPC, Annex II, Labelling and 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

	latest EMEA/QRD template. Change(s) to the manufacturing process for the finished product				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	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 Extension of Indication	14/12/2006	18/01/2007	SmPC and 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 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 ac
IA/0078	IA_28_Change in any part of primary packaging material not in contact with finished product IA_30_a_Change in supplier of packaging components - deletion of supplier	15/12/2006	n/a		
II/0075	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. Update of Summary of Product Characteristics and Package Leaflet	18/10/2006	29/11/2006	SmPC and 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	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	21/09/2006	20/10/2006	SmPC and 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.

	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". Update of Summary of Product Characteristics and Package Leaflet				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	The Marketing Authorisation Holder applied to extend the range of 25mg and 50mg presentations to include a liquid formulation in pre-filled syringes. Annex I_2.(d) Change or addition of a new pharmaceutical form	27/07/2006	26/09/2006	SmPC, Labelling and 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	The Marketing Authorisation Holder applied to add a new paediatric 25 mg multidose strength to the product range. Annex I_2.(c) Change or addition of a new strength/potency	01/06/2006	04/08/2006	SmPC, Labelling and 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	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 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'. Update of Summary of Product Characteristics and Package Leaflet	27/04/2006	31/05/2006	SmPC and 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. 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
II/0070	Change(s) to the test method(s) and/or specifications for the active substance	27/04/2006	03/05/2006		
IA/0071	IA_09_Deletion of manufacturing site	12/04/2006	n/a		
II/0066	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. Update of Summary of Product Characteristics and	23/02/2006	03/04/2006	SmPC and 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

	Package Leaflet				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) 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 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. Update of Summary of Product Characteristics and Package Leaflet	26/01/2006	13/03/2006	SmPC and 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 wer
II/0067	Change(s) to the manufacturing process for the active substance	23/02/2006	03/03/2006		
IA/0068	IA_37_a_Change in the specification of the finished product - tightening of specification limits	09/01/2006	n/a		
IB/0064	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	25/10/2005	n/a		
II/0054	This variation relates to an update of section 4.4	23/06/2005	01/08/2005	SmPC and PL	This variation relates to data submitted by the MAH

	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. Update of Summary of Product Characteristics and Package Leaflet				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	The Marketing Authorisation Holder applied to add Wyeth Grange Castle as an additional site for the manufacture of etanercept active substance. Change(s) to the manufacturing process for the active substance Change(s) to the manufacturing process for the finished product	23/06/2005	22/07/2005	Annex II	
IA/0062	IA_09_Deletion of manufacturing site	11/07/2005	n/a		
IA/0061	IA_05_Change in the name and/or address of a manufacturer of the finished product	21/06/2005	n/a	Annex II and PL	

IA/0059	IA_09_Deletion of manufacturing site	02/05/2005	n/a	Annex II and PL	
X/0047	Extension of the Marketing Authorisation for Enbrel 50 mg. Annex I_2.(c) Change or addition of a new strength/potency	20/01/2005	28/04/2005	SmPC, Annex II, Labelling and 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".
IB/0058	IB_30_b_Change in supplier of packaging components - replacement/addition	29/03/2005	n/a		
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	SmPC, Annex II, Labelling and PL	
II/0048	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	15/12/2004	10/03/2005	SmPC and 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.

	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. Update of Summary of Product Characteristics and Package Leaflet				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. 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		
IB/0052	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	08/10/2004	08/10/2004	SmPC, Labelling and	

				PL	
II/0040	The Marketing Authorisation Holder applied for a new therapeutic indication to include "Treatment of adult patients with moderate to severe plaque psoriasis". The MAH propose to amend the SPC sections 4.1 (Therapeutic Indications), 4.2 (Posology and method of administration), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties) and 5.2 (Pharmacokinetic properties) and the package leaflet sections 1 (What Enbrel is and what it is used for), 3 (How to take Enbrel) and 4 (Possible side effects). Extension of Indication	29/07/2004	24/09/2004	SmPC and PL	
II/0044	Change(s) to the manufacturing process for the finished product	16/09/2004	23/09/2004		
IB/0051	IB_37_a_Change in the specification of the finished product - tightening of specification limits	21/09/2004	n/a		
IA/0049	IA_28_Change in any part of primary packaging material not in contact with finished product	29/07/2004	n/a		
II/0042	This variation relates to an update of section 4.8 of the Summary of Product Characteristics to add the term "cutaneous vasculitis" following the evaluation of the seventh Enbrel Periodic Safety Update Report (PSUR). The relevant section of the Package Leaflet has been amended accordingly. Minor changes related to the source of reports of serious infections in the SPC and the frequency of serious allergic	22/04/2004	23/07/2004	SmPC and PL	

	reactions (in Package Leaflet) have been also introduced in the same sections. The list of the local representatives in the Package Leaflet has been updated. Update of Summary of Product Characteristics and Package Leaflet				
II/0037	The Marketing Authorisation Holder applied for amendments to the SPC sections 4.2 (posology and method of administration), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties) and 5.2 (Pharmacokinetic properties) and package leaflet sections 3 (How to take Enbrel) and 4 (Possible Side Effects) to reflect the clinical experience with 50 mg Enbrel administered once weekly. Update of Summary of Product Characteristics and Package Leaflet	22/04/2004	23/07/2004	SmPC and PL	
II/0043	Change(s) to the test method(s) and/or specifications for the finished product	03/06/2004	09/06/2004		
II/0036	This Type II variation relates to an extension of the current therapeutic indications for Enbrel so it may be used in combination with methotrexate for the treatment of active rheumatoid arthritis in adults, when the response to disease-modifying antirheumatic drugs has been inadequate, and, to inhibit the progression of disease-associated structural damage in patients with rheumatoid arthritis, as measured by x-ray. Consequential	26/02/2004	10/05/2004	SmPC and PL	

	changes have been made in Sections 4.4, 4.8, 5,1 of the SPC. In addition, the MAH proposes to update Sections 6.3 and 6.6 of the SPC according to QRD templates. Relevant sections of the Package Leaflet have been updated accordingly. The List of local representatives of the Marketing Authorisation Holder has been updated. Extension of Indication Update of Summary of Product Characteristics and Package Leaflet				
IB/0041	IB_30_b_Change in supplier of packaging components - replacement/addition	01/03/2004	n/a		
IB/0039	IB_31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits	10/02/2004	n/a		
II/0033	Extension of Indication	25/09/2003	16/01/2004	SmPC and PL	
IB/0038	IA_37_a_Change in the specification of the finished product - tightening of specification limits IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening	19/12/2003	n/a		
II/0035	Update of or change(s) to the pharmaceutical documentation	22/10/2003	28/10/2003		
II/0034	Change(s) to container	24/07/2003	24/10/2003	SmPC, Labelling and	

				PL	
II/0031	Registration of additional manufacturing sites for the active substance and finished product. Change(s) to the manufacturing process for the active substance Change(s) to the manufacturing process for the finished product	26/06/2003	13/08/2003	Annex II	
II/0032	Change(s) to the manufacturing process for the active substance	24/07/2003	07/08/2003		
II/0029	Update of Summary of Product Characteristics and Package Leaflet	19/03/2003	26/06/2003	SmPC and PL	
II/0030	Update of Summary of Product Characteristics	23/01/2003	22/04/2003	SmPC	
II/0025	Extension of Indication Update of Summary of Product Characteristics	19/02/2002	05/12/2002	SmPC, Annex II and PL	
II/0028	New presentation(s)	30/05/2002	16/09/2002	SmPC, Labelling and PL	
II/0027	Update of Summary of Product Characteristics and Package Leaflet	30/05/2002	16/09/2002	SmPC and PL	
I/0026	01_Withdrawal of the manufacturing authorisation for a site of manufacture	15/02/2002	22/02/2002		
II/0017	Extension of Indication	18/10/2001	06/02/2002	SmPC and PL	

II/0024	Change(s) to the manufacturing process for the active substance	17/01/2002	22/01/2002		
II/0022	New presentation(s)	03/10/2001	17/12/2001	SmPC, Labelling and PL	
II/0019	Update of or change(s) to the pharmaceutical documentation	18/10/2001	25/10/2001		
I/0020	24_Change in test procedure of active substance	26/07/2001	31/07/2001		
II/0018	Quality changes	27/06/2001	16/07/2001		
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/07/2001	06/08/2001	PL	
II/0014	Update of or change(s) to the pharmaceutical documentation	25/01/2001	03/05/2001		
II/0012	Quality changes	14/12/2000	03/05/2001		
II/0011	Quality changes	26/04/2001	03/05/2001		
II/0010	Quality changes	26/04/2001	03/05/2001		
II/0009	Quality changes	26/04/2001	03/05/2001		
II/0008	Quality changes	14/12/2000	03/05/2001		
II/0007	Quality changes	14/12/2000	03/05/2001		

II/0006	Quality changes	14/12/2000	03/05/2001		
II/0005	Quality changes	26/04/2001	03/05/2001		
II/0013	Update of Summary of Product Characteristics and Package Leaflet	16/11/2000	23/04/2001	SmPC and PL	
II/0001	Update of Summary of Product Characteristics and Package Leaflet	31/10/2000	23/04/2001	SmPC and PL	
I/0003	20_Extension of shelf-life as foreseen at time of authorisation	16/11/2000	13/03/2001	SmPC	
I/0015	20_Extension of shelf-life as foreseen at time of authorisation	02/02/2001	n/a	SmPC	
I/0016	20a_Extension of shelf-life or retest period of the active substance	20/12/2000	12/01/2001		
I/0002	20a_Extension of shelf-life or retest period of the active substance	16/11/2000	12/01/2001		
I/0004	20a_Extension of shelf-life or retest period of the active substance	16/11/2000	n/a		