Remicade

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification issued on	Commission Decision issued /amended on	Product Information	Summary
II/0241	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	30/11/2023	n/a		
II/0243	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	26/10/2023		SmPC and PL	
IB/0244	B.I.e.5.c - Implementation of changes foreseen in an	24/10/2023	n/a		

	approved change management protocol - For a biological/immunological medicinal product				
IA/0245	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	06/10/2023	n/a		
II/0242	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	31/08/2023	n/a		
IB/0240	B.I.e.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	02/05/2023	n/a		
PSUSA/10759 /202208	Periodic Safety Update EU Single assessment - infliximab	14/04/2023	n/a		PRAC Recommendation - maintenance
IB/0239/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	15/03/2023	n/a		

	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer				
N/0237	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/09/2022	23/01/2023	PL	
IB/0236	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	20/06/2022	n/a		
II/0231	Submission of the final report of the Remicade AntiRheumatic Therapy in Sweden (ARTIS) registry study. The ARTIS registry study was performed to fulfill a post-authorisation measure in the RMP for Remicade. The updated RMP v20.1. has also been submitted, including revisions agreed in previous procedures. 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		n/a
IB/0234	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/04/2022	n/a		
IB/0233	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/02/2022	23/01/2023	SmPC, Labelling and PL	To update sections 4.4, 4.5, 4.6 of the SmPC, the Patient Reminder Card in Annex IIIA and section 2 of the Package Leaflet with regards to the administration of live vaccines to

					infants following in utero exposure to Remicade. This update follows the outcome of LEG assessment procedure EMEA/H/C/000240/LEG/159.2, dated 11 November 2021.
IB/0232/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer 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.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)	16/12/2021	n/a		
IB/0230	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process	10/11/2021	n/a		

	of the AS				
II/0229	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	14/10/2021	n/a		
II/0227	Update of the breast-feeding information in sections 4.4, 4.5 and 4.6 of the SmPC to reflect the latest findings from literature regarding excretion of infliximab in human milk and the lack of impact on the development of breastfed infants. Annexes II, IIIA and IIIB have been updated to include information on breast-feeding for patients. The local representative section in the Package leaflet has also been updated C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	16/09/2021	15/11/2021	SmPC, Annex II, Labelling and PL	A comprehensive, integrated search of the major biomedical literature databases for all reports/articles relating to the use of infliximab as well as a search of the GMS Global Safety Database for medically confirmed cases from all sources cumulatively were performed. Limited data from published literature indicate infliximab has been detected at low levels in human milk at concentrations up to 5% of the maternal serum level. Infliximab has also been detected in infant serum after exposure to infliximab via breast milk. While systemic exposure in a breastfed infant is expected to be low because infliximab is largely degraded in the gastrointestinal tract, the administration of live vaccines to a breastfed infant when the mother is receiving infliximab is not recommended unless infant infliximab serum levels are undetectable. Infliximab could be considered for use during breast-feeding. For more information, please refer to the Summary of Product Characteristics.
IB/0228	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/07/2021	15/11/2021	SmPC and PL	
IAIN/0226	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	23/10/2020	15/11/2021	SmPC, Annex II and PL	

PSUSA/10759 /201908	Periodic Safety Update EU Single assessment - infliximab	17/04/2020	n/a		PRAC Recommendation - maintenance
II/0225/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.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product	13/02/2020	n/a		
II/0223	Update of section 4.8 of the SmPC and relevant section of the PL to include cerebrovascular accidents as undesirable effect with unknown frequency. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/09/2019	24/10/2019	SmPC and PL	With this variation, the Remicade product information is updated to include cerebrovascular accident (CVA) in close temporal relationship to an infusion of infliximab in section 4.8 of the SmPC and the Package leaflet. From the data sources analysed, an increased background risk of cardiovascular events is observed in many of the patient groups targeted by the Remicade indications and long-term, Remicade does not seem to increase this risk further (on the contrary there are indications that the drug, through its anti-inflammatory effects can actually decrease the cardiovascular/cerebrovascular risk). However, Remicade treatment has been associated with short-term,

					infusion-related reactions that could theoretically increase the acute risk of Cardio vascular events during/shortly after an infusion.
II/0218	Submission of the final study report on Remicade for the RABBIT Cohort 2 portion of the registry. Rheumatoide Arthritis - Beobachtung der Biologika-Therapie (RABBIT) is a German RA registry established as a prospective observational cohort study on the long-term safety and effectiveness of biologic disease-modifying anti-rheumatic drugs in patients with RA. RMP (v19) was updated with the conclusion of the study. The MAH also revised the list of safety concerns in the RMP as requested in the assessment of LEG 156 and as a consequence the patient reminder card. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/06/2019	24/10/2019	Annex II and Labelling	With this variation the final report of the Remicade RABBIT Cohort 2 study (with a data cut-off of 31 October 2017) is submitted, and the list of safety concerns in the RMP is updated. The RABBIT study aims to capture data on the Remicade safety concerns. RABBIT Cohort 2 did not show evidence of an increased incidence of study outcomes among Remicade initiators matched to csDMARD treatment. Furthermore, no new safety concerns for Remicade were observed in the RABBIT Cohort 2 study, and the results confirm the established safety profile of Remicade. The risk for increased risk for infections during anti-TNF-treatment is well known and considered adequately covered in the SmPC. Based on the data included in this submission, no update of the Remicade product information is warranted. It is also agreed that this data in itself does not warrant any changes to the RMP Summary of Safety Concern. However, within this procedure, a thorough analysis of the RMP Summary of Safety Concern was made to align with the new GVP Module V and the patient reminder card has been updated accordingly.
IB/0221	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	14/05/2019	n/a		
IA/0222/G	This was an application for a group of variations.	10/05/2019	n/a		

	A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer				
IAIN/0220	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/03/2019	24/10/2019	SmPC and PL	
II/0217	Update of section 4.8 of the SmPC in order to add the adverse drug reaction "acute generalised exanthematous pustulosis (AGEP)" with a frequency rare. The package leaflet is updated accordingly. 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	31/01/2019	24/10/2019	SmPC and PL	A review of post-marketing data found 4 cases that reported a plausible temporal relationship between exposure to infliximab and the development of acute generalised exanthematous pustulosis (AGEP) and 4 cases that reported resolving symptoms or the resolution of symptoms after infliximab was withdrawn. In another case, the symptoms resolved between infliximab cycles and recurred upon the next administration, suggestive of a positive dechallenge/rechallenge drug-effect. Three cases were identified as sentinel, 2 reported AGEP and 1 reported ALEP. No clinical trial cases were reported and only 1 event from observational studies and registries was identified, which was considered likely indicative of the rarity of these disorders. Based on this analysis AGEP is added as new adverse drug reaction with a frequency rare in section 4.8 of the SmPC.
IAIN/0219	B.III.2.a.1 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of	18/12/2018	n/a		

	a Member State - AS				
II/0214	Update of the RMP (version 18.0 succession 2) and Annex II-D of the Product Information to remove the request of educational material from Annex II, with the exception of the Patient Reminder Card which should continue to be distributed. The term "patient alert card" was changed to "patient reminder card" in Sections 4.2 and 4.3 of the SmPC, Annex IIIA and the PL. In addition, the MAH has updated the package leaflet with some missing warnings and ADRs already reflected in the SmPC, as requested by CHMP, and has introduced some minor QRD related changes in section 4.8 of the SmPC. Formatting errors have been corrected in section 5.1 and 5.2 of the SmPC. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	18/10/2018	24/10/2019	SmPC, Annex II and PL	The MAH conducted surveys among the relevant prescribers to measure the effectiveness of the Educational Program on the comprehension of the Program. The results of the latest surveys submitted with the present application indicate a high awareness of the safety profile of Remicade among the prescribers. Furthermore, the Educational Material does not seem to be the main source of information: the risk management has been integrated in guidelines and recommendations over the years and is now part of routine clinical practice. Therefore, it was considered acceptable to remove the Educational Program for prescribers as a risk minimization measure. However, the Patient Reminder Card will continue to be distributed in order to remind patients of the most important risks and their symptoms, as well as the importance of informing caregivers of their medication.
IA/0216/G	This was an application for a group of variations. B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-	13/09/2018	n/a		

	significant specification parameter (e.g. deletion of an obsolete parameter)				
IB/0215	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	13/08/2018	n/a		
II/0209	Update of the current warning on colon cancer and dysplasia of Section 4.4 of the SmPC based on final report of the OPUS Registry (Prospective, Observational, Non-Interventional, Post-marketing Safety Surveillance Program in Subjects with UC; P04808) as per MEA 121. In addition, the MAH is taking the opportunity to update the warning on screening tests for tuberculosis to align it with current medical practice, add a reminder on the patient alert card in package leaflet and include some editorial changes in line with the QRD template. The RMP has also been updated to remove the risks of hepatobiliary events, sarcoidosis/sarcoid-like reaction, and colon carcinoma/dysplasia in adults with UC and to add long-term safety follow-up as missing information for adults with UC. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/07/2018	17/10/2019	SmPC, Labelling and PL	OPUS was a prospective, non-randomized, observational, parallel-group, postmarketing safety surveillance registry designed to collect long-term (5 years) safety data in patients with moderate to severe active UC who were selected by their physician for treatment with Remicade or standard therapy. The primary endpoint of the OPUS registry study is the incidence of AEs, as categorized into 9 pre-specified AE categories of interest including serious infections, infusion-related reactions, fatalities and malignancies. Based on the final OPUS safety analyses, no new safety concerns were observed, and these results further confirm that the benefit/risk profile is considered unchanged. The warning on colon cancer and dysplasia has been updated to reflect that current data do not indicate that infliximab treatment influences the risk for developing dysplasia or colon cancer. However, since the possibility of increased risk of cancer development in patients with newly diagnosed dysplasia treated with Remicade is not established, the risk and benefits of continued therapy to the individual patients should be carefully considered by the clinician.

II/0213/G	This was an application for a group of variations. Update of section of 4.8 of the SmPC in order to add the following adverse reaction: 'Linear IgA Bullous Dermatosis (LABD)' with a 'rare' frequency. In addition, the Marketing authorisation holder (MAH) took the opportunity to add additional instructions for obese Adult patients in section 6.6 of the SmPC; relevant sections of the PL have been updated accordingly. The MAH also took the opportunity to introduce some editorial changes in the Product Information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2018	17/10/2019	SmPC and PL	Based on a cumulative review of Linear IgA Bullous Dermatosis (LABD), a causal relationship between infliximab exposure and the development of LABD cannot be excluded. The update of the product information is supported by the identification of 3 post-marketing cases with a temporal relationship between the initiation of infliximab and the development of LABD symptoms, the identification of 3 post-marketing cases exhibiting a positive rechallenge or worsening of symptoms upon subsequent dosing of infliximab, and a spontaneous RR higher than the worldwide incidence rate range.
II/0212	Update of section 4.4 of the SmPC to include a warning recommending adult patients to be brought up to date with all vaccinations if possible prior to initiating Remicade therapy (in line with the current warning for children) and to clarify that patients on infliximab may receive concurrent vaccinations, except for live vaccines. Relevant sections of the package Leaflet and the RMP (v 15.1) were updated accordingly. The MAH took the opportunity the update the product information in accordance with the latest	26/04/2018	17/10/2019	SmPC and PL	The product information has been updated to recommend that patients, if possible, be brought up to date with all vaccinations in agreement with current vaccination guidelines prior to initiating Remicade therapy. Patients on infliximab may receive concurrent vaccinations, except for live vaccines. In a subset of 90 adult patients with rheumatoid arthritis from the ASPIRE study a similar proportion of patients in each treatment group (methotrexate plus: placebo [n=17], 3 mg/kg [n=27] or 6 mg/kg Remicade [n=46]) mounted an effective two-fold increase in titers to a polyvalent

	QRD template and include minor editorial changes. 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				pneumococcal vaccine, indicating that Remicade did not interfere with T-cell independent humoral immune responses. However, studies from the published literature in various indications (e.g. rheumatoid arthritis, psoriasis, Crohn's disease) suggest that non-live vaccinations received during treatment with anti-TNF therapies, including Remicade, may elicit a lower immune response than in patients not receiving anti-TNF therapy.
IB/0210/G	This was an application for a group of variations. B.II.g.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supporting data C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	01/03/2018	17/10/2019	SmPC, Labelling and PL	
IB/0211	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	22/02/2018	n/a		
II/0204	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	09/11/2017	17/10/2019	SmPC, Annex II and PL	Results from the C0168T71 observational study showed statistically significant increases for Caesarean-sections, preterm and small for gestational age births and low birth weights in women exposed during pregnancy to infliximab (with or without immunomodulators/corticosteroids) compared to women exposed to immunomodulators and/or corticosteroids only. The potential contribution of exposure to inflixumab and/or the severity of the underlying disease in these outcomes remains unclear. Based on these results is recommended that infliximab should only be used during pregnancy if clearly needed.

					An updated analysis on pregnancy data and birth outcomes on prospectively collected pregnancies exposed to infliximab did not indicate an increase in the rate of malformation in the newborn.
II/0205	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	21/09/2017	n/a		
IB/0207	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	11/07/2017	n/a		
IA/0206/G	This was an application for a group of variations. B.III.2.a.2 - Change of specification(s) of a former non EU Pharmacopoeial substance to fully comply with the Ph. Eur. or with a national pharmacopoeia of a Member State - Excipient/AS starting material B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	30/06/2017	n/a		
II/0201/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/06/2017	n/a		
PSUSA/10231 /201608	Periodic Safety Update EU Single assessment - infliximab (except for biosimilars)	06/04/2017	n/a		PRAC Recommendation - maintenance

IA/0203	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	09/01/2017	n/a		
IB/0202	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	05/01/2017	n/a		
IA/0200/G	This was an application for a group of variations. 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.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	06/12/2016	n/a		
N/0197	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/11/2016	17/10/2019	Labelling	
II/0195/G	This was an application for a group of variations. B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a	15/09/2016	n/a		

	biological AS 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				
II/0194	Update of section 4.8 of the SmPC in order to update the safety information on myocardial ischemia/infarction. In addition, the Marketing authorisation holder (MAH) took the opportunity to delete the terms 'exceedingly rare' and 'very rare' and to avoid the use of the term 'rare' in certain instances in sections 4.4 and 4.8 of the SmPC. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to include some editorial changes in the product information. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/06/2016	17/10/2019	SmPC and PL	Events (some fatal) of myocardial ischaemia/infarction and arrhythmia have also been reported, some in close temporal association with infusion of infliximab.
IA/0196/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved	19/05/2016	n/a		

	manufacturer				
IB/0193/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	23/11/2015	n/a		
II/0191	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/09/2015		SmPC and PL	A population-based retrospective cohort study using data from Swedish national health registries found an increased incidence of cervical cancer in women with rheumatoid arthritis treated with infliximab compared to biologics-naïve patients or the general population, including those over 60 years of age. Periodic screening should continue in women treated with Remicade, including those over 60 years of age.
II/0188	Update of sections 4.4, 4.5, 4.6 and 4.8 of the SmPC in order to include updated pregnancy information following submission of the final report of the Pregnancy and Infant Outcomes Registry and additional reports on infections and agranulocytosis in neonates and infants in utero exposure to Remicade. The physician educational programme in the Annex II, the Patient Alert Card in the Labelling and the Package Leaflet are updated accordingly. In addition, the Marketing authorisation holder took the opportunity to revise the wording on additional risk minimisation activities in Annex II in line with the	24/09/2015		SmPC, Annex II, Labelling and PL	In patients receiving anti TNF therapy, limited data are available on the response to vaccination with live vaccines or on the secondary transmission of infection by live vaccines. Use of live vaccines can result in clinical infections, including disseminated infections. The concurrent administration of live vaccines with Remicade is not recommended. In infants exposed in utero to infliximab, fatal outcome due to disseminated Bacillus Calmette Guérin (BCG) infection has been reported following administration of BCG vaccine after birth. At least a six month waiting period following birth is recommended before the administration of live

	RMP. The updated RMP version 11.0 has been agreed. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				vaccines to infants exposed in utero to infliximab. Cases of agranulocytosis have also been reported.
II/0190	Update of section 6.6 of the SmPC in order to clarify that diluents other than 0.9% sodium chloride for infusion are not to be used for dilution of the reconstituted product following relevant clarification requests from healthcare professionals. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/07/2015		SmPC and PL	No specific safety concern attributable to the dilution of infliximab with dextrose has been identified.
II/0186/G	This was an application for a group of variations. 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 B.II.f.1.e - Stability of FP - Change to an approved stability protocol	23/04/2015	08/07/2015	SmPC, Labelling and PL	
IA/0189	B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	15/04/2015	n/a		

IA/0187/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 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.III.1.b.4 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Deletion of certificates (in case multiple certificates exist per material) B.III.1.b.3 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability - Updated certificate from an already approved manufacturer	13/03/2015	n/a		
II/0184	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	22/01/2015	n/a		
IB/0185	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/01/2015	n/a		
IB/0183/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the	11/11/2014	n/a		

	obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
II/0182/G	This was an application for a group of variations. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/09/2014	n/a		
II/0181/G	This was an application for a group of variations. This was an application for a group of variations to change aspects of the manufacturing process, batch size and in-process tests and limits for the finished products. 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.3.c - Change in the manufacturing process of the finished or intermediate product - The product is	25/09/2014	n/a		

	a biological/immunological medicinal product and the change requires an assessment of comparability 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.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits				
II/0179	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	08/07/2015	SmPC, Labelling and PL	
PSUV/0180	Periodic Safety Update	25/04/2014	19/06/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0180.
IB/0178	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	11/10/2013	n/a		
IG/0341	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	31/07/2013	n/a		
WS/0400	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008.	27/06/2013	25/07/2013	SmPC and PL	The MAH's proposal to revise the PI was prompted by a single post-marketing case of Bacillus Calmette-Guerin (BCG) disseminated Mycobacterium bovis infection after concurrent use of infliximab for the treatment of ulcerative

	Update of sections 4.4 and 4.5 of the SmPC in order to add information regarding administration of live vaccines and therapeutic infectious agents concurrently with Remicade and Simponi. The Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				colitis and use of BCG by bladder instillation for the treatment of bladder cancer. A clear causal association between infliximab and the onset of disseminated BCG infection could not be determined due to confounding factors but could not be excluded. Upon analysis, the MAH concluded that this case represented a situation similar to receiving a live vaccine because BCG is a live attenuated form of Mycobacterium bacillus. The risks of infection and complications from infections following administration of a live vaccine have been reported to be much higher in patients whose immune systems have been compromised than in the healthy population. The MAH therefore proposed to update the product information to change the section heading of the Vaccination section to reflect the need to consider other therapeutic infectious agents, not just vaccines and to add a warning to not administer therapeutic infectious agents concurrently with Remicade or Simponi. This was agreed by the CHMP.
IA/0176	B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information	10/06/2013	n/a		
IB/0173	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	17/05/2013	25/07/2013	SmPC and PL	To add the term "worsening of symptoms of dermatomyositis" to the table of Section 4.8 of the SmPC as requested by the PRAC/CHMP. The PIL is updated accordingly. In addition, the MAH took the opportunity to update the contact details in the list of local representatives for Ireland.

II/0172	Update of section 4.4 of the SmPC in order to add a statement enabling traceability of the medicinal product. In addition, the MAH took the opportunity to make minor changes to the Package Leaflet and to revise the list of local representatives in the PL to amend contact details for the representatives of The Netherlands and Portugal. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	25/04/2013	25/07/2013	SmPC and PL	In order to increase the traceability for a specific batch and also to enable distinguishing between the use of biosimilars and the original product when assessing spontaneous adverse event reports, the following statement, not specific for Remicade, and enabling traceability of the medicinal product is added to the SmPC: "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".
IA/0174/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - 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	18/04/2013	n/a		
II/0162/G	This was an application for a group of variations. change to a test on the finished product, change to batch release arrangements B.II.d.2.c - Change in test procedure for the finished product - Replacement of a biological/ immunological/immunochemical test method or a method using a biological reagent B.II.b.2.a - Change to batch release arrangements	21/03/2013	n/a		

	and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place				
II/0170	Change to the SmPC relating to new Quality data 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	25/07/2013	SmPC and PL	
IAIN/0171	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/12/2012	n/a		
WS/0314	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/10/2012	22/11/2012	SmPC and PL	
WS/0312	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of sections 4.4 and 4.8 of the SmPC in order to add a warning and safety information regarding cases of melanoma and Merkel cell carcinoma (MCC). The Package Leaflet is updated accordingly. C.I.4 - Variations related to significant modifications	18/10/2012	22/11/2012	SmPC and PL	The cumulative review of registries, clinical trials and postmarketing cases of MCC (or neuroendocrine carcinoma of the skin) coincident with infliximab or golimumab use identified 19 reports for infliximab and none for golimumab. All 19 reports were postmarketing cases. No MCC cases were observed in registries and clinical trials. Of the 19 reports there were 2 fatalities reported in patients either taking multiple immunosuppressants concomitantly with infliximab or with limited information regarding medical history. Of the 19 reports, most of them had confounding

	of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				factors (i.e. one or more risk factors for MCC such as prior immunosuppressant history, concomitant immunosuppressant therapies, and/or a history of malignancy) limiting the causality assessment with infliximab. Based on this review, MCC is considered causally associated with the use of infliximab, and a drug class effect to TNF inhibitors. Key factors supporting this conclusion include the biological plausibility based on immunosuppression by TNF-α inhibitors, the apparent sensitivity of MCC to immunosuppression, and the elevated reporting rate compared with the background rate of this type of cancer, all which suggest an association of MCC with this drug class. MCC is therefore added to section 4.8, with a frequency category of "Not known" for both infliximab and golimumab, as the frequemcy of the event cannot be estimated from the available data. The severity and seriousness of the event of MCC also justify its addition to section 4.4 to warn the physicians that cases of MCC have been reported in patients treated with TNF blocker therapy and to recommend periodic skin examination, particularly for patients with risk factors for skin cancer.. The cumulative review of melanoma cases, coincident with infliximab or golimumab use, from registries, clinical trials and postmarketing identified 385 reports for infliximab and 14 for golimumab. For infliximab, there were 2 reports from clinical trials, 333 from postmarketing and 50 from registries. For golimumab there were 6 clinical trials reports, 7 postmarketing and 1 registry reports. In the FDA AERS database, there were significant numbers of cases of melanoma events with all of the TNF-α blockers. In more than 50% of the cases there were associated risk factors limiting the causality assessment with the drugs. Based on

					the overall data, it remains unclear whether a causal relationship exists between infliximab or golimumab use and the development of melanoma, however the possible contribution of infliximab or golimumab use to the risk cannot be excluded. Based on the data, the frequency category of melanoma is "rare" (□1/10,000 and <1/1,000) for both infliximab and golimumab.
II/0167	Update of section 4.2 of the Summary of Product Characteristics to recommend that a continued therapy with a shortened interval should be carefully considered in paediatric Crohn's disease patients who show no evidence of additional therapeutic benefit after a change in the dosing interval. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/10/2012	22/11/2012	SmPC	Although no data exist to establish a greater risk of adverse events in paediatric patients with Crohn's disease at doses greater than 5 mg/kg, or at a dosing interval shorter than every 8 weeks, it is considered prudent to recommend to the physicians to have a careful consideration for further exposure in these paediatric patients who show no evidence of additional therapeutic benefit after dose interval adjustment. Continuing higher doses of any medication in the absence of therapeutic benefit is not desirable. This recommendation is also aligned with similar recommendations already in place in the infliximab product information for adult patients with Crohn's disease or rheumatoid arthritis.
IB/0166/G	This was an application for a group of variations. 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) B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.2.a - Change in test procedure for AS or	07/09/2012	n/a		

	starting material/reagent/intermediate - 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.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
IA/0165/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - 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.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	21/05/2012	n/a		
IB/0164	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	21/03/2012	n/a		
II/0161	Update of section 5.2 of the SmPC to reflect pharmacokinetics data of infliximab in children based on results of a pharmacokinetics modelling and simulation analysis. The MAH also took the opportunity to update the SmPC, Annex II, Labelling and Package Leaflet in line with the QRD template.	16/02/2012	19/03/2012	SmPC, Annex II, Labelling and PL	Population pharmacokinetic analysis based on data obtained from patients with Ulcerative colitis (N=60), Crohn's disease (N=112), Juvenile Reumathoid Arthritis (N=117) and Kawasaki Disease (N=16) with an overall age range of 2 months to 17 years indicated that exposure to infliximab was dependent on body weight in a non-linear

	Minor typographical corrections were also made throughout the Product Information in all EU languages. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				way. Following administration of 5 mg/kg Remicade every 8 weeks, the predicted median steady state infliximab exposure (area under concentration time curve at steady state, AUCss) in paediatric patients aged 6 years to 17 years was approximately 20% lower than the predicted median steady state drug exposure in adults. The median AUCss in paediatric patients aged 2 years to less than 6 years was predicted to be approximately 40% lower than that in adults, although the number of patients supporting this estimate is limited. Since the efficacy and safety of infliximab in paediatric subjects aged 2 years to <6 years have not been evaluated in adequately-designed clinical studies, the clinical significance of the relatively lower infliximab exposure predicted by the population PK model in this young age group is unknown.
IB/0163/G	This was an application for a group of variations. B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation 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	08/03/2012	n/a		
II/0150	Extension of indication for the treatment of severely active ulcerative colitis, in paediatric patients aged 6 to 17 years, who have had an inadequate response to conventional therapy including corticosteroids and 6-MP or AZA, or who are intolerant to or have medical contraindications for such therapies. Sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC	19/01/2012	21/02/2012	SmPC, Annex II and PL	Please refer to the Scientific Discussion "Remicade/H/C/000240/II/150" for further information.

	have been updated accordingly as well as Annex II and IIIB. The MAH also took the opportunity to update the list of local representatives for Belgium, Estonia Lithuania, Hungary and Portugal in Annex IIIB. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0160/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.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	30/09/2011	n/a	Annex II	
IA/0159	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	29/07/2011	n/a		
II/0156	Update of sections 2, 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 4.8, 5.1 and 5.2 in line with the SmPC guideline and the QRD template. The package leaflet is updated accordingly. The contact details of the local representatives for Denmark, Germany, Greece, Cyprus, Latvia, Finland and UK are also updated in	23/06/2011	26/07/2011	SmPC, Annex II and PL	Section 4.8 is updated with inclusion of an introductory paragraph providing a summary of the safety profile of infliximab and describing the most serious and most frequently occurring adverse reactions in agreement with the risks identified in the Risk Management Plan. The MAH also updated the frequency across all events in section 4.8.

	the package leaflet. Annex II is updated to reflect the approved PSUR submission cyle. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				In addition the SmPC has been rearranged and amended to meet current SmPC and QRD recommendations in sections 2, 4.1, 4.2, 4.4, 4.5, 4.6, 4.7, 5.1 and 5.2. Available information on paediatric patients has been summarized or moved in the various relevant sections, in accordance with the SmPC guideline. Editorial changes were made throughout these sections.
II/0155	Update of section 4.4 of the SmPC to strengthen the existing warnings and precautions regarding invasive fungal infections. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	23/06/2011	26/07/2011	SmPC	Based on a literature review the warnings and precautions regarding invasive fungal infections are strengthened by adding a recommendation that in patients treated with Remicade, an invasive fungal infection such as aspergillosis, candidiasis, pneumocystosis, histoplasmosis, coccidioidomycosis or blastomycosis should be suspected if patients develop a serious systemic illness. Consultation with a physician with expertise in the diagnosis and treatment of invasive fungal infections should be consulted at an early stage when investigating these patients, and initiation of appropriate empiric antifungal therapy should be considered while a diagnostic workup is being performed taking into account both the risk for severe fungal infection and the risks of anti-fungal therapy.
II/0147	Update of section 4.2, 4.8 and 6.6 to add information allowing adult patients treated by infliximab for all approved indications and who tolerated at least 3 initial 2 hour infusions, to receive subsequent infusions of infliximab over a period of not less than 1 hour during maintenance therapy. The package leaflet was updated accordingly. The MAH also took the opportunity to update the list of local representatives in the package leaflet.	14/04/2011	17/06/2011	SmPC and PL	An analysis of pooled phase 3 clinical study data was performed to assess the effect of shortened infusion duration on the risk of infusion-related reactions. This analysis compared infliximab administered at a low infusion rate (?6 mg/kg/2-hr) to infliximab administered at a high infusion rate (>6 mg/kg/2-hr equivalent to >3 mg/kg/1-hr), using the high infusion rate as a surrogate for a shortened infusion duration. The results of this analysis showed that 13% and 19% of patients receiving infliximab

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				at a low infusion rate with or without concomitant immunomodulators, respectively, experienced an infusion-related reaction. This compares to 15% and 16% of patients receiving infliximab at a high infusion rate, with or without concomitant immunomodulators, respectively. The proportion of patients experiencing a serious infusion-related reaction was 0.4%-0.7% regardless of the infusion rate. In a subset of patients treated with 5 or 10 mg/kg throughout the complete study period (ulcerative colitis studies), a similar pattern as in the overall population was seen. Overall based on the data provided, in carefully selected adult patients who have tolerated at least 3 initial 2-hour infusions of Remicade (induction phase) and are receiving maintenance therapy, consideration may be given to administering subsequent infusions over a period of not less than 1 hour. If an infusion reaction occurs in association with a shortened infusion, a slower infusion rate may be considered for future infusions if treatment is to be continued. Shortened infusions at doses >6 mg/kg have not been studied.
II/0142	Extension of indication in patients with moderately active Crohn's disease. Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC and section 1 of the package leaflet are updated accordingly. Annex II is updated to reflect the last version of the RMP. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	17/03/2011	20/04/2011	SmPC, Annex II and PL	Please refer to the Scientific Discussion "Remicade/H/C/000240/II/142" for further information.

II/0141/G	This was an application for a group of variations. To introduce an in-process control during the manufacture of the drug substance. B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue	17/03/2011	20/04/2011	Annex II	
IB/0153	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	18/04/2011	n/a		
IA/0154	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	07/04/2011	n/a	Annex II	
IA/0152/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding	02/03/2011	n/a		

	manufacturer for batch release) B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer				
II/0149	Change in the manufacturing process of the finished product B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	17/02/2011	01/03/2011		
II/0148	Introduction of a Post-approval Change Management Protocol (PCMP) for Remicade active substance virus filtration modernization B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS	17/02/2011	01/03/2011		
II/0146	Update of section 4.4 of the SmPC to recommend discontinuation of Remicade in the management of patients developing demyelinating disorders. "Optic neuritis" and "seizure" were consequently removed from section 4.4 in order to simplify and enhance the clarity of the text.	20/01/2011	21/02/2011	SmPC	The review of literature provided by the MAH showed that re-challenge with or continuation of TNF(alfa) inhibitors appeared to present a higher risk of recurrence or continued symptoms of neuropathy. In the case reports reviewed in the literature, most patients who developed demyelinating disorders improved or had resolution of symptoms without treatment following discontinuation of

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				TNF(alfa) inhibitors. Therefore, based on the available information in the literature, considering discontinuation of infliximab is warranted in the management of patients who develop demyelinating disorders. The proposed change of the SmPC text regarding recommending discontinuation of Remicade if the described demyelinating disorders develop is therefore endorsed.
II/0145	Update of section 4.6 "Pregnancy and lactation" of the SmPC based on a review of the available pregnancy information. Section 2 of 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	20/01/2011	21/02/2011	SmPC and PL	Further to the review of information received from ongoing post-marketing data monitoring sources, including data from a pregnancy registry that assessed the potential for an increased incidence of infection, preterm birth, low birth weight, and very low birth weight in infants exposed to infliximab in utero, the product information was updated with information on transplacental transfer of infliximab and the detection of infliximab up to 6 months post-partum in the serum of infants whose mothers were exposed to infliximab during pregnancy, with the consequence that these infants may be at increased risk for infection. Additionally, administration of live vaccines to infants exposed to infliximab in utero is not recommended for 6 months following the mother's last infliximab infusion during pregnancy.
WS/0066	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 4.4. of the SmPC to add a recommendation for routine hepatitis B virus (HBV) testing as well as a recommendation to consult with a hepatitis B expert for patient tested positive for	16/12/2010	27/01/2011	SmPC and PL	The Marketing Authorization Holder (MAH) of Remicade and Simponi performed an assessment of guidelines and literature on the management of patients with HBV infection. As a result of a review of recently-issued guidelines and the medical literature regarding HBV testing of patients prior to initiating or receiving immunosuppressive therapy, the product information for infliximab (Remicade) and golimumab (Simponi) have been

	HBV infection. The corresponding section of the package leaflet is updated accordingly. Furthermore, the list of local representatives in the PIL has been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				revised to indicate the following: 1. Patients should be tested for HBV before initiating treatment with infliximab or golimumab, and 2. For patients who test positive for HBV infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.
IA/0151/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH 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.a - Administrative change - Change in the name and/or address of a manufacturer responsible for batch release 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)	19/01/2011	n/a	SmPC, Annex II, Labelling and PL	
II/0144	Update of section 4.4 of the SmPC to add a special warning regarding the "risk of serious infections in elderly patients". Section 4.8 is updated accordingly. The section 4 of the package leaflet is updated accordingly. A cross-reference to section 4.4 and 4.8 is also added to section 4.2. This variation	21/10/2010	29/11/2010	SmPC and PL	Analyses of serious infection by various risk factors conducted in all infliximab clinical studies conducted in rheumatoid arthritis indicate an association with higher risk for subjects above 65 years of age. One of those had a fatal outcome. The review showed that the incidence of serious infections was greater in infliximab plus

	application is submitted further to the request of the CHMP following assessment of the FUM 0139. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				methotrexate treated patients 65 years and older (11.3%) than in those under 65 years of age (4.6%). In patients treated with methotrexate alone, the incidence of serious infections was 5.2% in patients 65 years and older compared to 2.7% in patients under 65. Physicians are reminded to pay particular attention regarding the risk of infection when treating the elderly population with infliximab.
II/0143	Update of section 4.8 of the SmPC to add "sarcoid-like reaction" as a rare undesirable effect. The Package leaflet is updated accordingly. This variation is submitted to fulfil follow-up measure (FU2 140.1). C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/10/2010	29/11/2010	SmPC and PL	A cumulative assessment of cases of sarcoid-like reactions received through 23 February 2010 from clinical studies, solicited sources, including registries, and spontaneous sources was conducted. A total of 18 cases originated from clinical studies, 12 of which were excluded from the review as they involved subjects with pre-existing sarcoidosis. The remaining 6 cases (4 serious, 2 non-serious) were reported from clinical studies involving an approved indication for infliximab and reflected new-onset sarcoidosis. A total of 12 solicited cases of sarcoid-like reaction were identified (9 serious, 3 non-serious) of which 4 serious cases were evaluable. Forty-nine (49) spontaneous cases, including 14 cases reported from the literature were identified. New onset sarcoid-like reaction involving infliximab at the time of the event was reflected in 25 evaluable spontaneous cases. In the majority of cases, the sarcoid-like reaction resolved after discontinuation of infliximab, which may suggest an association between infliximab and sarcoid-like reaction. In the general population (not treated with infliximab), sarcoidosis resolves in the majority of patients. The difference may be in the time to resolution which was less than 1 year in this case series and seems to be less than that reported in the general population.

					Overall, based on this cumulative review of cases of sarcoid-like reaction with infliximab, sarcoid-like reaction is considered an ADR for infliximab. Key factors supporting this conclusion include literature reports of sarcoidosis with TNF-alpha inhibitors, and a small number of well-documented cases of sarcoid-like reaction associated with infliximab therapy reported to the MAH. There is no clear mechanism for the development of sarcoid-like reactions due to TNF alpha inhibition nevertheless the risk cannot be excluded. The frequency chosen for this event is rare, 0.07 per 100 subject-years (95% CI: 0.02, 0.17). This is based on the incidence of sarcoidosis
II/0140	Changes in the manufacturing process of the active substance 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 medicinal product and is not related to a protocol	20/05/2010	03/06/2010		
II/0139	Update of 4.4 and 4.8 of the SmPC to add viral infections, of section 4.4 of the SmPC to add neutropenia with concurrent use of anakinra and information regarding the switching between biological disease-modifying antirheumatic drugs, and of section 4.4 of the SmPC with information on haematologic reactions. The PL is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/03/2010	27/04/2010	SmPC and PL	In the infliximab clinical trials, there have been reports of viral infections, some of which were serious. The product information currently lists viral infections as an ADR in the undesirable effects table in section 4.8 of the SmPC. Section 4.4 and 4.8 of the SmPC currently list several types of infections however, viral infections is not listed. Viral infection has therefore been added to the existing list of serious infections in section 4.4 and 4.8 of the SmPC. The product information already advises against concurrent use of infliximab with anakinra due to the increased risk of serious infections. Because an increased risk of neutropenia

					was also noted during the concurrent administration of anakinra and another TNF-blocking agent, section 4.4 of the SmPC has been updated to detail this risk. In clinical practice switching between the various biologic DMARDs available for treatment occurs. As each of these products is associated with increased risk of infections, it is possible that temporal overlap of their administration and exposure could exacerbate that risk. Section 4.4 of the SmPC has therefore been updated advising that monitoring for evidence of infection should continue during the transition from one biological DMARD product to another. There have been reports of pancytopenia, leukopenia, neutropenia, and thrombocytopenia in patients receiving TNF-blockers, including infliximab. Several mechanisms behind cell depletion have been proposed. Section 4.4 of the SmPC has been updated with details on these haematological reactions. Patients should also be advised to seek immediate medical attention if they develop signs and symptoms suggestive of blood dyscrasias (e.g. persistent fever, bruising, bleeding, pallor). Discontinuation of Remicade therapy should be considered in patients with confirmed significant haematologic abnormalities.
II/0137	Update of section 4.4 of the Summary of Product Characteristics (SmPC) to include paediatric malignancy and leukaemia in the existing warning on malignancies and lymphoproliferative disorders. Section 4.8 is updated to add leukaemia, worsening of psoriasis and change in reporting frequency of lymphoma. Sections 2 and 4 of the Package Leaflet (PL) have been updated accordingly.	18/02/2010	26/03/2010	SmPC and PL	A postmarketing cumulative review of all malignancies in paediatric and young adult patients with infliximab showed that thirty-five malignancies have been reported in patients 22 years of age or younger who were exposed to infliximab at age 18 or younger. Six cases described patients with maternal (in utero) or paternal exposure. There were 16 lymphomas/leukaemias and 13 solid tumours reported. Twenty five malignancies were reported with concomitant use of immunosuppressants. Some of the reported tumour

	Update of Summary of Product Characteristics and Package Leaflet				types are not unexpected in a paediatric population and some have been observed in the setting of immunosuppression. A few of the malignancies appear to be unusual occurrences in a paediatric population. Based on the data presented, a causal relationship between infliximab and the development of paediatric malignancies cannot be established. It is possible that concomitant exposure to other immunosuppressants and/or presence of underlying autoimmune diseases were contributory factors. Nevertheless, given its mechanism of action as TNF-blocking agent it cannot be excluded that infliximab may be also a contributing factor in the development of the observed malignancies. Therefore, mention is made in the SmPC that cases of malignancies in the post-marketing setting have been reported among children, adolescents and young adults (up to 22 years of age) treated with TNF-blocking agents, including infliximab. Separately a cumulative review of leukaemia cases reported with infliximab use from clinical trials, disease specific registries, postmarketing reports and published literature did not establish a causal relationship between the development of leukaemia and infliximab or TNF-antagonists use. Nevertheless, part of the reviewed data suggests that there may be an increased risk of leukaemia in patients treated with TNF-antagonists, including infliximab. As a result, the SmPC includes a warning that cases of leukaemia have been reported in patients treated with TNF-ant
II/0138	Update of section 4.8 of the SmPC to include parasitic infections as new adverse events and update of the warning on early recognition of	21/01/2010	15/03/2010	SmPC and PL	Based on postmarketing data the review of parasitic diseases associated with infliximab revealed that the large majority of reports described infections with protozoal

	infections in section 4.4. This update is made further to the CHMP request following assessment of PSUR 17-18 covering the period 24.08.07 to 23.08.08 and is based on postmarketing safety data. The MAH took the opportunity to update the contact details of the local representatives in Czech Republic, Ireland, Malta, Austria, Rumania and the UK. Update of Summary of Product Characteristics and Package Leaflet				organisms, with ectoparasitic and nematodal infections accounting for a small minority. While the data in this regard can not be refuted, the biological mechanism by which infliximab leads to an increase in infections of bacterial, viral, and fungal types appears not one which would limit the spectrum of parasitic infections to protozoal organisms. Therefore "parasitic infections" has been added a new adverse event in section 4.8 of the SmPC. Serious infections are a well-known safety concern for all TNF-? inhibitors. The current warnings and precautions for use section insistently alerts prescribers to take appropriate action with respect to infections i.e. early recognition of atypical clinical presentations of serious infections is critical in order to minimize delays in diagnosis and treatment. Nevertheless, a review of rare and unusual infections in PSUR 19 and 20 showed that such infections may, in some cases, present in a very typical manner but are unlikely to be recognized given their low prevalence in clinics outside of an infectious diseases clinic. Therefore, early recognition of rare and unusual infections which may actually have a typical presentation has been also reflected in section 4.4 for completeness of the warning.
II/0134	Change in the purification of the active substance. Change(s) to the manufacturing process for the active substance	22/10/2009	12/11/2009		
II/0135	Update of Summary of Product Characteristics and Labelling	24/09/2009	29/10/2009	SmPC and PL	

IB/0136	IB_17_b_Change in the storage conditions for the active substance	25/08/2009	n/a		
II/0130	Change in growth media components. Change(s) to the manufacturing process for the active substance	23/07/2009	29/07/2009		
II/0133	Update of Summary of Product Characteristics	29/05/2009	03/07/2009	SmPC	
R/0128	Renewal of the marketing authorisation.	23/04/2009	02/07/2009	SmPC, Annex II and Labelling	Based on the 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 the benefit risk of Remicade continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity.
II/0132	Addition of a new Finished Product manufacturing site. Change(s) to the manufacturing process for the finished product	29/05/2009	12/06/2009		
II/0131	Changes in the active substance manufacturing process. Change(s) to the manufacturing process for the active substance	29/05/2009	12/06/2009		

IB/0129	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	26/03/2009	n/a		
N/0124	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/03/2009	n/a	Labelling and PL	
II/0126	To strengthen the warning on infections in section 4.4 of the SPC further to a review of reports of invasive fungal infections. The PL was updated accordingly. The marketing authorisation holder took the opportunity to update the contact details for Bulgaria, Czech Republic, Netherlands, Austria, Poland, France, and Finland in the PL. Update of Summary of Product Characteristics and Package Leaflet	22/01/2009	06/03/2009	SmPC and PL	Patients taking medicines such as infliximab are more susceptible to serious infections. It is very important that healthcare professionals recognise in timely manner cases of infection, in particular cases of invasive fungal infections in patients treated with infliximab. The benefit risk of the treatment in patients which have travelled in areas of high risk of endemic fungal infections must be considered. This is also applicable in patients which develop a new infection while undergoing treatment. In certain cases, the treatment might need to be stopped. The product information was therefore updated to strengthen the currently existing warnings on infections and serious infections.
II/0125	To update sections 4.4 and 4.8 of the SPC on cases of hepatosplenic T-cell lymphoma reported in patients with ulcerative colitis. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	22/01/2009	06/03/2009	SmPC and PL	Cases of hepatosplenic T-cell lymphoma had previously been identified in adolescent and young adult patients with Crohn's disease. Further to a review of available safety information the existing warning on hepatosplenic T-cell lymphoma was updated to reflect that cases have also been observed in adults (although most of the patients were adolescent or young adult males) and in patients with ulcerative colitis. This type of cancer has usually resulted in death. All patients were on concomitant treatment with azathioprine or 6-mercaptopurine, therefore the potential risk with the combination of these medicinal products and

					infliximab should be considered.
IB/0127	IB_36_a_Change in shape or dimensions of the container/closure - sterile ph. forms/biologicals	02/02/2009	n/a		
II/0123	To introduce adaptations to the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance	22/01/2009	27/01/2009		
II/0118	Changes to the active substance manufacturing facility. Change(s) to the manufacturing process for the active substance	25/09/2008	02/10/2008		
IB/0122	Addition of pack size of 5 vials to the already available Remicade 1, 2 and 3 vials packs. IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	28/08/2008	28/08/2008	SmPC, Labelling and PL	
IB/0121	Addition of pack size of 4 vials to the already available Remicade 1, 2 and 3 vial packs. IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	28/08/2008	28/08/2008	SmPC, Labelling and PL	
II/0120	Change in the purification process of Remicade active substance.	24/07/2008	29/07/2008		

	Change(s) to the manufacturing process for the active substance				
II/0119	Changes in the active substance manufacturing process at the Malvern and Leiden sites. Change(s) to the manufacturing process for the active substance	24/07/2008	29/07/2008		
II/0117	To update the current statement on tuberculosis in section 4.4 of the SPC following assessment of periodic safety update reports covering the period from 24 August 2006 to 23 August 2007. Update of Summary of Product Characteristics	26/06/2008	29/07/2008	SmPC	In the periodic safety update report, a cumulative review of all reports (up to 23 August 2007) of tuberculosis (TB) received for infliximab was presented. It was noted that the majority of cases of TB reported were of extrapulmonary disease (i.e., disease located outside of the lungs). The product information already included a warning on TB, but this was revised to strengthen the message on the potential risk of extrapulmonary TB.
II/0114	Deletion of the statements "do not freeze" in the Summary of Product Characteristics (sections 6.4) and related deletions in the Labelling and Package Leaflet. Change(s) to labelling	30/05/2008	10/07/2008	SmPC, Labelling and PL	
II/0115	Update of summary of product characteristics and package leaflet. To update sections 4.4 and 4.8 of the SPC regarding peripheral demyelinating diseases associated with infliximab therapy based on data from clinical trials and from spontaneous reports received in the	24/04/2008	18/06/2008	SmPC and PL	Reports from clinical trials and the postmarketing setting on peripheral demyelinating diseases were analysed. A causal relationship between infliximab and certain neurological problems could not be excluded, including chronic inflammatory demyelinating polyneuropathy (a disease that affects the nervous system causing progressive weakness and reduced sensation in the legs

	postmarketing setting. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				and arms) and multifocal motor neuropathy (another disease that affects the nervous system and leads to muscle weakness usually in the arms and hands). The information on neurological events in the product information was reorganised and updated to reflect the potential relationship between infliximab and these events.
II/0116	Change to the use of chromatography columns used in the manufacturing process of the active substance. Change(s) to the manufacturing process for the active substance	30/05/2008	11/06/2008		
II/0113	Change to the specifications and test methods for source and starting materials of non-biological origin used in the manufacturing process of the active substance. Change to the test procedure and/or specification of a raw material	24/04/2008	28/04/2008		
II/0111	Update of or change(s) to the pharmaceutical documentation	24/04/2008	28/04/2008		
II/0112	Update of summary of product characteristics To update section 4.8 of the SPC by merging the undesirable effects collected in clinical studies with the post marketing reports and revising the terminology and the frequency categories, to bring it in line with the current version of SPC guideline.	19/03/2008	23/04/2008	SmPC	The undesirable effects section was reviewed to bring it in line with the current SPC guideline. All events observed with infliximab were placed in the same table irrespective of their origin (e.g., clinical trials, post-authorisation safety studies or spontaneous reporting). The frequency of events was re-organised and the events were aligned in order of decreasing seriousness. Where appropriate, adverse

	Update of Summary of Product Characteristics				reaction descriptions were changed into MedDRA terms.
II/0107	To update section 5.1 to include results available from clinical studies in subjects with ulcerative colitis on colectomy, hospitalisations and surgeries. The ATC code was also updated in accordance with the WHO ATC/DDD alterations. Update of Summary of Product Characteristics	21/02/2008	08/04/2008	SmPC	Please refer to the Scientific Discussion: Remicade-H-240-II-107-AR
II/0110	Change(s) to the manufacturing process for the active substance	24/01/2008	28/01/2008		
II/0108	Update of summary of product characteristics and package leaflet To update section 4.8 regarding intersticial lung disease, and to add clarification on adverse events with fatal outcome to reflect the most recent safety information available and following update of the Company's Core Data Sheet. Additionally, the Swedish details in list of local representatives of the package leaflet were updated. Update of Summary of Product Characteristics and Package Leaflet	15/11/2007	21/12/2007	SmPC and PL	Based on a review of data from postmarketing experience, the undesirable effects section was updated to include interstitial lung disease (a disease that is characterised by inflammation and progressive fibrosis of the pulmonary connective tissue) and rapidly progressive interstitial lung disease as adverse events. A clarification on fatal outcome of some adverse drug reactions in the post-marketing setting was also included.
II/0109	Change(s) to the manufacturing process for the active substance Change(s) to the test method(s) and/or	13/12/2007	19/12/2007		

	specifications for the active substance				
II/0106	Update of Summary of Product Characteristics and Package Leaflet To update sections 4.2 and 5.1 of the SPC regarding definition of response for induction, dose escalation, mucosal healing, corticoid management and quality of life in Crohn's disease in adults. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	18/10/2007	30/11/2007	SmPC and PL	Based on analysis of data from clinical studies in Crohn's disease (CD), the product information was updated. In severe active CD, the time for assessment of initial response was extended to 6 weeks, after the second dose. However, if a patient does not achieve a response after the second dose, no further treatment should be given. Although comparative data are lacking, limited data are available in patients with severe CD and fistulising CD that indicate that some patients may regain response with dose escalation, although continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit after dose adjustment. Improvements in quality of life measures, reduction in disease-related hospitalisations and corticosteroid use were seen in patients with severe active CD and fistulising active CD disease. In patients with fistulising disease it was shown that maintenance therapy with infliximab reduced disease-related surgeries. Furthermore, there is limited evidence of mucosal healing in infliximab treated patients.
II/0105	Update of SPC, annex II, labelling and PL To update section 4.4 regarding tuberculosis and section 4.8 regarding skin and subcutaneous tissue disorders based on data from spontaneous reports received in the postmarketing experience. The product information was updated in accordance with the current EMEA/QRD templates. Update of Summary of Product Characteristics,	18/10/2007	30/11/2007	SmPC, Annex II, Labelling and PL	The tuberculosis warning was updated to recommend that if latent tuberculosis is suspected, an expert on this disease should be consulted. Additionally, in patients with risk factors for tuberculosis and a negative test for latent disease, or patients with past history of tuberculosis without confirmation of an adequate course of treatment, anti-tuberculosis therapy should be considered. The undesirable effects section was updated to include the events of toxic epidermal necrolysis, Stevens-Johnson Syndrome and erythema multiforme, which are severe skin

	Labelling and Package Leaflet				diseases. Rash, swelling of hands and face are already listed as possible side effects in the PL. Patients should immediately tell their doctor if they notice any of these symptoms. The product information was generally updated to bring it in line with the current EMEA/QRD templates (version 7.2).
II/0100	Extension of Indication To update the psoriatic arthritis indication to include improvement of physical function and reduction of the rate of progression of structural damage of active arthritis in adult patients with psoriatic arthritis. Extension of Indication	18/10/2007	30/11/2007	SmPC and PL	Please refer to the Scientific Discussion: Remicade-H-240-II-100-AR
II/0104	Change(s) to the manufacturing process for the active substance	15/11/2007	26/11/2007		
II/0095	To update the ankylosing spondylitis indication to include patients who have responded inadequately to conventional therapy, regardless of their HLA-B27 status or serological markers level. Additionally, corrections were introduced in the package leaflet on the list of local representatives for Italy, Latvia, Malta, Nederlands, Norway, Poland and Romenia. Extension of Indication	20/09/2007	30/10/2007	SmPC and PL	Please refer to the Scientific Discussion: Remicade-H-240-II-95-AR
II/0102	Change(s) to the test method(s) and/or specifications for the active substance	19/07/2007	24/07/2007		

	Change(s) to the test method(s) and/or specifications for the finished product				
II/0101	To update section 5.1 of the SPC to include improvement in nail psoriasis and in some quality of life measures based on clinical trial data and publications available from in adult patients with moderate to severe plaque psoriasis. Update of Summary of Product Characteristics	21/06/2007	24/07/2007	SmPC	Data from clinical trials and publications indicated that a number of subjects with nail psoriasis being treated with infliximab for their moderate to severe plaque psoriasis showed improvement of their nail disease. Improvements were also demonstrated in some patient-reported outcome measures used in clinical studies for the assessment of treatments of moderate to severe plaque psoriasis, like the dermatology life quality index (DLQI) and in components of the short form 36 health survey (SF-36).
II/0098	To update sections 4.4 and 4.8 of the SPC to reflect the most recent safety information available from clinical trials and postmarketing experience. This follows an update of the company's core safety information regarding hepatitis B reactivation and hepatobiliary events, and the inclusion of new onset psoriasis and pustular psoriasis. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	21/06/2007	24/07/2007	SmPC and PL	Based on safety analysis of clinical trials and postmarketing data, the product information was updated: 1. the warning on reactivation of hepatitis B virus (HBV) was updated to strengthen the message that patients at risk for HBV reactivation should inform their doctors and be monitored for signs and symptoms throughout the treatment and for several months following termination of treatment; 2. the undesirable effects section was updated to include new onset psoriasis and pustular (palmar/plantar) psoriasis, as this has been observed very rarely in patients treated for other indications; 3. the liver adverse events figures (transaminase elevations in clinical trials) were updated per indication, number of patients and median follow-up.
II/0097	Change(s) to the manufacturing process for the active substance	21/06/2007	27/06/2007		
IA/0103	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	14/06/2007	n/a		

II/0096	Change(s) to the manufacturing process for the active substance	24/05/2007	06/06/2007		
II/0075	To update section 4.1 of the SPC, to include treatment of severe active Crohn's disease in children aged 6 to 17 years. Section 4.2, 4.4, 4.8, 5.1 and 5.2 were subsequently updated. The PL was updated in accordance with the changes proposed to the SPC. Furthermore, a correction was introduced in the Lithuanian local representative contact details. Annex II was updated regarding the conditions or restrictions with regard to the safe and effective use of the medicinal product. Extension of Indication	22/03/2007	30/05/2007	SmPC and PL	Please refer to the Scientific Discussion: Remicade-H-240-II-75-AR
IA/0099	IA_09_Deletion of manufacturing site	13/04/2007	n/a		
II/0093	To update section 5.1 of the SPC to include information on the increase of haemoglobin levels from baseline associated with the administration of infliximab in patients with rheumatoid arthritis and anaemia. This change follows the review of relevant clinical studies. Update of Summary of Product Characteristics	22/02/2007	27/03/2007	SmPC	Retrospective analysis of studies in rheumatoid arthritis were performed to examine the effect of infliximab on blood haemoglobin concentration in subjects who were anaemic at baseline. This analysis was also performed in studies in psoriatic arthritis and ankylosing spondylitis for support. The results indicated that after treatment with infliximab, rheumatoid arthritis patients with reduced haemoglobin levels exhibited increased haemoglobin levels, compared with baseline. The pharmacodynamic properties

					section of the SPC was updated to reflect this information.
II/0094	Change(s) to the manufacturing process for the finished product	22/02/2007	01/03/2007		
II/0090	Change(s) to the manufacturing process for the active substance	22/02/2007	01/03/2007		
II/0092	Change(s) to the manufacturing process for the active substance	24/01/2007	06/02/2007		
II/0091	Change(s) to the manufacturing process for the active substance	24/01/2007	06/02/2007		
II/0088	To update sections 4.2 and 5.1 of the SPC to include dose escalation up to 7.5 mg/kg or increase frequency of 3 mg/kg of infliximab administration up to every 4 weeks in rheumatoid arthritis patients with an inadequate response or patients that lost response to infliximab after 12 weeks of therapy. The possibility of delegation of infliximab administration to qualified healthcare professionals other than the prescribing physician is also included. The package leaflet was updated accordingly. Additionally, the marketing authorisation holder took the opportunity to update the list of local representatives in the PL (Latvia) and to include the two new EU Member States (Bulgaria and Romania). Update of Summary of Product Characteristics and Package Leaflet	16/11/2006	04/01/2007	SmPC and PL	Available clinical data indicate that some subjects with rheumatoid arthritis might need dose escalation. The posology section was updated to reflect that if a clinical response is not achieved within 12 weeks of treatment, or if a patient loses response after this period, some patients might receive an increase of the dose of infliximab. This will be done step-wise up to a maximum of 7.5 mg/kg every 8 weeks. Alternatively, the possibility for shorter intervals of administration (every 4 weeks) might be considered for the individual patient. If adequate response is achieved, patients should be continued on the selected dose or dose frequency. Additionally, the SPC was updated to reflect that infliximab infusions can be administered and supervised by healthcare professionals other than the prescribing physician, provided that the healthcare professionals are qualified and trained to detect any infusion related issues.

II/0087	To update sections 4.2, 4.4 and 4.8 of the SPC to include safety information on the treatment of patients with juvenile idiopathic arthritis. The PL was updated accordingly. Additionally, the marketing authorisation holder took the opportunity to harmonise the wording for the psoriatic arthitis indication with that of other anti TNF agents. Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	27/10/2006	SmPC and PL	The product information was updated to include information from a safety analysis of a clinical trial performed in 120 patients (age range: 4-17 years old) with active juvenile idiopathic arthritis despite treatment with methotrexate. The observed adverse events (infusion reactions, development of antibodies to infliximab and infections) were listed in the SPC and a statement included indicating that infliximab is not recommended for use in children ?17 years due to insufficient data on safety and efficacy.
II/0085	To update sections 4.2, 4.8, and 6.6 of the SCP to include a change in the recommended infusion duration for patients with rheumatoid arthritis who tolerated the first three infusions. The PL was updated accordingly. Additionally, the marketing authorisation holder took the opportunity to update the list of local representatives (Denmark, Iceland, Latvia, Lithuania, Luxembourg and Malta). Update of Summary of Product Characteristics and Package Leaflet	21/09/2006	27/10/2006	SmPC and PL	Based on safety analysis of clinical trials and published data, the product information was updated to reflect that patients with rheumatoid arthritis being treated with infliximab might be eligible for shortened infusions over a period of not less than 1 hour, provided that they have tolerated 3 initial 2-hour infusions.
II/0089	Change(s) to the manufacturing process for the finished product	18/10/2006	23/10/2006		
II/0086	Change(s) to the manufacturing process for the active substance	21/09/2006	27/09/2006		

II/0077	Update of summary of product characteristics and package leaflet Update of sections 4.4 and 4.8 of the SPC to include the latest information related to lymphoma and non-lymphoma malignancies, further to the review of malignancy data from clinical trials and long term follow-up, and the assessment of PSUR 11 and 12 covering the period from 24 August 2004 to 23 August 2005. The PL has been updated in accordance with the changes proposed to the SPC. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	01/09/2006	SmPC and PL	In line with the CHMP recommendations further to the assessment of the 11th and 12th PSURs, and to fulfil ongoing commitments, the MAH applied to update the product information. The update related to the sections on cancer, including lymphoma. In clinical trials of infliximab, the incidence of lymphoma in infliximab-treated patients was higher than expected in the general population, but the occurrence of lymphoma was rare. Caution should be exercised when considering TNF-blocking therapy for patients with a history of malignancy or when continuing treatment in patients who develop a malignancy. Sections 4.4 and 4.8 of the SPC were updated to reflect this information. The PL was updated accordingly to the SPC changes.
II/0069	Update of section 4.1 of the SPC, to change the therapeutic indication of infliximab from third to second line therapy in patients with severe, active Crohn's disease. Furthermore, to update section 4.4 on the use of infliximab in patients with fibrotic strictures due to Crohn's disease. These changes were based on post-marketing experience. Extension of Indication	27/07/2006	01/09/2006	SmPC and PL	Please refer to the Scientific Discussion: Remicade-H-240-II-69-AR
II/0082	Change(s) to the manufacturing process for the active substance	27/07/2006	07/08/2006		
II/0078	Change(s) to the manufacturing process for the active substance	27/07/2006	07/08/2006		

II/0084	Update of Summary of Product Characteristics and Package Leaflet Update of sections 4.4 and 4.8 of the SPC to reflect the latest information on post-marketing cases of hepatosplenic T-cell Lymphoma (HSTL) in paediatric and young adult patients with Crohn's disease. The PL was updated in accordance with the changes proposed for the SPC. Update of Summary of Product Characteristics and Package Leaflet	01/06/2006	04/07/2006	SmPC and PL	Six cases of a rare type of hepatosplenic T-cell lymphoma were identified in adolescent and young adult patients with Crohn's disease. All patients were on concomitant treatment with azathioprine or 6-mercaptopurine. Based on the data presented, a causal relationship of hepatosplenic T-cell lymphoma and infliximab therapy cannot be excluded. The relevant sections of the SPC were updated to include the information on this finding. The PL was updated to reflect the changes of the SPC.
II/0081	Update of Summary of Product Characteristics Update of sections 4.4 and 4.8 of the SPC further to the request from the CHMP following assessment of PSURs No 11 and 12, covering the period from 24 August 2004 to 23 August 2005. The changes relate to opportunistic infections and Pneumocystis jiroveci pneumonia (PJP) reports originated from post-marketing data. Update of Summary of Product Characteristics	01/06/2006	04/07/2006	SmPC	In line with the CHMP recommendations further to the assessment of the 11th and 12th PSURs, the MAH applied to update the warnings and undesirable effects sections of the summary of product characteristics. The relevant sections were updated regarding opportunistic infections observed in infliximab treated patients, which include but are not limited to pneumocystosis, histoplasmosis, cytomegalovirus infection, atypical mycobacterial infections, listeriosis and aspergillosis. The wording was strengthened to highlight the importance of infections and their early recognition.
II/0073	Extension of Indication Update of section 4.1 of the SPC, to change the psoriatic arthritis indication to include the use of infliximab alone or in combination with	01/06/2006	04/07/2006	SmPC and PL	Please refer to the Scientific Discussion: Remicade-H-240-II-73-AR

	methotrexate. Sections 4.2, 4.5, 4.8 and 5.1 were subsequently updated. The Package Leaflet (PL) was updated in accordance with the changes proposed to the SPC. Extension of Indication				
II/0080	Change(s) to the manufacturing process for the active substance	01/06/2006	08/06/2006		
II/0079	Change(s) to the manufacturing process for the active substance	01/06/2006	08/06/2006		
IA/0083	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	31/05/2006	n/a		
II/0076	Change(s) to the manufacturing process for the active substance	23/03/2006	29/03/2006		
II/0065	Extension of Indication Update of section 4.1 (Therapeutic indications) of the SPC to include treatment of patients with moderately to severely active ulcerative colitis. Sections 4.2 (Posology and method of administration), 4.4 (Special warnings and special precautions for use) and 5.1 (Pharmaceutical properties) have consequently been updated. Extension of Indication	26/01/2006	28/02/2006	SmPC and PL	Please refer to the Scientific Discussion: Remicade-H-240-II-65-AR

IB/0074	IA_09_Deletion of manufacturing site IB_31_b_Change to in-process tests/limits during manufacture - addition of new tests/limits	13/12/2005	n/a		
II/0072	Change(s) to the manufacturing process for the finished product	17/11/2005	22/11/2005		
II/0071	Change(s) to the manufacturing process for the active substance	17/11/2005	22/11/2005		
II/0066	Change(s) to the manufacturing process for the finished product	13/10/2005	19/10/2005		
II/0070	Change(s) to the test method(s) and/or specifications for the active substance	15/09/2005	29/09/2005		
II/0068	Update of sections 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects) of the SPC to include safety findings on malignancies in patients with chronic obstructive pulmonary disease (COPD). Update of Summary of Product Characteristics	27/07/2005	29/09/2005	SmPC	The COPD study was an exploratory clinical trial in patients with moderate-to-severe chronic obstructive pulmonary disease who were either smokers or ex-smokers. Although small and with uncertainties, the study showed that there is a difference in malignancy incidence observed between infliximab and placebo treated patients. This study provided a signal for increased incidence of smoking-related malignancies with inflixmab exposure, in a patient population with a heavy smoking history, and thus being at high risk for malignancy.
II/0061	Update of section 4.1 (Therapeutic Indications) of the SPC to include treatment of patients with moderate to severe plaque psoriasis. Sections 4.2 (Posology and method of administration), 4.4	27/07/2005	29/09/2005	SmPC and PL	Please refer to the Scientific Discussion: Remicade-H-240-II-61-AR

	(Special warnings and special precautions for use), 4.8 (Undesirable effects), and 5.1 (Pharmacodynamic Properties) have consequentially been updated. Relevant sections of the PL are updated accordingly. Extension of Indication				
II/0063	Update of sections 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects) of the SPC to include information on increased infections and pneumonia, following a cumulative analysis of serious infections observed in rheumatoid arthritis studies. Update of Summary of Product Characteristics	23/05/2005	01/08/2005	SmPC	The observed increased incidence of pneumonia in clinical trials in rheumatoid arthritis patients treated with infliximab plus methotrexate, as compared with patients treated with methotrexate alone, warranted the addition of pneumonia in the warning and undesirable effects sections of the SPC.
II/0064	Update of sections 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects) of the SPC to include information on hepatobiliary events and reactivation of hepatitis B following a review of the available data from recently completed trials and data from spontaneous reports. Relevant sections of the PL are updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	26/05/2005	28/06/2005	SmPC and PL	A review of occurrence of hepatobiliary events in clinical trials and post-marketing available data was performed. Very rare cases of jaundice and non-infectious hepatitis, some with features of autoimmune hepatitis, have been observed in the post-marketing experience of Remicade. Isolated cases of liver failure resulting in liver transplantation or death have occurred. A warning was introduced in the Product Information, as patients with symptoms or signs of liver dysfunction should be evaluated for evidence of liver injury. If jaundice and/or elevations of liver enzymes above upper limit of normal develop, Remicade should be discontinued. Most of the more severe events occurred in patients with

					multifactorial risk factors including severe background disease.Immunosuppressive medicinal products increase the risk for hepatitis B reactivation. Reactivation of hepatitis B occurred in patients receiving Remicade, who are chronic carriers of this virus (i.e. surface antigen positive).
II/0062	Update of section 4.6 (Pregnancy and lactation) to include data from post-marketing reports of a limited number of exposed pregnancies and section 4.2 (Posology and method of administration), 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects) to include information on delayed hypersensitivity following the assessment of the renewal. Update of Summary of Product Characteristics	26/05/2005	28/06/2005	SmPC	The MAH presented the current post-marketing cumulative experience with exposure to infliximab during pregnancy. In view of the limited experience the post-marketing reports available do not indicate unexpected effects on pregnancy outcome. However, the available clinical experience is too limited to exclude a risk, therefore the administration of infliximab is not recommended during pregnancy. Attempts are being made to explore possible ways of gathering birth outcome data for infants born of mothers exposed to infliximab and follow-up of infants up to 1 year after birth. Following the experience gathered from the use of Remicade from clinical studies delayed hypersensitivity reactions are categorised as uncommon. Signs and symptoms included pain in the muscles and/or pain in a joint with fever and/or rash, with some patients experiencing itching, swelling of the face, hand or lip due to fluid, difficulty in swallowing, urticaria, sore throat and headache
II/0057	Change(s) to the manufacturing process for the active substance	16/03/2005	23/03/2005		
II/0048	Change(s) to the manufacturing process for the	16/03/2005	23/03/2005		

	finished product				
II/0060	Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product	17/02/2005	25/02/2005		
II/0052	Change(s) to the manufacturing process for the active substance	17/02/2005	25/02/2005		
II/0056	Update of sections 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects) of the SPC on malignancies and lymphoproliferative disorders following a review of the safety information available. Change(s) to the test method(s) and/or specifications for the active substance Change(s) to the test method(s) and/or specifications for the finished product Update of Summary of Product Characteristics	15/12/2004	26/01/2005	SmPC	The MAH applied to update the text in sections 4.4 "Special warnings and special precautions for use" and 4.8 "Undesirable effects" on malignancies and lymphoproliferative disorders. The purpose was to revise the warnings section and to include details of the post-marketing experience on malignancies and lymphoproliferative disorders, including incidence. In clinical trials, more cases of lymphoma have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare. Additionally, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation. With the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.
II/0053	Update of sections 4.4 (Special warnings and special precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction)	18/11/2004	10/01/2005	SmPC	Revision of the warnings on combination use of TNFa inhibitors and anakinra in section 4.4 of the SPC and addition of information that the combination of Remicade

	and 4.8(Undesirable effects) of the SPC following the assessment of the 9th PSUR (reporting period 24.08.03-23.02.04) to include information on new onset of heart failure based on post-marketing reports and to revise the warning on combination use of TNFa inhibitors and anakinra. Update of Summary of Product Characteristics				and anakinra is not recommended in section 4.5. The proposed new wording in section 4.8 relating to new onset of heart failure adequately alerts prescribing physicians. The post-marketing reports of worsening heart failure and new onset heart failure were also reflected as rare events in section 4.8.
IA/0059	IA_13_a_Change in test proc. for active substance - minor change	10/12/2004	n/a		
IA/0058	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	23/11/2004	n/a		
IA/0055	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	09/11/2004	n/a		
II/0046	The Marketing Authorisation Holder (MAH) applied for the extension of the therapeutic indication to include patients with active psoriatic arthritis in SPC section 4.1. The SPC sections 4.2 and 5.1 were updated with respectively the posology for the treatment of active psoriatic arthritis, and with information about the IMPACT trial. The Package Leaflet has been revised accordingly. Extension of Indication	29/07/2004	24/09/2004	SmPC and PL	
R/0050	Renewal of the marketing authorisation.	23/06/2004	20/09/2004		

II/0049	Update of SPC section 4.8 (Undesirable effects) to include pancreatitis as requested by CPMP following assessment on PSUR8 covering the period from 24.02.03 to 23.08.03; in addition the MAH proposes to add agranulocytosis. Update of Summary of Product Characteristics	22/04/2004	08/06/2004	SmPC	
II/0045	Update of the SPC, based on the ASPIRE study: update of section 4.1 to add treatment of methotrexate -naive subjects with early rheumatoid arthritis, of section 4.4 to add information about use of infliximab concurrently with live vaccines and of section 5.1 to add information about the ASPIRE trial. The MAH took this opportunity to also introduce minor spelling changes in the SPC. The PL is changed accordingly. In addition the MAH has completed the list of local representatives to include the 10 accession countries in accordance with EMEA/QRD templates. Extension of Indication	22/04/2004	08/06/2004	SmPC and PL	
N/0051	To amend the list of local representatives to include all new representatives addresses from new member states. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/05/2004	n/a	PL	
II/0044	Update of the Summary of Product Characteristics	17/12/2003	09/03/2004	SmPC and PL	

	(SPC) sections 4.2 (Posology and method of administration), 4.4 (Special warnings and special precautions for use) and 4.8 (Undesirable effects). Based on the CPMP assessment of PSUR6, covering the timeperiod 24/02/2002-23/08/2002 SPC changes are proposed for infusion rate/infusion related reactions and vasculitis. Furthermore, the MAH include a warning regarding stricturing C.D, in line with the CPMP request following the evaluation of PSUR7, covering the timeperiod 24/08/2002-23/02/2003. Also further to the the CPMP evaluation of the fourth annual reassessment, the MAH proposes to reword a sentence in section 4.2 regarding continuation of therapy in patients who show no evidence of therapeutic benefit. The Package Leaflet has also been amended accordingly. Update of Summary of Product Characteristics and Package Leaflet				
S/0037	Annual re-assessment.	20/11/2003	08/03/2004	SmPC and Annex II	
II/0047	Change(s) to the test method(s) and/or specifications for the active substance	26/02/2004	05/03/2004		
II/0043	Change(s) to the manufacturing process for the finished product	17/12/2003	22/12/2003		

II/0032	updates the Summary of Product Characteristics to include data from the ACCENT II trial with regard to the long term treatment (46 weeks) of Crohn's disease patients with draining enterocutaneous (perianal, abdominal) and/or rectovaginal fistulas. The following sections are amended: section 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.4 (Special warnings and special precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.8 (Undesirable effects), and 5.1 (Pharmacodynamic properties). The Package Leaflet has also been amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/07/2003	20/10/2003	SmPC and PL	updates the Summary of Product Characteristics to include data from the ACCENT II trial with regard to the long term treatment (46 weeks) of Crohn's disease patients with draining enterocutaneous (perianal, abdominal) and/or rectovaginal fistulas. The following sections are amended: section 4.1 (Therapeutic indications), 4.2 (Posology and method of administration), 4.4 (Special warnings and special precautions for use), 4.5 (Interaction with other medicinal products and other forms of interaction), 4.8 (Undesirable effects), and 5.1 (Pharmacodynamic properties). The Package Leaflet has also been amended accordingly.
I/0042	15a_Change in IPCs applied during the manufacture of the product	03/10/2003	15/10/2003		
II/0038	Change(s) to the test method(s) and/or specifications for the active substance	25/09/2003	30/09/2003		
I/0040	24_Change in test procedure of active substance	25/09/2003	30/09/2003		
I/0039	12_Minor change of manufacturing process of the active substance	25/09/2003	30/09/2003		
I/0041	11b_Change in supplier of an intermediate	29/08/2003	17/09/2003		

	compound used in manufacture of the active substance				
I/0035	15_Minor changes in manufacture of the medicinal product	24/07/2003	29/07/2003		
II/0022	Change(s) to the manufacturing process for the active substance	25/04/2003	10/07/2003	Annex II	
S/0028	Annual re-assessment.	20/02/2003	15/05/2003	SmPC, Annex II, Labelling and PL	
II/0029	Update of Summary of Product Characteristics	20/02/2003	15/05/2003	SmPC	
II/0025	Update of Summary of Product Characteristics and Package Leaflet	20/02/2003	15/05/2003	SmPC and PL	
II/0024	Extension of Indication Update of Summary of Product Characteristics and Package Leaflet	20/02/2003	15/05/2003	SmPC and PL	
I/0030	12_Minor change of manufacturing process of the active substance	25/04/2003	02/05/2003		
I/0034	12a_Change in specification of starting material/intermediate used in manuf. of the active substance	16/04/2003	24/04/2003		
I/0031	20a_Extension of shelf-life or retest period of the active substance	12/03/2003	25/03/2003		

I/0027	04_Replacement of an excipient with a comparable excipient	07/01/2003	13/01/2003		
I/0026	12_Minor change of manufacturing process of the active substance	21/11/2002	09/12/2002		
II/0023	Update of Summary of Product Characteristics and Package Leaflet	25/07/2002	14/10/2002	SmPC and PL	
II/0017	Update of Summary of Product Characteristics	25/04/2002	11/07/2002	SmPC	
II/0021	Change(s) to the test method(s) and/or specifications for the finished product	27/06/2002	04/07/2002		
N/0020	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/06/2002	20/06/2002	PL	
I/0019	12_Minor change of manufacturing process of the active substance	30/05/2002	03/06/2002		
S/0015	Annual re-assessment.	17/01/2002	17/05/2002		
II/0016	Update of Summary of Product Characteristics	17/01/2002	17/05/2002	SmPC	
II/0011	Update of or change(s) to the pharmaceutical documentation	25/04/2002	30/04/2002		
I/0013	04_Replacement of an excipient with a comparable excipient 01_Change following modification(s) of the manufacturing authorisation(s)	02/10/2001	n/a		

	15a_Change in IPCs applied during the manufacture of the product				
N/0014	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/09/2001	08/02/2002	PL	
II/0009	Update of Summary of Product Characteristics and Package Leaflet	29/03/2001	31/07/2001	SmPC and PL	
II/0012	Update of Summary of Product Characteristics and Package Leaflet	01/03/2001	27/06/2001	SmPC and PL	
I/0008	20_Extension of shelf-life as foreseen at time of authorisation	07/02/2001	n/a	SmPC, Labelling and PL	
II/0004	Extension of Indication	21/09/2000	29/01/2001	SmPC and PL	
N/0007	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/01/2001	23/02/2001	PL	
I/0006	30_Change in pack size for a medicinal product	08/09/2000	16/11/2000	SmPC, Labelling and PL	
I/0005	30_Change in pack size for a medicinal product	08/09/2000	16/11/2000	SmPC, Labelling and PL	
II/0001	Extension of Indication	16/02/2000	27/06/2000	SmPC and PL	
I/0003	12_Minor change of manufacturing process of the active substance	16/12/1999	27/06/2000		

I/0002	20_Extension of shelf-life as foreseen at time of authorisation	12/11/1999	08/02/2000	SmPC	