Humira

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
N/0214	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/10/2022		PL	
IB/0213	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	30/09/2022	n/a		

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

IA/0212	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	06/07/2022	n/a		
IA/0211/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	02/09/2021	16/12/2021	Annex II	
IA/0210	B.II.e.5.b - Change in pack size of the finished product - Deletion of a pack size(s)	02/07/2021	16/12/2021	SmPC, Labelling and PL	
IA/0209	B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test	16/06/2021	n/a		
IAIN/0208	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/04/2021	16/12/2021	SmPC and PL	
IA/0207	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	01/04/2021	n/a		
IA/0206	A.7 - Administrative change - Deletion of manufacturing sites	22/12/2020	16/12/2021	SmPC, Annex	

				II and PL	
IB/0205	B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	21/12/2020	n/a		
II/0198	Extension of indication to include treatment of moderately to severely active ulcerative colitis in paediatric patients from 6 years of age for Humira; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC for 40mg/0.8mL, 40mg/0.4mL and 80mg/0.8mL presentations are updated. The MAH took the opportunity to introduce minor editorial changes to sections 5.1, 5.2 and 5.3 of the SmPC for all the presentations. The Package Leaflet is updated in accordance. Furthermore, the PI is being brought in line with the latest QRD template (version 10.1). Version 15.1 of the RMP is also agreed. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	15/10/2020	20/11/2020	SmPC and PL	Please refer to Scientific Discussion 'Humira-H-C-000481-II-0198'
IA/0204	B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	29/10/2020	n/a		
IB/0202	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	20/10/2020	n/a		

IAIN/0203	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/10/2020	20/11/2020	SmPC and PL	
IB/0201	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	17/09/2020	n/a		
PSUSA/10783 /201912	Periodic Safety Update EU Single assessment - adalimumab	03/09/2020	n/a		PRAC Recommendation - maintenance
IA/0200	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	24/08/2020	n/a		
IA/0199/G	This was an application for a group of variations. B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.f.1.e - Stability of FP - Change to an approved stability protocol	07/07/2020	n/a		
IB/0196	B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place	30/01/2020	n/a		
IB/0193	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/11/2019	28/04/2020	SmPC and PL	
IA/0194	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the	13/11/2019	n/a		

	finished product, including quality control sites (excluding manufacturer for batch release)				
IB/0192	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/11/2019	n/a		
II/0187	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority Update of section 5.1 of the SmPC to reflect results from the final report from study M11-327: A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate Uveitis, Posterior Uveitis, or Panuveitis; listed as a category 3 study in the RMP. Furthermore editorial changes and a brief description of the study design were also added to section 5.1 of the SmPC. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	16/05/2019	28/04/2020	SmPC	Of the 424 subjects included in the uncontrolled long-term extension of Studies UV I and UV II, 60 subjects were regarded ineligible (e.g. due to deviations or due to complications secondary to diabetic retinopathy, due to cataract surgery or vitrectomy) and were excluded from the primary analysis of efficacy. Of the 364 remaining patients, 269 evaluable patients (74%) reached 78 weeks of open-label adalimumab treatment. Based on the observed data approach, 216 (80.3%) were in quiescence (no active inflammatory lesions, AC cell grade ≤ 0.5+, VH grade ≤ 0.5+) with a concomitant steroid dose ≤ 7.5 mg per day, and 178 (66.2%) were in steroid-free quiescence. BCVA was either improved or maintained (< 5 letters deterioration) in 88.6% of the eyes at week 78. Data beyond Week 78 were generally consistent with these results but the number of enrolled subjects declined after this time. Overall, among the patients who discontinued the study, 18% discontinued due to adverse events, and 8% due to insufficient response to adalimumab treatment.
IA/0191	A.7 - Administrative change - Deletion of manufacturing sites	15/04/2019	n/a		
II/0185	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	11/04/2019	n/a		

	of studies to the competent authority				
II/0184/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place 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	21/03/2019	29/04/2019	Annex II	
II/0189	B.I.a.1.j - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Replacement or addition of a site where batch control/testing takes place and any of the test method at the site is a biol/immunol method	07/03/2019	n/a		
IAIN/0190	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	04/03/2019	n/a		

IB/0186/G	This was an application for a group of variations. Please refer to the Recommendations section above. B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products 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 B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	01/03/2019	29/04/2019	PL	No new safety concerns or signals were identified within the RABBIT study report. The increased risks for infections during anti-TNF treatment and the possible association with malignancies are well known among prescribers and adequately covered in both the product information and the RMP. Further data on these issues are anticipated to be retrieved through still on-going Humira RMP-listed studies (mainly other registry studies). From the analysis of this data no update of the product information was considered necessary.
IB/0188	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	22/02/2019	n/a		
II/0182	Submission of an updated RMP version 14.2 in order to update the list of safety concerns in relation to prior assessments and in line with GVP Module V. In addition and as a consequence of the RMP update, the Annex II of the Product Information is updated in relation to the additional minimisation measure of the Patient Reminder Card. Consequential minor changes to the SmPC and PL are also made. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of	31/10/2018	29/04/2019	SmPC, Annex II and PL	

	change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				
II/0173	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	31/10/2018	n/a		
II/0179	Update of section 4.8 of the SmPC in order to add Lichenoid skin reactions with a rare frequency following a signal detection request (EPITT ref. No. 19128) for cumulative review (SDA106). The Package Leaflet is updated accordingly. The MAH took also the opportunity to include some minor QRD and editorial changes in the Package leaflet. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/07/2018	29/04/2019	SmPC and PL	
IB/0183	B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	23/07/2018	29/04/2019	SmPC, Labelling and PL	
II/0170	Update of section 4.6 and 4.4 of the SmPC in order to update information on pregnancy based on results from the OTIS (study number M03-604) pregnancy registry and a review of pregnancy cases from the MAH's safety database. The Package Leaflet is updated accordingly.	28/06/2018	29/04/2019	SmPC and PL	A large number (approximately 2100) of prospectively collected pregnancies exposed to adalimumab resulting in live birth with known outcomes, including more than 1500 exposed during the first trimester, does not indicate an increase in the rate of malformation in the newborn. In a prospective cohort registry, 257 women with rheumatoid arthritis (RA) or Crohn's disease (CD) treated

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				with adalimumab at least during the first trimester and 120 women with RA or CD not treated with adalimumab were enrolled. There were no distinct differences between adalimumab-treated and untreated women for the primary and also for secondary endpoints and no stillbirths or malignancies were reported. The interpretation of data may be impacted due to methodological limitations of the study, including small sample size and non-randomized design. Adalimumab should only be used during pregnancy if clearly needed. Limited information from the published literature indicates that adalimumab is excreted in breast milk at very low concentrations with the presence of adalimumab in human milk at concentrations of 0.1% to 1% of the maternal serum level. Given orally, immunoglobulin G proteins undergo intestinal proteolysis and have poor bioavailability. No effects on the breastfed newborns/infants are anticipated. Consequently, Humira can be used during breastfeeding.
IB/0178/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g.	15/06/2018	29/04/2019	SmPC, Labelling and PL	

	tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
IA/0181	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	24/05/2018	n/a		
II/0172	Update of sections 5.1 and 5.2 of the SmPC for 40mg/0.8ml and 40mg/0.4 ml Prefilled pen and prefilled syringe in order to add information on non-radiographic axial spondyloarthritis following final results from Humira remission-withdrawal-retreatment study (M13-375) listed in the RMP. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/04/2018	29/04/2019	SmPC	673 patients with active nr-axSpA who had an inadequate response to ≥ 2 NSAIDs, or an intolerance to or a contraindication for NSAIDs enrolled into the open-label period of Study nr-axSpA II during which they received Humira 40 mg eow for 28 weeks. Patients who achieved sustained remission for at least 12 weeks (N=305) during the open-label period were then randomized to receive either continued treatment with Humira 40 mg eow (N=152) or placebo (N=153) for an additional 40 weeks in a double-blind, placebo-controlled period (total study duration 68 weeks). Subjects who flared during the double-blind period were allowed Humira 40 mg eow rescue therapy for at least 12 weeks. The primary efficacy endpoint was the proportion of patients with no flare by Week 68 of the study. By Week 68, patients receiving

					continuous Humira treatment showed statistically significant greater improvement of the signs and symptoms of active nr-axSpA as compared to patients allocated to treatment withdrawal during the double-blind period of the study. For more information please refer to the Summary of Product Characteristics.
II/0175	Update of sections 4.2 and 5.2 of the SmPC in order to include 80mg every other week (eow) as an alternative dosing option to the current approved 40 mg weekly dose in the following relevant indications: Rheumatoid arthritis (RA), Crohn's disease (CD), paediatric CD (patients ≥ 40 kg), psoriasis (Ps), ulcerative colitis (UC), hidradenitis suppurativa (HS), and adolescent HS. As a consequence section 4.1 and 5.1 of the SmPC for the 80 Mg strength has been modified to introduce relevant information on Rheumatoid Arthritis. Furthermore the MAH has taken the occasion to introduce some editorial changes. 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	22/03/2018	23/04/2018	SmPC and PL	Some patients who experience a decrease in their response to Humira 40 mg every other week may benefit from an increase in dosage to 40 mg adalimumab every week or 80 mg every other week. Population pharmacokinetic and pharmacokinetic/pharmacodynamic modelling and simulation predicted comparable adalimumab exposure and efficacy in patients treated with 80 mg every other week when compared with 40 mg every week (including adult patients with RA, HS, UC, CD or Ps, patients with adolescent HS, and paediatric patients ≥40 kg with CD).
IA/0180/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	16/04/2018	n/a		

	manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites				
T/0176	Transfer of Marketing Authorisation	06/02/2018	15/03/2018	SmPC, Labelling and PL	
N/0174	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/02/2018	15/03/2018	PL	
X/0164/G	This was an application for a group of variations. The MAH applied for a new strength/potency (20 mg) for adalimumab solution for injection in pre-filled syringe. In addition, the MAH proposed an update of sections 4.2 of the SmPC in order to introduce new fixed dose regimen (posology) for the paediatric indications of Juvenile idiopathic arthritis (JIA), Paediatric plaque psoriasis, Paediatric Crohn's disease, and Paediatric Uveitis. The Package Leaflet and Labelling are updated accordingly. Furthermore, the marketing authorisation holder took the opportunity to introduce editorial changes to align wording and layout of the Product Information and to amend the statement relating to anti-adalimumab antibody development in JIA patients, which will reside in section 5.1 of the Humira SmPCs (20 mg and 40 mg presentations). Annex I_2.(c) Change or addition of a new strength/potency	12/10/2017	08/12/2017	SmPC, Labelling and PL	Please refer to the published Assessment Report Humira H-481-X-164-G-AR.

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0171/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.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	10/11/2017	n/a		
PSUSA/57/201612	Periodic Safety Update EU Single assessment - adalimumab (except for biosimilars)	14/09/2017	10/11/2017	PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/57/201612.
II/0169	Update of section 5.1 of the SmPC based on interim data from the OLE Study M11-327 in non-infectious uveitis (A Multicenter Open-Label Study of the Long-term Safety and Efficacy of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Non-infectious Intermediate, Posterior, or Panuveitis)	12/10/2017	08/12/2017	SmPC	Of the 417 subjects included in the uncontrolled long-term extension of Studies UV I and UV II, 46 subjects were regarded ineligible (e.g. developed complications secondary to diabetic retinopathy, due to cataract surgery or vitrectomy) and were excluded from the primary analysis of efficacy. Of the 371 remaining patients, 276 evaluable patients reached 78 weeks of open-label adalimumab

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				treatment. Based on the observed data approach, 222 (80.4%) were in quiescence (no active inflammatory lesions, AC cell grade ≤0.5+, VH grade ≤0.5+) with a concomitant steroid dose ≤7.5 mg per day, and 184 (66.7 %) were in steroid-free quiescence. BCVA was either improved or maintained (< 5 letters deterioration) in 88.4% of the eyes at week 78. Among the patients who discontinued the study prior to week 78, 11% discontinued due to adverse events, and 5% due to insufficient response to adalimumab treatment.
II/0163	Extension of Indication to include a new indication for Humira for the treatment of paediatric chronic non-infectious anterior uveitis in patients from 2 years of age who have had an inadequate response to or are intolerant to conventional therapy, or in whom conventional therapy is inappropriate; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet was updated in accordance. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement an alternative format statement for blind/partially sighted patients in the Package Leaflet. Furthermore, the MAH has made some editorial changes to the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	20/07/2017	05/09/2017	SmPC and PL	Please refer to the published Assessment Report Humira H-481-II-163.
II/0168	Update of section 5.1 of the SmPC in order to update information on the long-term safety, tolerability, and	20/07/2017	05/09/2017	SmPC	Patients participating in Studies HS-I and HS-II were eligible to enroll into an open label extension study in which

	efficacy of adalimumab in subjects with moderate to severe hidradenitis suppurativa after finalisation of phase III open-label extension study M12-555. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Humira 40mg was administered every week. Mean exposure in all adalimumab population was 762 days. Throughout all 3 studies patients used topical antiseptic wash daily. Among patients who were at least partial responders at Week 12, and who received continuous weekly Humira therapy, the HiSCR rate at Week 48 was 68.3% and at Week 96 was 65.1%. Longer term treatment with Humira 40 mg weekly for 96 weeks identified no new safety findings.
II/0167	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	15/06/2017	05/09/2017	SmPC, Labelling and PL	The SmPC has been updated to include Humira prefilled pen 80 mg solution for injection. The Labelling and Package Leaflet have been updated accordingly.
II/0162	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/05/2017	n/a		
II/0159	Submission of study P06-134: "A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of Humira in Subjects with Moderately to Severely Active Crohn's Disease" in fulfilment for MEA 056.9. The study includes also some paediatric patients and fulfils obligations according to article 46 of the paediatric Regulation (EC) No 1901/2006. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/05/2017	n/a		

IB/0165	C.I.3.z - 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 - Other variation	19/04/2017	05/09/2017	SmPC	
X/0157	Extension application to add a new strength of 80 mg (80 mg/0.8 ml) for adalimumab solution for injection in single-use pre-filled syringe, for subcutaneous injection. Annex I_2.(c) Change or addition of a new strength/potency	26/01/2017	24/03/2017	SmPC, Labelling and PL	
II/0158	Update of section 5.1 of the SmPC in order to add information on the study results from study M13-674. The Package Leaflet is updated in accordance. Furthermore, the PI is brought in line with the latest QRD template version 10.0. The MAH has also taken the occasion to correct some editorial mistakes in the PI. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/01/2017	24/03/2017	SmPC and PL	Please refer to the published Assessment Report Humira H-481-II-158-AR.
II/0154	Extension of Indication to include the treatment of adolescents from 12 years of age with hidradenitis suppurativa for Humira; as a consequence, sections 4.1, 4.2, 5.1 and 5.2, of the SmPC are updated. The Package Leaflet and the RMP (version 12.1.1) are updated in accordance.	10/11/2016	12/12/2016	SmPC and PL	Please refer to the published Assessment Report Humira H-481-II-154-AR.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0161/G	This was an application for a group of variations. B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	02/12/2016	n/a		
IB/0160	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/11/2016	n/a		
II/0156	Update of section 5.1 of the SmPC in order to include additional 8-year safety and efficacy data from study DE013. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	12/12/2016	SmPC	Upon completion of the first 104 weeks, 497 patients enrolled in an open-label extension phase in which 40 mg of Humira was administered every other week up to 10 years. In the open-label extension for RA study V, ACR response rates were maintained when followed for up to 10 years. Of 542 patients who were randomised to Humira 40 mg every other week, 170 patients continued on Humira 40 mg every other week for 10 years. Among those, 154 patients (90.6%) had ACR 20 responses; 127 patients (74.7%) had ACR 50 responses; and 102 patients (60.0%) had ACR 70 responses.

					Of 342 subjects originally randomized to Humira monotherapy or Humira/methotrexate combination therapy who entered the open-label extension study, 171 subjects completed 10 years of Humira treatment. Among those, 109 subjects (63.7%) were reported to be in remission at 10 years. In the open-label extension of RA study V, the mean change from baseline at Year 10 in the modified Total Sharp Score was 10.8, 9.2 and 3.9 in patients originally randomized to methotrexate monotherapy, Humira monotherapy and Humira/methotrexate combination therapy, respectively. The corresponding proportions of patients with no radiographic progression were 31.3%, 23.7% and 36.7% respectively. Among the 250 subjects who completed the open-label extension study, improvements in physical function were maintained through 10 years of treatment.
N/0155	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/07/2016	12/12/2016	PL	
II/0146	Extension of Indication to include treatment of non-infectious intermediate, posterior and panuveitis in adult patients who have had an inadequate response to corticosteroids, in patients in need of corticosteroid-sparing, or in whom corticosteroid treatment is inappropriate. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC were updated. The warning in SmPC section 4.4 on neurological events was extended to provide additional advice on the monitoring and possible need for discontinuation in	26/05/2016	24/06/2016	SmPC, Annex II, Labelling and PL	Please refer to the published Assessment Report Humira H-481-II-146-AR

	case of demyelinating disorders. The Package Leaflet was updated in accordance. Furthermore, the PI is being brought in line with the latest QRD template version 10 and the MAH took the opportunity to make editorial amendments throughout the PI. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
II/0147	Extension of Indication for the treatment of paediatric Crohn's disease to include the treatment of moderately active Crohn's disease for Humira; as a consequence, sections 4.1, 4.2, 4.8, 5.1 of the SmPC are updated. In addition, the Marketing authorisation holder (MAH) took the opportunity to implement editorial corrections to the Labelling. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	01/04/2016	11/05/2016	SmPC and Labelling	Please refer to the published Assessment Report Humira H-481-II-147-AR.
II/0149	Extension of Indication to include 1st line treatment of moderate to severe chronic plaque psoriasis in adult patients; as a consequence SmPC section 4.1 has been updated and the Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement minor changes in sections 4.2 and 5.1 of the SmPC, to align Annex II with the latest QRD template and to update the contact details of the local representatives in Spain and	25/02/2016	04/04/2016	SmPC, Annex II and PL	Please refer to the scientific discussion Humira EMEA/H/C/000481/II/0149 for further information.

	Estonia in the Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0153	B.II.g.4.b - Changes to an approved change management protocol - Minor changes that do not change the strategy defined in the protocol	09/03/2016	n/a		
IA/0152	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	17/02/2016	n/a		
IAIN/0151/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	21/12/2015	n/a		
IB/0150/G	This was an application for a group of variations. B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.b.2.e - Change in test procedure for AS or	17/12/2015	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
II/0142	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	26/11/2015	n/a		
II/0143	Update of sections 4.2 of the SmPC, in order to add alternative weekly dosing frequency option for adult patients with plaque psoriasis who have an inadequate response to Humira 40 mg every other week (excluding paediatric presentation), and in section 5.1 with information reflecting data from previously submitted clinical studies supporting frequency change in posology. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to make minor corrections in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	22/10/2015	19/11/2015	SmPC and PL	Beyond 16 weeks, patients with inadequate response to 40 mg of Humira every other week may benefit from an increase in dosing frequency to 40 mg every week. The benefits and risks of continued weekly Humira therapy should be carefully reconsidered in a patient with an inadequate response after the increase in dosing frequency. If adequate response is achieved with an increased dosing frequency, the dose may subsequently be reduced to 40 mg every other week. In an open-label extension study, for patients who dose escalated from 40 mg every other week to 40 mg weekly due to a PASI response below 50%, 26.4% (92/349) and 37.8% (132/349) of patients achieved PASI 75 response at Week 12 and 24, respectively.
IG/0617	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	10/11/2015	n/a		
II/0145/G	This was an application for a group of variations.	05/11/2015	04/04/2016	SmPC, Labelling and	

	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes			PL	
IB/0144	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	02/09/2015	n/a		
II/0137	Extension of Indication to include the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adult patients with an inadequate response to conventional systemic HS therapy. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is being updated accordingly. In addition, the MAH proposed minor editorial changes in the SmPC and Package Leaflet.	25/06/2015	28/07/2015	SmPC and PL	Please refer to the scientific discussion Humira EMEA/H/C/0481/II/0137 for further information.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IG/0591/G	This was an application for a group of variations. A.1 - Administrative change - Change in the name and/or address of the MAH C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	24/07/2015	19/11/2015	SmPC, Labelling and PL	
II/0139	Update of section 5.1 of the SmPC in order to update the efficacy information following further review of the data submitted in the final CSR of study M10-791. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2015	28/07/2015	SmPC	In the open-label extension of study M10-791, improvement in the signs and symptoms was maintained with Humira therapy through Week 156. Significant improvement of signs of inflammation as measured by hs-CRP and MRI of both Sacroiliac Joints and the Spine was maintained in Humira-treated patients through Week 156 and Week 104, respectively. Improvement in health-related quality of life and physical function was maintained during the open-label extension through Week 156.
II/0138/G	This was an application for a group of variations. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.II.b.3.c - Change in the manufacturing process of	25/06/2015	28/07/2015	SmPC, Labelling and PL	To introduce an Adalimumab 40 mg/0.4 mL Pre –filled Syringe (PFS) containing the new 100 mg/mL adalimumab solution for injection as an alternative presentation to the currently marketed 40 mg/0.8 mL PFS.

	the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.a.5 - Change in concentration of a single-dose, total use parenteral product, where the amount of AS per unit dose (i.e. the strength) remains the same B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
N/0140	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/05/2015	28/07/2015	PL	

II/0134	Extension of Indication to include the treatment of severe chronic plaque psoriasis in children and adolescents from 4 years of age who have had an inadequate response to or are inappropriate candidates for topical therapy and phototherapies As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated and the Package Leaflet is being updated accordingly. In addition, the MAH proposed minor editorial changes in the SmPC and Package Leaflet. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	26/02/2015	26/03/2015	SmPC and PL	Please refer to the scientific discussion Humira EMEA/H/C/0481/II/0134 for further information.
PSUV/0131	Periodic Safety Update	25/09/2014	19/11/2014	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0131.
II/0130	Update of Risk Management Plan (RMP) version 11.1. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required	25/09/2014	n/a		
IG/0476	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the	24/09/2014	n/a		

	PSMF location				
IAIN/0135	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	19/09/2014	19/11/2014	Annex II and PL	
II/0127	Extension of Indication to include the treatment of active enthesitis-related arthritis in patients, 6 years of age and older, who have had an inadequate response to, or who are intolerant of, conventional therapy. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The package leaflet is updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	24/07/2014	01/09/2014	SmPC and PL	Please refer to the scientific discussion HUMIRA EMEA/H/C/000481/II/0127 for further information.
N/0133	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/08/2014	19/11/2014	PL	
IB/0132/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	11/07/2014	n/a		

	control/testing takes place				
II/0129	Update of section 5.1 of the SmPC in order to add data on safety and efficacy in adult patients with moderate to severe chronic plaque psoriasis with concomitant hand and/or foot psoriasis who were candidates for systemic therapy (Study M10-405). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	01/09/2014	SmPC	In Study M10-405, adalimumab was well tolerated and demonstrated to have a favorable benefit-risk balance for up to 28 weeks in adult subjects with moderate to severe chronic plaque psoriasis involving the hands and/or feet. At Week 16, a statistically significantly greater proportion of patients who received Humira achieved PGA of 'clear' or 'almost clear' for the hands and/or feet compared to patients who received placebo (30.6% versus 4.3%, respectively [P = 0.014]). The safety profile of adalimumab-treated subjects was consistent with what has been observed in other adalimumab clinical trials in subjects with chronic plaque psoriasis. Adalimumab was generally safe and well tolerated as evaluated by TEAEs including deaths and SAEs, TEAEs of special interest, laboratory values, and vital signs values. No new safety signal was generated by this study. In addition, no signals or trends of clinical concern were observed for any safety parameter.
II/0128	Submission of the final Clinical Study Report for M10-791 'A Multicenter Study of the Efficacy and Safety of the Human Anti-TNF Monoclonal Antibody Adalimumab in Subjects with Axial Spondyloarthritis'. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/04/2014	n/a		In total, 190 patients have been enrolled and received Humira for a total of 412 patient years. The primary study endpoint, measured over the course of the study, was ASAS40 response at Week 12. The study duration was 156 weeks; the mean duration of exposure was 792 days, and median 1008. Half of the subjects receiving any adalimumab experienced a TEAE, and 8% discontinued due to this. No particular AE seems to be associated with withdrawal from the study. Consistent with the known safety profile of Humira, nasopharyngitis, bronchitis and sinusitis were the most commonly reported AEs. The CHMP

					concluded that no new safety concerns have been raised within this study.
II/0123	Update of section 5.1 of the SmPC based on additional analyses from studies M06-826, M06-827 and M10-223 submitted in support of the ulcerative colitis indication in procedure EMEA/H/C/00481/II/82. In addition the MAH took the opportunity to update section 4.4 of the SmPC in order to add a statement enabling traceability of the medicinal product. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/03/2014	01/09/2014	SmPC	Based on the data collected in placebo-controlled Studies M06-826 and M06-827 and the open-label extension Study M10-223, lower rates of all-cause hospitalisations and UC-related hospitalisations were observed for the adalimumab-treated arm compared to the placebo arm. The number of all cause hospitalisations in the adalimumab treatment group was 0.18 per patient year vs. 0.26 per patient year in the placebo group and the corresponding figures for UC-related hospitalisations were 0.12 per patient year vs. 0.22 per patient year. Based on the data from the placebo-controlled Study M06-827, treatment with adalimumab resulted in improvements in the Inflammatory Bowel Disease Questionnaire (IBDQ) score. Results from Study M06-827 allowed addition of Week 52 efficacy data in Week 8 responders per full Mayo score. Of those patients who had a response at Week 8, 47% were in response, 29% were in remission, 41% had mucosal healing, and 20% were in steroid-free remission for ≥ 90 days at Week 52. Based on data from all patients that received at least one dose of adalimumab in studies M06-826, M06-827 or M10-223, the remission rate in subjects treated with adalimumab for at least 3 years is added. Following 3 years of adalimumab therapy, 75% (301/402) subjects continued to be in clinical remission per partial Mayo score supporting a sustained efficacy in responders. In order to increase the traceability for a specific batch and also to enable distinguishing between the products used when assessing spontaneous adverse event reports, the following statement, not specific for Humira, and enabling

					traceability of the medicinal product is added to the SmPC: "In order to improve traceability of biological medicinal products, the trade name and batch number of the administered product should be clearly recorded".
II/0125	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	18/12/2013	n/a		Please refer to the scientific discussion HUMIRA EMEA/H/C/000481/II/0125 for further information.
IG/0379	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	15/11/2013	n/a		
II/0121	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	19/09/2013	n/a		
II/0120	Update of section 4.8 and 5.1 of the SmPC to update information relevant to the latest study data from: RA studies DE009, DE011, DE013, DE019, DE031, DE018, and DE020; UC studies M06-826, M06-827, and M10-223; nr-axSpA study M10-791; JIA 2 to < 4 years old study M10-444; and paediatric Crohn's disease study M06-806. In addition the MAH took the opportunity to make an editorial changes concerning the expression of the age range in paediatric population in section 4.1 and 4.2 and to bring the Product Information in line with the version 9 of the QRD template.	19/09/2013	06/02/2014	SmPC, Annex II and PL	Based on the updated safety data provided, patient numbers and percentages of patients who discontinued treatment due to adverse events were updated with additional data from DE013. Patient numbers in pivotal and controlled and open label trials as well as data from pivotal studies during the controlled period were updated with additional data from DE013, DE019 and M06-806. The injection site reactions and infections sections were updated accordingly. The malignancy section was updated for all controlled clinical studies and their open label extension studies, with regards to patient numbers, duration of exposure and malignancy incidence rates. The Hepato-biliary section was updated to include data from the

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				paediatric Crohn's disease study (M06-806) to inform that in the Phase 3 trial in patients with paediatric Crohn's disease which evaluated efficacy and safety of two body weight adjusted maintenance dose regimens following body weight adjusted induction therapy up to 52 weeks of treatment, ALT elevations ≥ 3 x ULN occurred in 2.6% of patients all of whom were exposed to concomitant immunosuppressants at baseline.
IB/0122	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	22/08/2013	06/02/2014	SmPC and PL	
II/0108/G	This was an application for a group of variations. To add an alternative manufacturer site and quality control testing site for Humira pre-filled syringes B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products. B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	25/07/2013	n/a		
IB/0119	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The	23/07/2013	n/a		

	proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer				
II/0116	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	27/06/2013	n/a		
IA/0118	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	07/06/2013	n/a		
N/0117	"Update of the local representatives contact details for Hungary, Czech Republic, The Netherlands, Portugal, Slovakia and the United Kingdom." Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/05/2013	06/02/2014	PL	"Update of the local representatives contact details for Hungary, Czech Republic, The Netherlands, Portugal, Slovakia and the United Kingdom."
IA/0115	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	22/03/2013	06/02/2014	Annex II	
IB/0114	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	08/03/2013	n/a		

IG/0272	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/03/2013	n/a		
II/0095/G	This was an application for a group of variations. Change in the manufacturer of the active substance, where no Ph. Eur. Certificate of Suitability is part of the approved dossier Change in batch size (including batch size ranges) of active substance or intermediate Changes in the manufacturing process of the active substance B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.a.3.c - Change in batch size (including batch size ranges) of AS or intermediate - The change requires assessment of the comparability of a biological/immunological AS 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	21/02/2013	06/02/2014	Annex II	In order to expand the commercial production capability for adalimumab drug substance, this variation is being submitted to obtain approval of the Lonza Biologics Tuas, PTE Ltd (LBT) facility (20000 L bioreactor scale in Tuas, Singapore) as an adalimumab manufacturing facility in addition to the currently approved Abbott Bioresearch Center (ABC; 6000 L bioreactor scale), Abbott Biotechnology, Ltd. (ABL; 12000 L bioreactor scale), and Lonza Biologics Porriño, S.L. (LBP, 10000 L bioreactor scale) facilities. The currently approved AY-07 manufacturing process has been appropriately scaled to the 20000 L bioreactor scale at LBT. Data are presented to justify that the adalimumab drug substance manufactured at LBT (20000 L) is comparable to that manufactured by at ABC (6000 L), LBP (10000 L), and ABL (12000 L) such that drug substance from all four facilities may be used to formulate drug product for the commercial market upon the approval of this variation. Details of the facility and equipment design for the LBT facility are also presented. In addition to the addition of the LBT facility for adalimumab drug substance manufacturing, data are presented to justify the use of an alternative supplemented yeast extract (TC Yeastolate UF), which has been qualified at laboratory scale and was included in two validation batches at the 20000 L scale. This alternative

					supplemented yeast extract may be used at any of the four adalimumab drug substance manufacturing sites upon approval of this variation.
IAIN/0112	B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking	06/02/2013	06/02/2014	SmPC and PL	
II/0107	Update of section 4.4 of the SmPC to amend information concerning allergic reactions and correct, in section 4.8 of the SmPC, the number of patients who developed a malignancy within a year of starting therapy in clinical studies across the approved indications. Furthermore, the PI is being brought in line with the latest QRD template. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	17/01/2013	25/02/2013	SmPC, Annex II, Labelling and PL	The warnings and precautions section concerning allergic reactions previously stated that no serious allergic reactions have been associated with adalimumab during clinical trials. This section is updated based on current data in the clinical database: serious allergic reactions have been seen during the double blind period of pivotal adalimumab clinical trials with frequencies categorised as rare. The number of patients who were on adalimumab for at least 1 year or who developed a malignancy within a year of starting therapy for controlled and open label extension studies in all approved indications has been updated to reflect the correct number (5545 instead of 5433) in the undesirable effects section.
II/0102	Extension of indication to include the treatment of paediatric subjects with active polyarticular juvenile idiopathic arthritis (JIA) from 4 to 17 years of age to 2 to 17 years of age. As a consequence of this new indication, sections 4.1, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package leaflet is updated in accordance. C.I.6.a - Change(s) to therapeutic indication(s) -	17/01/2013	25/02/2013	SmPC and PL	Please refer to the scientific discussion HUMIRA EMEA/H/C/000481/II/0102 for further information.

	Addition of a new therapeutic indication or modification of an approved one				
II/0099/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits 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	13/12/2012	25/02/2013	SmPC, Labelling and PL	
IAIN/0111/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.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) A.5.b - Administrative change - Change in the name	12/12/2012	25/02/2013	Annex II and PL	

	and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer 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)				
IAIN/0110	B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	11/12/2012	n/a		
N/0109	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/11/2012	25/02/2013	PL	
II/0105	Update of sections 4.4 and 4.8 of the SmPC in order to add Merkel cell carcinoma as a new adverse event with unknown frequency. This update is based on a review of postmarketing and clinical trials cases as well as a literature search. The Package Leaflet is updated accordingly. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	18/10/2012	22/11/2012	SmPC and PL	The cumulative search of the company clinical and postmarketing databases for reports of possible Merkel Cell Carcinoma (MCC) or neuroendocrine carcinoma of the skin coincident with adalimumab therapy identified 15 reports of MCC. One report was from clinical trials and there were 14 postmarketing reports. Of the 14 postmarketing reports, most of them had confounding factors and/or limited information to fully assess causality with adalimumab and 1 report had no confounding factors or alternative etiology reported. The 1 report of MCC from a clinical trial also had confounding factors. There were no fatalities due to MCC among the total of 15 reports of MCC. Although it is not clear whether the appearance of MCC in patients receiving adalimumab might be due to a number of factors such as other TNF inhibitor therapy, the underlying autoimmune diseases, sun exposure, the patient's age, or exposure to

					other non-biologic immunosuppressant therapy, the possible contribution of adalimumab use to the risk cannot be excluded. Therefore MCC is added to section 4.8 'Undesirable effects' of the SmPC, with a frequency category of "unknown". The severity and seriousness of the event of MCC also justify its addition to section 4.4 'Special warnings and precautions for use' to warn the prescribing physicians that cases of MCC have been reported in patients treated with TNF-antagonists including adalimumab. The Risk Management Plan was updated to include MCC as an important identified risk.
II/0104	Update of section 5.1 of the SmPC with data from the 10 year study, DE019 (adalimumab in rheumatoid arthritis patients receiving treatment with methotrexate), regarding ACR response, radiographic response and physical function. 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	Study DE019 was a multicenter, randomized, double-blind, placebo-controlled study of adalimumab in subjects with RA receiving concurrent MTX. The study included a 10 year open-label extension phase for subjects who previously completed, the 52 week, double-blind phase. The 1-year data from the double-blind phase of the study were submitted as part of the original adalimumab marketing authorisation application. Efficacy results from the open-label extension phase of the study showed that the long-term administration of adalimumab in responding patients with RA receiving concomitant MTX resulted in a maintained reduction in the signs and symptoms of RA; maintained improvement in physical function; maintained inhibition of structural joint damage in a majority of subjects and maintained improvement in patient-reported quality of life. No new safety signals were identified in this 10-year study. The majority of the reported adverse events and serious adverse events were consistent with the well-characterised adalimumab safety profile as described in the

					currently approved prescribing information for adalimumab.
II/0088	Extension of indication for the treatment of severe, active Crohn's disease in paediatric subjects (6 to 17 years of age) who have had an inadequate response to conventional therapy including primary nutrition therapy, a corticosteroid, and an immunomodulator, or who are intolerant to or have contraindications for such therapies. Sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated accordingly as well as the package leaflet and Annex II. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	18/10/2012	22/11/2012	SmPC, Annex II and PL	Please refer to the scientific discussion HUMIRA EMEA/H/C/000481/II/0088 for further information.
II/0092	Update of section 4.8 of the SmPC to add the events of liver failure, hepatitis and to update information on hepatic changes. The Package Leaflet is updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	20/09/2012	24/10/2012	SmPC and PL	The MAH has undertaken a detailed review of liver failure and related serious liver events occurring in adalimumab controlled clinical trials and the postmarketing setting. Results showed that there are postmarketing reports of liver failure among adalimumab treated patients. The analysis does not suggest a primary causal relationship between adalimumab therapy and these hepatic events. Although a relationship to adalimumab cannot be established, the severity and seriousness of the event of liver failure justify its addition to section 4.8 of the SmPC with a frequency category of unknown. The MAH performed an additional comprehensive review of reports of toxic hepatitis, cytolytic hepatitis, hepatotoxicity, hepatitis, acute hepatitis, hepatitis fulminant and drug induced liver injury in adalimumab controlled clinical trials and postmarketing reports. The data showed a reasonable possibility for a

					causal relationship between adalimumab and hepatitis justifying its addition to section 4.8 of the SmPC with a frequency category of rare. As the events of liver failure that may occur during adalimumab therapy may be preceded by milder liver events, the hepatobiliary disorder section in 4.8 is updated to reflect that there have been post-marketing reports of liver failure as well as less severe liver disorders that may precede liver failure, such as hepatitis including autoimmune hepatitis (added within EMEA/H/C/000481/II/0093) in patients receiving adalimumab. The incidence of hepatic enzyme elevations in clinical studies was also reviewed to provide more detailed information on the extent of the elevations.
T/0106	Transfer of Marketing Authorisation	24/09/2012	23/10/2012	SmPC, Labelling and PL	
II/0098	Change of administration device B.IV.1.c - Change of a measuring or administration device - Addition or replacement of a device which is an integrated part of the primary packaging	20/09/2012	n/a		Replacement of current firing subassembly of the autoinjector for the pen presentation with an improved device.
II/0094	Extension of indication for the treatment of adult patients with moderately active Crohn's disease who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant. Sections 4.1, 4.2, 4.8 and 5.1 of the SmPC have been updated accordingly as well as the package leaflet.	19/07/2012	23/08/2012	SmPC and PL	Please refer to the scientific discussion Humira EMEA/H/C000481/II/85 for further information.

	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IA/0103	B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method	08/08/2012	n/a		
II/0100	Update of section 4.4 of the SmPC to align this section with information on vaccination and neurological events that is currently outlined in section 4.6 and 4.8 of the SmPC. Wording improvement to the warning concerning concurrent administration of biologic DMARDS or TNF-antagonists is also made. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/06/2012	23/07/2012	SmPC	Optic neuritis, which was added to section 4.8 of the SmPC as an adverse event seen in the postmarketing setting (EMEA/H/C/481/II/24) is now been added as an example of a central nervous system demyelinating disease in the Neurological Events warning in section 4.4. Wording in the vaccination warning is aligned with the wording added through EMEA/H/C/481/II/87 in the Pregnancy and Lactation section to recommend that infants exposed to adalimumab in utero are not administered live vaccines for at least 5 months following the mother's last injection of adalimumab during pregnancy. Wording improvement to the warning concerning concurrent administration of biologic DMARDS or TNF-antagonists is also made cover potential interactions with other biological DMARDs than anakinra and abatacept as well as all TNF antagonists.
II/0097	Update of section 4.8 of the SmPC to add pyrexia as new adverse reaction, based on a cumulative review of reports of pyrexia events coincident with adalimumab treatment. The package leaflet is updated accordingly. C.I.3.b - Implementation of change(s) requested	21/06/2012	23/07/2012	SmPC and PL	The MAH performed a cumulative review of reports of pyrexia events coincident with adalimumab treatment observed in clinical trials and postmarketing setting. In clinical studies across all indications, the incidence rates of pyrexia were not different between adalimumab treatment group and the control group. However, the review of the postmarketing reports indicated there were 139 reports,

	following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				among the 2143 medically confirmed reports, without an alternate etiology for pyrexia such as infection or disease flare. In the majority of the 139 reports, pyrexia resolved with or without antipyretic treatment and did not lead to the discontinuation of adalimumab. In many reports, there was also a temporal relationship between the administration of adalimumab and the development of pyrexia. In 3 reports, pyrexia was accompanied by a positive dechallenge and/or rechallenge reaction. In each of the 3 reports, pyrexia without any accompanying medical problems other than the underlying medical conditions occurred after each injection of adalimumab. The pyrexia event in each case resolved without any antipyretic medication following the discontinuation of adalimumab. Based on this data the event of pyrexia is added to section 4.8 of the SmPC. The frequency of "Common" for the event has been determined from the data observed in the pivotal controlled trials.
II/0096	Update of section 4.4 of the SmPC to amend the existing warning on tuberculosis (TB) to inform on the possibility of reactivation of TB in patients on Humira therapy, despite having been treated prophylactically for TB. The Package Leaflet is updated in accordance. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	21/06/2012	23/07/2012	SmPC and PL	A cumulative search of the MAH's global safety database for reports of TB coincident with adalimumab therapy was conducted for the period of 31 December 2002 to 31 December 2010. The review identified 112 patients having reactivated TB coincident with adalimumab use. Of these 112 patients identified as having reactivated TB, most (nearly 60%) were reported to have received TB prophylactic treatment, though the reports had limited information on the anti-TB medications, dosage and treatment duration. There were numerous reports where it is not known whether prophylactic treatment was provided. It appears that in many cases the diagnosis of reactivated TB was made based upon a positive PPD skin test but a

					negative chest X-ray, however in some cases documentation suggests that the diagnosis was reached solely on the basis of a positive PPD test (and therefore these cases could have represented false-positive diagnoses due, for example, to prior vaccination for TB). Nevertheless, overall, there seems to be a non-negligible risk of TB reactivation in spite of prophylactic treatment in certain patients. Therefore physicians should be made aware that despite prophylactic treatment for tuberculosis, cases of reactivated tuberculosis have occurred in patients treated with adalimumab.
II/0085	Extension of indication for the treatment of adults with severe axial spondyloarthritis without radiographic evidence of AS, but with objective signs of inflammation by elevated CRP and/or MRI, who have had an inadequate response to, or are intolerant to, non-steroidal anti-inflammatory drugs. Sections 4.1, 4.2, 4.4, 4.8 and 5.1 of the SmPC have been updated accordingly as well as the package leaflet and Annex II. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	21/06/2012	23/07/2012	SmPC, Annex II and PL	Please refer to the scientific discussion Humira EMEA/H/C000481/II/85 for further information.
II/0093	Update of section 4.8 of the SmPC in order to add autoimmune hepatitis based on a review of postmarketing and clinical trials cases as well as literature search. The PL was updated in accordance. C.I.3.b - Implementation of change(s) requested	24/05/2012	27/06/2012	SmPC and PL	A cumulative review identified 198 reports of non-infectious hepatitis. Of these, 49 were consumer reports and 149 were medically confirmed. Of the 149 medically confirmed reports, 113 reports were considered out of scope and 9 originated from clinical trials. Of the 27 post-marketing reports remaining, 17 had limited information which

	following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				prevented proper evaluation, 8 were assessed to be confounded and 2 did not have an alternate etiology. Overall, the majority of reported post-marketing cases had confounding factors or limited information to properly assess the event. In some cases with limited information there are reported elements such as presence of auto-antibodies or recovery after withdrawal that could make the diagnosis of autoimmune hepatitis plausible. Of the 49 consumer reports, 6 were reports of autoimmune hepatitis but none of them provided sufficient information for appropriate assessment. In the placebo controlled trials there were no reports of autoimmune hepatitis in patients receiving either placebo, methotrexate or adalimumab. Expanding to the open-label data set a total of 9 reports was identified. Of these, 4 events of autoimmune hepatitis (2 serious and 2 non-serious) in 3 individuals were identified. In 2 of the 3 cases the event was considered by the investigator as possibly related to study drug. The remaining cases did not meet the case definition for autoimmune hepatitis. The estimated incidence rate in all exposed adalimumab patients of clinical trials is <0.1 autoimmune hepatitis events per 100 patient years. While there were several cases with confounders or limited information, it is not possible to exclude the contribution of adalimumab to the development of autoimmune hepatitis given the temporal relationship between adalimumab therapy and the development of autoimmune hepatitis in most of these reports. Consequently autoimmune hepatitis is added to section 4.8 of the SmPC as new adverse event with a frequency of rare. The RMP was updated to include autoimmune hepatitis as an important identified risk.

IB/0101	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	08/06/2012	n/a		
II/0086/G	This was an application for a group of variations. Change to the primary packaging B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.2.b - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.e.3.b - Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products	15/03/2012	20/04/2012	SmPC, Labelling and PL	Change in immediate packaging of the finished product – Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products. Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier Change in test procedure for the immediate packaging of the finished product - Other changes to a test procedure (including replacement or addition) Change in the specification parameters and/or limits of the immediate packaging of the finished product - Addition of a new specification parameter to the specification with its corresponding test method
II/0091	Update of section 4.4 of the SmPC to add legionellosis to the existing infection warning. The	16/02/2012	04/04/2012	SmPC and Annex II	A total of 13 reports of Legionella infection coincident with adalimumab use in clinical trials and 102 reports from

	variation is based on a review of clinical studies, postmarketing safety data and literature. Annex II is updated to reflect the new RMP version number. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				postmarketing database were analyzed in this review. Of the 102 postmarketing cases, 95 were medically confirmed reports and 7 were from consumers. Of the 95 medically confirmed reports, there were 5 reports that did not meet the case definition of Legionella infection. Of the 90 reports remaining, 67 were assessed to be confounded, 11 had limited information which prevented proper evaluation, and 12 did not have an alternate etiology. Five reports of Pneumonia Legionella had fatal outcome but also confounding factors or alternative aetiologies for the event. In 12 of the 13 reports in clinical trials, the events of Legionella infection were considered either probably or possibly related to study drug. One of these cases had a fatal outcome confounded by concomitant methotrexate and steroids. Overall the majority of reported cases had confounding factors or alternative aetiologies for the event. While there were confounders, it is not possible to exclude the contribution of adalimumab to the development of Legionella infection given the temporal relationship between adalimumab therapy and the development of infection in most of these reports. Consequently legionellosis is added to the warning section concerning infections as serious infections that have been reported in patients receiving adalimumab. Legionellosis is also covered in the educational program for serious infections as described in the RMP.
II/0082	Extension of indication for the treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and	15/03/2012	04/04/2012	SmPC, Annex II and PL	Please refer to the scientific discussion HUMIRA EMEA/H/C000481II/82 for further information.

	6-mercaptopurine (6- MP) or azathioprine (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 have been updated accordingly as well as Annex II and IIIB. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				
IB/0090	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	07/02/2012	n/a		
II/0087	Update of section 4.4 of the SmPC to re-emphasise the importance of exercising caution when considering combinations with azathioprine (AZA) or 6-mercaptopurine (6-MP) with adalimumab. The warning on Hepatitis B reactivation is also reinforced to recommend HBV testing for all patients before initiating treatment with adalimumab. Section 4.6 is updated to inform on the possible placental transfer of adalimumab and the increased risk of infection in newborns that have been exposed during pregnancy and to recommend not administering live vaccines to these infants for at least 5 months following the mother's last dose of adalimumab. The Package leaflet is updated accordingly. Annex II is also updated to reflect the approved PSUR cycle as well as the new RMP version number.	15/12/2011	20/01/2012	SmPC, Annex II and PL	Rare postmarketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with TNF antagonists, including adalimumab. Some of these hepatosplenic T-cell lymphomas have occurred in young adult patients on concomitant treatment with AZA or 6-MP used for Crohn’s disease therefore the potential risk with the combination of AZA or 6-MP and Humira should be carefully considered by the treating physician. Reactivation of hepatitis B has occurred in patients receiving a TNF-antagonist, including adalimumab, who are chronic carriers of this virus (i.e. surface antigen positive). Some cases had a fatal outcome. Patients should therefore be tested for HBV infection – irrespective of any risk factors - before initiating treatment with adalimumab. For patients who test positive for hepatitis B infection, consultation with a physician with expertise in the treatment of hepatitis B is recommended.

	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH				Data from the literature and post-marketing indicate that adalimumab may cross the placenta into the serum of infants born to women treated with adalimumab during pregnancy. Overall, infants exposed in-utero to adalimumab may be at increased risk for infection. Administration of live vaccines to infants exposed to adalimumab in utero is not recommended for at least 5 months following the mother's last adalimumab injection during pregnancy.
II/0083	Update of section 4.8 of the SmPC to bring it in line with the guideline on summary of product characteristics (September 2009). The Package Leaflet is updated accordingly. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	17/11/2011	19/12/2011	SmPC and PL	Section 4.8 is updated with inclusion of an introductory paragraph providing a summary of the safety profile of adalimumab 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 adverse drug reactions events from postmarketing surveillance and clinical trials in section 4.8.
IA/0089	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)	15/12/2011	n/a		
II/0084	Update of section 4.4 to amend the period during which it is recommended that patients be monitored for the occurrence of infections after adalimumab therapy is discontinued based upon considerations of adalimumab elimination. The Package leaflet is	22/09/2011	24/10/2011	SmPC and PL	The MAH applied to reduce the 5 months monitoring period for the occurrence of infections in patients after termination of adalimumab treatment. The 5-months period relates to the worst case value on the terminal half-life. It has been used to establish the period in which pregnancies should be

	updated accordingly. The MAH also took the opportunity to align the wording of the neurological events warning in section 4.4 with the events listed in section 4.8 and to correct typographical errors in section 4.2 of the paediatric vial presentation. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				prevented and breast feeding avoided as well as for monitoring of infections after discontinuation of adalimumab treatment. Based on single dose studies the average mean half-life of adalimumab is 14 days. The CHMP however considered that, although the mean estimated half-life has been found to be 14 days, it generally varies between 10 and 20 days, and that the upper 99% interval in a population analysis was 25.7 days. As variability exists for the estimation of half-life the calculation of the monitoring period cannot be based on an average value. A conservative approach using the estimated upper 99% interval of 25.7 days gives a time period of 129 days. Based on this result the CHMP accepted to shorten the monitoring period for infections from 5 to 4 months. The period in which pregnancies should be prevented and breast feeding avoided remain unchanged.
II/0081/G	This was an application for a group of variations. Extension of the therapeutic indication to include treatment of active polyarticular juvenile idiopathic arthritis in the paediatric population aged from 4 to 12 years. As part of this grouped variation, several consequential minor quality changes have been submitted, including changes on the product packaging and delivery device. Sections 1, 4.1, 4.2, 5.1, 5.2, 6.3, 6.5 of the SmPC, the package leaflet and labelling are updated accordingly. Minor editorial corrections are also made throughout the SmPC. Annex II is updated to reflect the last version of the RMP. The MAH also took the opportunity to remove the alert card from Annex III-A.	17/02/2011	18/03/2011	SmPC, Annex II, Labelling and PL	Please refer to the Scientific Discussion "Humira/H/C/000481/II/0081-G" for further information.

	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for biological/immunological medicinal products. 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 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 B.II.e.1.a.3 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Sterile medicinal products and biological/immunological medicinal products B.II.e.5.c - Change in pack size of the finished product - Change in the fill weight/fill volume of sterile multidose (or single-dose, partial use) parenteral medicinal products, and biological/immunological multidose parenteral medicinal products B.II.e.6.a - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that affects the product information B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.f.1.b.1 - Stability of FP - Extension of the shelf				

	life of the finished product - As packaged for sale (supported by real time data) B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking B.IV.1.a.1 - Change of a measuring or administration device - Addition or replacement of a device which is not an integrated part of the primary packaging - Device with CE marking B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier				
II/0075	Update 5.1 of the SmPC for the indication Psoriasis to reflect results from Study M03-658 evaluating the long-term safety and efficacy of adalimumab treatment in subjects with moderate to severe chronic plaque psoriasis. Section 4.8 is amended to update the patients number exposed in clinical trials to include data from Study M03-658 and to update	20/01/2011	21/02/2011	SmPC	Study M03-658 was a multi-center open-label continuation study in moderate to severe chronic plaque psoriasis subjects who completed a preceding psoriasis clinical study with adalimumab. Patients participating in all Phase 2 and Phase 3 psoriasis studies were eligible to enrol into this open-label extension trial, where Humira was given for at least an additional 108 weeks. A total of 233 PASI 75

	the malignancies rates observed in clinical trials accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				(Psoriasis Area and Severity Index) responders at Week 16 and Week 33 received continuous Humira therapy for 52 weeks in Psoriasis Study I (REVEAL), and continued adalimumab in the open-label extension trial. PASI 75 and Physician's Global Assessment (PGA) of clear or minimal response rates in these patients were 74.7% and 59.0%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks). In an analysis in which all patients who dropped out of the study for adverse events or lack of efficacy, or who dose-escalated, were considered non-responders, PASI 75 and PGA of clear or minimal response rates in these patients were 69.6% and 55.7%, respectively, after an additional 108 weeks of open-label therapy (total of 160 weeks). Overall, a total of 347 stable responders participated in a withdrawal and retreatment evaluation in the open label extension study. During the withdrawal period, symptoms of psoriasis returned over time with a median time to relapse (decline to PGA "moderate" or worse) of approximately 5 months. None of these patients experienced rebound during the withdrawal period. A total of 76.5% (218/285) of patients who entered the retreatment period had a response of PGA "clear" or "minimal" after 16 weeks of retreatment, irrespective of whether they relapsed during withdrawal (69.1%[123/178] and 88.8% [95/107] for patients who relapsed and who did not relapse during the withdrawal period, respectively). A similar safety profile was observed during retreatment as before withdrawal. Incidence of immunogenicity was low (approximately 2%).
II/0080	Update of section 4.8 of the SmPC to add Sarcoidosis as requested by the CHMP based on review of	16/12/2010	21/01/2011	SmPC and PL	A cumulative review of reports of sarcoidosis events from the MAH clinical trial database (as of 27 April 2010) was

	postmarketing safety data. The PL is updated accordingly. In addition the MAH took the opportunity to make a correction in section 4.8 by re-introducing the term Pulmonary Fibrosis, and of section 2 of the PL for the warning for non-melanoma skin cancer. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				conducted. A total of five patients experienced 6 events of sarcoidosis from clinical trials. One of these 5 patients was a participant in a randomized controlled trial receiving adalimumab. There were no sarcoidosis events among the patients in the comparator arm. Of the 5 reports of sarcoidosis 4 were serious and 1 non-serious. One event of the 5 reports was deemed possibly related to adalimumab therapy and the other events were considered not related. A cumulative review of reports of sarcoidosis and related terms from the MAH postmarketing safety database was conducted. A total of 151 reports of possible sarcoidosis were retrieved from this search (as of 15 April 2010). Of these, 129 were medically confirmed. Of these 129 reports, 87 were excluded from the review as they reported erythema nodosum, pulmonary granuloma or granuloma without a specific diagnosis or evidence of sarcoidosis. Five further reports were excluded, 3 events were not related to adalimumab and 2 from blinded clinical trials in which the patient did not receive adalimumab or the study remains blinded. Of the 37 remaining medically confirmed reports, 24 described at least 1 serious event and 13 described non-serious events. Of the 37 reports, 22 had no apparent confounding factors or alternative aetiologies and 8 had potential confounding factors such as evidence of prior sarcoidosis which reappeared or worsened with adalimumab therapy. Overall, the causal relationship between the use of adalimumab and the appearance of sarcoidosis is difficult to establish in part because it is a difficult diagnosis to make and the aetiology is unknown. Given the number of medically confirmed cases without confounding factors or alternative aetiologies and evidence that TNF-? participates in sarcoidosis events, it is not

					possible to exclude that adalimumab may contribute in the appearance of sar
II/0079	Change in the batch size (including batch size ranges) of the finished product 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	18/11/2010	26/11/2010		
II/0078	Change in the manufacturing process of the finished product B.II.b.3.b - Change in the manufacturing process of the finished product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product	18/11/2010	26/11/2010		
II/0074	Update 4.8 of the SmPC to add pleural effusion as new undesirable effects observed in post marketing surveillance based on a cumulative analysis of pleural effusion event coincident with adalimumab use. The package leaflet is updated accordingly. The MAH corrected for consistency purposes statements in section 4.7 on event of visual impairment and in section 4.8 on injections site reactions. The MAH also took the opportunity to correct typographical errors in section 4.4 and 4.8 and to update Annex II to reflect the approved PSUR submission cycle and the last RMP version number. The contact details of all	22/07/2010	31/08/2010	SmPC, Annex II and PL	A review of spontaneous postmarketing reporting identified 174 cases of pleural effusion medically confirmed coicident with adalimumab therapy. A majority of the reports were serious (123/174, 71%), and described female patients (55%) taking adalimumab for rheumatoid arthritis (83%) with a median age of 61 years. Of these 174 reports, 142 (82%) identified an aetiology or confounding factors for pleural effusion. The most common aetiology described in these 142 reports was infection (93/142, 65%) followed by cardiac disease (20/142, 14%). Rheumatoid arthritis was the cause or a possible cause of pleural effusion in 22 reports (15%). The remaining 32 reports described no

	local representatives are also updated 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				definitive cause or confounding factors for the pleural effusion event (32/174, 18%). Pleural effusions are associated with a variety of medical conditions including the most common indication for adalimumab, rheumatoid arthritis. The other potential causes of pleural effusion include malignancy and infections which are currently identified as risks in the adalimumab SmPC. Overall, pleural effusion is a relatively common disorder in patients taking TNF inhibitors including adalimumab. Due to the large number of medically confirmed postmarketing reports, many of which described a serious event, the undesirable effect "pleural effusion" is added to section 4.8 of the SmPC. The package leaflet is updated accordingly.
IA/0077	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	30/07/2010	n/a		
IA/0076	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	22/07/2010	n/a		
II/0072	Update of section 4.1 and 5.1 of the SmPC based on the results of clinical studies M05-769, M04-690, M02-433, M02-403, M02-404 and M04-691 to remove the recommendation for concomitant administration of corticosteroid during induction treatment with adalimumab, to update the safety profile and to add information on the reduction of inflammatory markers in the colon, on mucosal healing and on the reduction of hospitalizations and surgeries. Section 4.8 is updated with the numbers	20/05/2010	01/07/2010	SmPC and PL	Result from Study M05-769 showed at week 12 a reduction of the number of cells expressing inflammatory markers in the colon of patients with Crohn's disease including a significant reduction of expression of TNF? in the colon ($p<0.029$). Comparisons with placebo of the proportion of patients with intestinal mucosa healing at week 12 have shown evidence of mucosal healing in adalimumab treated patients. A total of 272/777 subjects from Study M04-690 and 117/276 subjects from Study M02-433 were followed

	of patients experiencing infection disorders and malignancies and lymphoproliferative disorders. The number of patients in clinical trials is also updated. Update of Summary of Product Characteristics				through at least 3 years of open-label adalimumab therapy. In Study M04-690 and Study M02-433, 69.5% (189/272 subjects) and 75.2% (88/117 subjects), respectively, continued to be in clinical remission at 3 years. Clinical response (CR-100) was maintained in 85.7% (233/272) subjects and 87.2% (102/117 subjects), respectively. Study M02-404 showed that with adalimumab maintenance therapy (both 40 mg every other week and 40 mg every week) the numbers of patients on active treatment requiring all-cause of hospitalization was smaller than in placebo-treated patients at week 56. The risk for Crohn's disease-related hospitalization was also statistically significantly reduced with adalimumab compared with placebo at Week 56. Post-hoc analyses of studies M05-769, M02-403, M04-691 and M02-404 have been conducted to evaluate the effect of concomitant administration of corticosteroids on the rates of clinical remission and response at Week 4 of adalimumab induction therapy. The pooled analyses in the subset of subjects with severe CD treated with 160 mg at Week 0 and 80 mg at Week 2 from Study M05-769, Study M02-403 and Study M04-691, as well as in the subset of subjects with severe Crohn's disease treated with 80 mg at Week 0 and 40 mg at Week 2 from Study M02-403 and Study M02-404, show that concomitant corticosteroid treatment during induction therapy does not offer advantages in subjects with severe CD. Therefore the recommendation of concomitant administration of corticos
II/0071	Update of section 4.4 "Special warnings and precautions for use" of the SmPC to add a statement on the higher risk for developing infections in the	22/04/2010	02/06/2010	SmPC and PL	Analyses of serious infection and death by various risk factors conducted in all adalimumab clinical studies conducted in rheumatoid arthritis indicate an association

	geriatric population and in patient with impaired lung function further to the request of the CHMP following assessment of the Follow-up measure (FUM) 059. The Package Leaflet is updated accordingly. Update of Summary of Product Characteristics and Package Leaflet				with higher risk for subjects above 65 years of age and for subjects with prior lung disease. The review showed that the frequency of serious infections among adalimumab treated subjects over 65 years of age (3.9%) was higher than for those under 65 years of age (1.4%). Some of those had a fatal outcome. Particular attention regarding the risk for infection should be paid when treating the elderly population. Analyses of risk factors for serious infection also identified lung disease as contributing risk factor for development of serious infections. Therefore the existing warning informing that patients taking TNF-blockers are more susceptible to serious infections is reinforced by adding that impaired lung function may increase the risk for developing infections.
II/0073	Update of section 4.8 of the Summary of Product Characteristics (SmPC) based on post-marketing events to add diverticulitis, erythema multiforme, alopecia and pulmonary embolism as new undesirable effects. The Package Leaflet (PL) was updated accordingly. In addition the MAH took the opportunity to update section 4.4 of the SmPC to harmonize the statement on Haematologic Reactions with the latest ADR table from clinical trials. Update of Summary of Product Characteristics and Package Leaflet	18/03/2010	29/04/2010	SmPC and PL	The company did an overall review of the safety database. A review of reports of diverticulitis showed a number of these patients had risk factors for diverticulitis, including advanced age, obesity, NSAID or corticosteroid use, or a history of diverticulitis or diverticulosis. This cumulative analysis of diverticulitis reports supports the reinstatement of diverticulitis in the SmPC as a post-marketing event. A total of 32 reports that described Steven Johnson syndrome (SJS) and erythema multiforme (EM) were retrieved from the search strategy, 23 reports of EM and 9 reports of SJS. Overall the cumulative analysis of postmarketing adverse event reports of EM and SJS confirms the previous inclusion of SJS in the SmPC and justifies the reinstatement of EM as postmarketing event in the SmPC as postmarketing events. The company safety database was reviewed for reports of alopecia. Eleven reports had no apparent confounding

					factors for hair loss identified. No identifiable pattern in the demographics or time to onset was seen that would distinguish these patients from those within the patient population treated with adalimumab. However due to the number of medically confirmed postmarketing reports, the addition of alopecia as postmarketing event to the CCDS and subsequently the SmPC is justified. Regarding embolic and thrombotic events, there were 19 medically confirmed reports, of which 9 (47%) were spontaneous reports from healthcare professionals or authorities, 8 (42%) were solicited reports (e.g., registries, observational studies) and 2 (11%) were reports from clinical trials. Pulmonary embolism is a possible but rare outcome of having thrombophlebitis. In spite of the risk factors and confounding factors, the role of adalimumab cannot be completely ruled out.
II/0070	To obtain approval of the Lonza Biologics Porrino, S.L. drug substance manufacturing site (10000 L bioreactor scale), in addition, the applicant incorporates several modifications in the manufacturing process (EMEA/H/C/000481/II/70) Change(s) to the manufacturing process for the active substance	18/03/2010	29/04/2010	Annex II	
II/0068	Update of section 4.4 of the Summary of Product Characteristics (SmPC) to include leukaemia and paediatric malignancy in the existing warning on malignancies and lymphoproliferative disorders and to amend the warning wording on invasive fungal	18/02/2010	23/03/2010	SmPC and PL	Cumulative reviews of the cases of leukaemia in adult and malignancies in paediatric patients reported with use of adalimumab in clinical trials, disease specific registries, postmarketing reports and published literature did not allow establishing a causal relationship between the

	infections. Section 4.8 is updated to include leukemia. The package leaflet is updated accordingly. In addition the MAH took the opportunity to make minor corrections and to include minor formatting changes in the SmPC and PL. Update of Summary of Product Characteristics and Package Leaflet				development of these malignancies and adalimumab. 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 adalimumab may be also a contributing factor in the development of the observed malignancies. Therefore mention is made in the SmPC that, in the post-marketing setting, cases of leukaemia and malignancies in children, adolescents and young adults (up to 22 years of age) have been reported in patients treated with a TNF-antagonist, including adalimumab. In paediatric patients approximately half the cases were lymphomas. The other cases represented a variety of different malignancies and included rare malignancies usually associated with immunosuppression. Overall, a risk for the development of malignancies in children and adolescents treated with TNF-blockers cannot be excluded. The warning wording on invasive fungal infections was amended in order to reinforce the message that diagnosis and administration of empiric antifungal therapy in patients taking adalimumab should be made in consultation with a physician with expertise in the care of patients with invasive fungal infection.
IA/0069	To change the adress of the Marketing Authorisation Holder IA_01_Change in the name and/or address of the marketing authorisation holder	09/12/2009	n/a	SmPC, Labelling and PL	

II/0067	Change in the manufacturing process of the finished product Change(s) to the manufacturing process for the finished product	22/10/2009	27/10/2009		
II/0066	Update of section 4.2 of the SPC to clarify when interruption of treatment may be necessary in rheumatoid arthritis (RA), e.g. before surgery or if a serious infection occurs. The marketing authorisation holder took the opportunity to regroup the wording on RA in section 3 of the PL for improved readability. Paediatrics to validate Update of Summary of Product Characteristics and Package Leaflet	23/07/2009	28/08/2009	SmPC and PL	A clarification to healthcare professionals was introduced in the posology section regarding treatment interruptions in rheumatoid arthritis patients being treated with adalimumab. Although not recommended, interruption of treatment with adalimumab may be needed for several reasons such as surgery or occurrence of certain adverse drug reactions. The information regarding efficacy and safety of re-introduction of treatment after discontinuation was already labelled and remained unchanged.
II/0064	Update of the summary of product characteristics (SPC) sections 4.4, to add parasitic infections, and 4.8 to add myocardial infarction, cerebrovascular accident and new onset or worsening of psoriasis based on data from periodic safety update reports covering the period from 01January 2008 to 31 December2008. The package leaflet (PL) was updated accordingly. Annex II was updated to reflect the new version of the risk management plan. Minor errors were corrected in the SPC and PL and the list of local representatives in the PL for Romania was updated.	23/07/2009	28/08/2009	SmPC, Annex II and PL	Based on analysis of postmarketing reports and a review of available literature, the undesirable effects section was updated to include myocardial infarction (heart attack), cerebrovascular accident (stroke) and new onset or worsening of psoriasis (including palmoplantar pustular psoriasis) as these events have been reported and a causal relationship with the treatment with adalimumab cannot be ruled out. The warning section was also updated as serious infections caused by parasites have also been reported.

	Update of Summary of Product Characteristics and Package Leaflet				
II/0061	To update section 4.8 of the SPC in accordance with a new methodology for identification of event frequency and to bring it in line with the latest SPC guideline. The package leaflet was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	24/07/2009	SmPC and PL	The methodology for determining adverse drug reactions (ADR) frequencies and the grouping of ADRs was reviewed and brought in line with the latest SPC guideline. In addition, the rates of malignancies were recalculated including subjects with an exposure of at least 1 year, as malignancies are long-term adverse effects.
II/0065	Extension of the Active Substance shelf-life. Change(s) to shelf-life or storage conditions	25/06/2009	06/07/2009		
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/04/2009	n/a	PL	
II/0062	To strengthen the warning on infections in section 4.4 of the SPC further to a review of reports of invasive fungal infections. Section 4.8 of the SPC and the PL were updated accordingly. The marketing authorisation holder took the opportunity to correct typos in the annexes and to update the contact details for Romania in the PL. Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/01/2009	25/02/2009	SmPC, Labelling and PL	Patients taking medicines such as adalimumab 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 adalimumab. The benefit risk of the treatment in patients which have been exposed to tuberculosis or have travelled in areas of high risk of tuberculosis or 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, serious infections and opportunistic infections. Furthermore different types of fungal infections were listed in the undesirable effects section.
R/0051	Renewal of the marketing authorisation.	26/06/2008	29/08/2008	SmPC, Annex II, Labelling and PL	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 Humira continues to be favourable. The CHMP is also of the opinion that the renewal can be granted with unlimited validity.
II/0039	To extend the therapeutic indication to include treatment of active polyarticular juvenile idiopathic arthritis in adolescents from 13 to 17 years of age. The annex II and package leaflet were updated accordingly. Additionally, the marketing authorisation holder took the opportunity to update the summary of product characteristics, labelling and package leaflet in accordance with the latest QRD template. Extension of Indication	24/07/2008	25/08/2008	SmPC, Labelling and PL	Please refer to the scientific discussion: Humira-H-481-II-39-AR
II/0056	To update sections 4.4 and 4.8 of the SPC to include information on post-marketing cases of hepatosplenic T-cell lymphoma. The PL was updated accordingly. Update of Summary of Product Characteristics and	26/06/2008	13/08/2008	SmPC and PL	Three cases of a rare type of hepatosplenic T-cell lymphoma were identified in patients with inflammatory bowel disease and rheumatoid arthritis treated with adalimumab. Some of the patients were also receiving azathioprine or 6-mercaptopurine for the treatment of inflammatory bowel disease. Based on the data presented,

	Package Leaflet				a causal relationship of hepatosplenic T-cell lymphoma and adalimumab 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.
IA/0060	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	31/07/2008	n/a		
II/0054	Change(s) to the test method(s) and/or specifications for the active substance	26/06/2008	22/07/2008		Change to the test methods for the active substance and consequential change to one active substance specification.
II/0053	To update section 5.1 of the SPC to include information on temporary treatment discontinuation as requested by the CHMP following assessment of a follow-up measure. The PL was updated accordingly. The MAH took the opportunity to update the PL contact details of the local representatives for Bulgaria, Denmark, Estonia, Greece, Italy, Latvia, Lithuania, Netherlands, Poland, Slovenia, Slovakia, and United Kingdom. Update of Summary of Product Characteristics and Package Leaflet	30/05/2008	17/07/2008	SmPC and PL	In some situations, such as during treatment of certain infections and prior to surgery or a dental procedure, treatment with adalimumab might need to be stopped. Data from clinical trials in rheumatoid arthritis patients suggest that re-introduction of adalimumab after discontinuation for 70 days and longer results in the same magnitude of efficacy and similar safety as before dose interruption. The product information was updated to reflect these findings.
II/0052	To update sections 4.4 and 4.5 of the SPC regarding coadministration with abatacept. A clarification on demyelinating diseases was included in section 4.4 and information on coadministration with anakinra was reflected in section 4.5. The PL was updated accordingly.	30/05/2008	17/07/2008	SmPC and PL	Clinical data showed that the combination of abatacept (which is used to treat adults with moderate to severe active rheumatoid arthritis) and TNF-antagonists such as adalimumab appears to increase the risk of infections, without showing increased clinical benefit. Therefore the product information was updated to state that the concomitant use these medicines is not recommended.

	Update of Summary of Product Characteristics and Package Leaflet				The current statement on demyelinating diseases (diseases in which the myelin sheath around the nerves is affected) including multiple sclerosis was harmonised across the SPC and PL. The section on interactions was updated to be in line with the already existing warning on the combination of adalimunab and anakinra.
II/0047	To update section 4.8 of the SPC to include Guillian-Barré syndrome and intestinal perforation further to the assessment of a periodic safety update report covering the period from 01.01.2007 to 30.06.2007. The PL was updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/04/2008	23/06/2008	SmPC and PL	Following a review of safety data the undesirable events section of the SPC was updated to include Guillian-Barré syndrome, a nervous system disorder which causes muscle weakness, abnormal sensations, tingling in the arms and upper body; and intestinal perforation. There were 7 reports of GBS included for the analysis. Five (71%) reports did not provide an apparent confounding factor for GBS. Four of the reports indicated positive de-challenge and no reports of positive re-challenge were noted. Although the cumulative analysis of GBS provided in PSUR 9 did not present new information about the risk of GBS in patients taking adalimumab, the SPC was updated by adding the specific term GBS to the broad category of demyelinating disorders, as the potential role of adalimumab could not be excluded. The PL was updated accordingly.
IB/0055	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	20/06/2008	n/a	SmPC	
IA/0059	IA_06_a_Change in ATC code: Medicinal products for human use	16/06/2008	n/a	SmPC	
IA/0058	IA_05_Change in the name and/or address of a	29/05/2008	n/a		

	manufacturer of the finished product				
II/0045	Change(s) to the manufacturing process for the finished product	19/03/2008	31/03/2008		
IA/0050	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	04/03/2008	n/a		
IA/0049	IA_05_Change in the name and/or address of a manufacturer of the finished product	04/03/2008	n/a		
IA/0048	IA_05_Change in the name and/or address of a manufacturer of the finished product	04/03/2008	n/a		
IA/0046	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	04/02/2008	n/a		
II/0044	Change(s) to the manufacturing process for the finished product	24/01/2008	28/01/2008		
II/0043	To update the psoriatic arthritis indication to include reduction in rate of progression of joint damage and improvement of physical function. The PL was updated in accordance with the changes proposed to the SPC. Additionally, the contact details for the local representatives for Poland, Finland and Sweden were revised. Extension of Indication	13/12/2007	17/01/2008	SmPC and PL	Please refer to the scientific discussion: Humira-H-481-II-43-AR
II/0038	To extend the indication to include treatment of adult	15/11/2007	19/12/2007	SmPC, Annex	Please refer to the scientific discussion:

	patients with moderate to severe chronic plaque psoriasis. The annex II and package leaflet were updated accordingly. Extension of Indication			II and PL	Humira-H-481-II-38-AR
II/0042	To update section 4.8 of the SPC to add "pancreatitis" following assessment of PSUR 8 covering the period from 1 July 2006 to 31 December 2006. Update of Summary of Product Characteristics	20/09/2007	09/10/2007	SmPC	Further to the assessment of post-authorisation data and review of all cases of pancreatitis that occurred during the controlled part of clinical trials, the causal association between adalimumab and pancreatitis could not be excluded. The product information for adalimumab was updated to include pancreatitis in the undesirable events section with a frequency of rare.
II/0041	Change(s) to the test method(s) and/or specifications for the active substance	19/07/2007	23/07/2007		
II/0037	To update section 5.1 of the SPC with 5 year results from an open label extension of a clinical trial in rheumatoid arthritis. Section 4.8 was consequentially updated. Update of Summary of Product Characteristics	24/05/2007	29/06/2007	SmPC	Results from an open label extension study in rheumatoid arthritis indicated that the reduction in rate of progression of structural damage is maintained up to 5 years in a subset of patients. Data also showed that efficacy in terms of ACR (American College of Rheumatology) response (criteria used in rheumatoid arthritis which allows for standardisation of trial outcomes and permits comparisons of treatment efficacy across clinical trials) was maintained in a group of patients who continued throughout the study period. 114 out of 207 patients continued on adalimumab 40 mg every other week for 60 months. Among those, 86, 72 and 41 patients had ACR 20/50/70 response. The SPC was updated to reflect

					these results.
II/0033	To update sections 4.1 of the SPC to include treatment of adult patients with moderately to severe active Crohn's disease. Sections 4.2, 4.8, 5.1 and 5.2 were consequently updated. The Package Leaflet (PL) was updated accordingly. Extension of Indication	22/02/2007	04/06/2007	SmPC, Annex II and PL	Please refer to the Scientific Discussion: EMEA-H-481-II-33-AR
II/0036	Change(s) to the manufacturing process for the active substance	22/03/2007	14/05/2007	Annex II	
II/0035	To update section 4.4 of the SPC regarding hepatitis B reactivation further to the update of the company's core data sheet. The PL was updated accordingly. In addition the MAH completed the list of local representatives in the PL to include the two new EU Member States (Bulgaria and Romania), and corrected the list of local representatives for Finland, Portugal and United Kingdom. Update of Summary of Product Characteristics and Package Leaflet	24/01/2007	05/03/2007	SmPC and PL	Based on the current safety information for adalimumab, a warning was added to the product information (PI) related to the reactivation of chronic hepatitis B. Reactivation of hepatitis B has occurred in patients receiving TNF-antagonists including adalimumab, who are chronic carriers of this virus. In some rare cases, especially if taking other medicines that suppress the immune system, reactivation of hepatitis B virus (HBV) had a fatal outcome. The PI now states that patients are advised to contact their doctors if they are carriers of HBV, have active HBV or think they might be at risk of contracting HBV.
II/0034	To update sections 4.5 and 5.1 of the SPC regarding antibodies to adalimumab as requested by the CHMP further to the assessment of pharmacokinetic data from a long term clinical trial.	24/01/2007	05/03/2007	SmPC	Based on the assessment of pharmacokinetic data, the SPC was updated to revise the numbers of subjects positive for anti-adalimumab antibodies observed in the clinical setting in patients on adalimumab monotherapy and patients on adalimumab and methotrexate. The formation of anti-

	Update of Summary of Product Characteristics				adalimumab antibodies was associated with increased elimination and reduced efficacy of adalimumab. Higher antibody values did not appear to affect safety.
II/0030	The Marketing Authorisation Holder applied for the addition of a new presentation in a single-use disposable pre-filled pen comprising the authorised pre-filled syringe sealed into a functional secondary packaging used to deliver the product. The presentation is available in 4 pack sizes: 1, 2, 4 and 6 pens. New presentation(s)	21/09/2006	07/11/2006	SmPC, Labelling and PL	The pen is composed of the approved prefilled syringe sealed into an autoinjector delivery system. The pen is for a single-use. The information provided in support of the pen confirm that this variation does not affect the quality of the product . The product information has been updated to include the presentations in a pre-filled pen.
II/0027	Update of sections 4.4 and 4.8 of the SPC further to the request from the CHMP following assessment of PSUR No 5, covering the period from 31 December 2004 to 30 June 2005. The changes relate to post-marketing reports on lupus-like illness, and data from recent clinical trials concerning immunogenicity of influenza and pneumococcal vaccines. Furthermore, the sections on infections and malignancies were also updated according to the current knowledge for anti-TNF therapies. The PL was updated in accordance with the changes proposed to the SPC. Additionally, the Marketing Authorisation Holder took the opportunity to update the list of local representatives (Austria and Slovenia). The annex II was updated to reflect the amendment of the periodicity of PSUR submission.	21/09/2006	07/11/2006	SmPC, Annex II and PL	In line with the CHMP recommendations following assessment of the 5th PSUR, the marketing authorisation holder (MAH) applied to update the warnings and undesirable effects sections of the SPC. The update aimed to detail the occurrence of lupus-like syndromes, serious infections and opportunistic infections and to revise the wording on tuberculosis. The sections on malignancies and lymphomas were updated with the latest figures from clinical trials and post-marketing data with adalimumab and information available from other anti-TNF agents, in particular to revise the wording regarding very rare cases of non melanoma skin cancer observed in patients taking adalimumab, and to include warning on the treatment of patients with chronic obstructive pulmonary disease as well as patients which are heavy smokers. Further to the assessment of available clinical trial data, the section on vaccinations was updated to reflect that patients on adalimumab may receive concomitant vaccination, except

	Update of Summary of Product Characteristics and Package Leaflet				for live vaccines. The PL was update in accordance with the changes proposed to the SPC. The annex II was amended to reflect that the MAH should continue to submit PSURs every 6 months.
II/0032	Change(s) to the manufacturing process for the finished product	27/07/2006	03/08/2006		
II/0031	Change(s) to the test method(s) and/or specifications for the active substance	27/07/2006	03/08/2006		
II/0028	Change(s) to the manufacturing process for the finished product	01/06/2006	07/06/2006		
II/0026	Update of section 4.1 of the SPC to extend the indication of adalimumab to include treatment of patients with severe active ankylosing spondylitis. Sections 4.2, 4.8 and 5.1 have consequently been updated. The PL was updated in accordance with the changes proposed to the SPC. Extension of Indication	27/04/2006	01/06/2006	SmPC and PL	This will refer to the scientific discussion of this CHMP Assessment report.
IA/0029	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	22/03/2006	n/a	Annex II	
II/0025	Change(s) to the manufacturing process for the active substance	26/01/2006	31/01/2006		

II/0024	Update of sections 4.4 and 4.8 following the CHMP assessment of PSUR No 4, covering the period from 1 July 2004 to 30 December 2004, to include the latest information from post-marketing reports and data from recent clinical trials on early rheumatoid arthritis and psoriatic arthritis. Minor corrections were introduced to section 4.2 of the SPC and section 3 of the PL. Furthermore, section 4.4 of the SPC and section 2 of the PL were updated with regard to latex in accordance with the Excipients Guideline. The PL was updated in accordance with the changes proposed to the SPC. Update of Summary of Product Characteristics and Package Leaflet	14/12/2005	20/01/2006	SmPC and PL	In line with the CHMP recommendations further to the assessment of the 4th PSUR, the MAH applied to update the warnings and undesirable effects sections of the summary of product characteristics. The warning section was updated regarding new onset of demyelinating disease and blood disorders. The undesirable effects section was updated mainly regarding hepatic enzyme elevations and hepatic events, lupus-like reactions, infections, pulmonary events and malignancies. The section 4.8 was reorganised in accordance to the medical dictionary for regulatory affairs (MedDRA) terminology. Furthermore, corrections were introduced in section 4.2 of the SPC on initiation and supervision of treatment of psoriatic arthritis and section 3 of the PL on the handling of the syringes. A warning was introduced regarding allergic reactions due to the rubber nature of the needle cover of the syringe (latex).
II/0022	Update of section 4.1 of the SPC to include treatment of patients with Psoriatic Arthritis. Sections 4.2, 4.8, 4.9 and 5.1 have consequentially been updated. The PL was updated in accordance with the SPC. Extension of Indication	23/06/2005	01/08/2005	SmPC, Annex II and PL	Please refer to the Scientific Discussion: EMEA-H-481-II-22-AR.
II/0021	Update of section 4.1 of the SPC to include treatment of recently diagnosed patients with moderately to severe active Rheumatoid Arthritis (RA) who have not been previously treated with methotrexate. Sections 4.8 and 5.1 have consequentially been updated. The PL was updated in accordance with the	23/06/2005	01/08/2005	SmPC and PL	Please refer to the Scientific Discussion: EMEA-H-481-II-21-AR.

	SPC. Extension of Indication				
II/0020	Change(s) to the manufacturing process for the active substance Change(s) to the test method(s) and/or specifications for the active substance	21/04/2005	27/04/2005		
II/0023	Update of the SPC, section 4.4 to include warnings regarding co-administration with anakinra, tuberculosis and congestive heart failure and section 4.8 to include cutaneous vasculitis, following the assessment of the 3rd PSUR (reporting period 31.12.03-30.06.04). Update of Summary of Product Characteristics	16/03/2005	25/04/2005	SmPC	In line with the CHMP recommendations further to the assessment of the 3rd PSUR, the MAH applied to update the warnings and undesirable effects sections of the Summary of Product Characteristics. The warning section on concurrent administration with anakinra was revised due to the occurrence of serious infections following concurrent use of anakinra with another TNF-antagonist. The wording on tuberculosis was also revised to include the information that this disease, including fatalities, had been reported in patients taking Humira. This section was also updated to include the safety information that cases of worsening congestive heart failure have been reported in patients receiving adalimumab. The section 4.8 "Undesirable effects" was updated following reports of occurrence of cutaneous vasculitis in patients taking Humira. This adverse effect has been reported with a frequency of rare.
II/0018	Change(s) to the manufacturing process for the active substance. Change(s) to the manufacturing process for the active substance	17/02/2005	25/02/2005		

II/0017	Change(s) to the manufacturing process for the active substance	17/02/2005	25/02/2005		
II/0019	Update of sections 4.4 and 4.8 of the SPC on malignancies and lymphoproliferative disorders following the assessment of the 3rd PSUR (reporting period 31.12.03-30.06.04). Update of Summary of Product Characteristics	15/12/2004	25/01/2005	SmPC and Annex II	In line with the CHMP recommendations further to the assessment of the 3rd PSUR, 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 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/0016	Change(s) to the manufacturing process for the finished product. Change(s) to the manufacturing process for the finished product	15/12/2004	21/12/2004		
II/0014	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	18/11/2004	23/11/2004		

II/0013	Change(s) to shelf-life or storage conditions	18/11/2004	23/11/2004		
IA/0015	IA_28_Change in any part of primary packaging material not in contact with finished product	06/10/2004	n/a		
II/0008	Update of or change(s) to the pharmaceutical documentation	16/09/2004	22/09/2004		
II/0012	Change(s) to the manufacturing process for the active substance	29/07/2004	02/08/2004		
II/0011	Change(s) to the manufacturing process for the active substance	29/07/2004	02/08/2004		
II/0010	Update of sections 4.4 and 4.8 of the SPC following the assessment of the first PSUR (reporting period 31 December 2002 - 30 June 2003) to include serious allergic reactions and warnings relating to surgical procedures. Update of Summary of Product Characteristics and Package Leaflet	03/06/2004	19/07/2004	SmPC and PL	Based on the submitted data, the CHMP agreed that the MAH should include in section 4.4 (Special warnings and special precautions for use) a warning with regard to surgical procedures and patients who have undergone arthroplasty and to add to sections 4.4 and 4.8 (Undesirable effects) "serious allergic reactions including anaphylaxis". A consequential change to the Package Leaflet, in section 2 (Before you use Humira), is proposed in order to reflect the safety warning relating to the possible risk of infection in patients undergoing surgery. Advice is already included in the current Package leaflet relating to allergic reactions and the existing wording also satisfactorily reflects the symptoms of anaphylaxis.
II/0006	Update of SPC section 4.1 (Therapeutic indications) to include an additional statement in the therapeutic	22/04/2004	10/06/2004	SmPC, Labelling and	Please refer to the Scientific Discussion: EMEA-H-481-II-

	indications to reflect results of a clinical study on the reduction of the rate of progression of structural damage and improvement of physical function, and consequential changes of SPC section 5.1 (Pharmacodynamic properties). Extension of Indication			PL	06-AR.
N/0009	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	29/03/2004	n/a	PL	
II/0007	Change(s) to the manufacturing process for the active substance. Change(s) to the manufacturing process for the active substance	26/02/2004	01/03/2004		
II/0003	Change(s) to the test method(s) and/or specifications for the active substance	17/12/2003	19/12/2003		
IA/0005	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	20/10/2003	n/a		
IA/0004	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	20/10/2003	n/a		
IA/0001	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	20/10/2003	n/a		