EMA/70892/2020

LIFMIOR

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
WS/1654	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from study (B1801311 - BADBIR) listed as a category 3 study in the RMP.	31/10/2019	n/a		The primary objective of this British Association of Dermatologists Biologics and Immunomodulators Register (BADBIR) was to investigate the long-term safety outcomes of psoriasis patients treated with biologic therapy. The data were collected during the observation of psoriasis patients treated with etanercept and conventional therapy who were

[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).

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	This is a prospective cohort study that compared patients treated with biologic interventions (etanercept, adalimumab, and ustekinumab) and patients with similar disease characteristics but exposed only to conventional non-biologic systemic therapies. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				registered in the BADBIR register between 01 September 2007 and 31 July 2018. As of the 31st of July 2018, 1811 patients were registered with the etanercept cohort (n=1379, 76%) or have switched to etanercept from another biologic therapy (n=432, 24%), and 5346 patients were registered for the conventional cohort. Patients were recruited into the etanercept cohort from 123 centres across the UK and the Republic of Ireland. The analyses indicated a significantly increased risk of serious infection (aHR 1.79; 95% CI 1.37,2.33), respiratory (aHR 2.42; 95% CI 1.18, 4.95), cardiac (aHR 1.63; 95% CI 1.04, 2.57), nervous system (aHR 2.18; 95% CI 1.32, 3.61), skin (non-cancer; aHR 1.55; 95% CI 1.07, 2.24) and malignant events (aHR 1.49; 95% CI 1.13, 1.95) for those psoriasis patients currently or previously receiving etanercept. Within these categories, psoriasis patients currently or previously receiving etanercept had a significantly increased risk of pneumonia (aHR 1.68; 95% CI 1.02, 2.77), septicaemia (aHR 2.78; 95% CI 1.21, 6.39), cellulitis (aHR 2.28; 95% CI 1.19, 4.37), other serious infection (aHR 1.93; 95% CI 1.33, 2.79), other cardiac (aHR 1.79; 95% CI 1.06, 3.04), other nervous system (aHR 1.92; 95% CI 1.12, 3.30), skin cancer (aHR 1.75; 95% CI 1.15, 2.66) and solid tumours (aHR 1.52; 95% CI 1.06, 2.19). A greater incidence of pregnancies was reported for female patients receiving etanercept during follow-up when compared to those receiving conventional therapy (aHR 1.93; 95% CI 1.14, 3.26). No other events differed significantly between those receiving conventional therapy and those receiving etanercept. The findings of the analyses suggest that patients exposed to etanercept have an increased risk of developing serious

					infections, respiratory, cardiac, nervous system and skin (non-cancer) serious adverse events (SAEs), and malignancies as compared with those exposed to conventional treatment after adjusting for potential confounders. The generalisation and external validity of this study results are limited due to the presence of potential bias, notably confounding by indication. Overall, these findings are consistent with the known safety profile of etanercept in the treatment of adult psoriasis. These reported risks have been well characterised through the risk management plan and are listed in the product information. No new safety concerns were identified. Overall, the results presented in this application are consistent with previous reported data and do not warrant amendment to the product information.
WS/1614	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report for the PURPOSE study, a category 3 study in the RMP. PURPOSE was a non-interventional, multi-centre, prospective, observational, cohort study to evaluate the long-term safety and effectiveness of etanercept prescribed by dermatologists to paediatric patients for the treatment of plaque psoriasis. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	03/10/2019	n/a		Out of the 72 patients enrolled in the PURPOSE study, 29 patients (40.4%) patients completed the 5-year follow up period. The main reasons for not completing the follow-up were early discontinuation due to the study ending prior to patient completing 5-year follow-up (27.8%, 20/72) and patients lost to follow-up (15.3%, 11/72). No serious or opportunistic infections, or malignancies were reported. There were 25 treatment-emergent SAEs, including 7 considered possibly related to etanercept. The most frequent reported SAEs were under the SOC "Skin and subcutaneous tissue disorders". No deaths were reported. The safety data are in line with the known safety profile for etanercept. Effectiveness of etanercept was evaluated in 32 patients, of whom (87.5%, 28/32) completed a 24-week course of therapy. The reasons for not completing a course of

					therapy were treatment being ineffective (3 patients) and lost to follow-up (1 patient). Of these 32 patients, 16 required more than one treatment period with other systemic therapies, mostly with other systemic biologics. Decrease in severity of plaque psoriasis after treatment with etanercept based on the judgment of the investigator was observed in 30/32 patients. The effectiveness data were too limited to draw conclusions.
IG/1139	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	20/09/2019	n/a		
IG/1087	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	15/04/2019	n/a		
IG/1082	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	05/04/2019	04/02/2020	SmPC and PL	
WS/1526	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from study (RABBIT register Cohort 2) listed as a category 3 study in the RMP. This is a prospective, non-interventional, observational, long-term cohort Germanic biologics register to evaluate the long-term effectiveness, safety, and costs associated with tumour necrosis	14/03/2019	n/a		The RABBIT register is an on-going long-term observational cohort study initiated in Germany in 2001. A total of 10,919 patients with RA were considered for the analyses. At enrolment, patients of the three exposure groups (Enbrel (n=1,537), other bDMARDs (n=6,030), csDMARDs (n=3,349)) had a mean age of 57 - 59 years, and 73 - 75% of the patients were female. Patients treated with Enbrel were comparable to patients treated with other bDMARDs in terms of some disease characteristics. The fully adjusted analysis of the complete cohort of the

	factor (TNF)-inhibitor therapies in the treatment of rheumatoid arthritis (RA) in comparison to cohorts of RA patients treated with conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) and biologic (b)DMARDs. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				RABBIT register did not reveal a negative impact of Enbrel on the outcomes of hospitalisations due to infection and pneumonia. After adjustment for available confounders, hazard ratios (HR) for stroke were significantly lower in patients treated with Enbrel compared to csDMARDs (on drug: HR=0.5 (95% CI 0.3; 0.9)). No effect of Enbrel on the outcomes of myocardial infarction, coronary artery disease and incident heart failure was observed. There was no significant association between patients currently exposed (on drug + 3 months risk window) or ever exposed to Enbrel and the risk for overall and first malignancies, lung cancer, lymphoma, malignant melanoma and NMSC. Thus, a reduced risk was seen for breast cancer in the group of Enbrel in the ever exposed analysis HR=0.5 (95% CI 0.2; 0.97)). Furthermore, a non-significantly elevated risk of leukaemia was revealed for Enbrel users relative to csDMARD treated patients (ever exposed: HR 1.9 (95% CI 0.7; 5.3)). Mortality risk was significantly reduced in patients currently receiving Enbrel (on-drug plus 3-months risk window: HR=0.6 (95%CI 0.4; 0.8)), but the result did not persist in the ever exposed approach. The spectrum of adverse pregnancy in patients receiving Enbrel did not differ from the other treatment groups. There were low numbers of tuberculosis, opportunistic infections, worsening of heart failure, glioblastoma, cervical cancer and central demyelination, and therefore no adjusted risks for these events were analysed. Results showed a reduced risk for stroke, breast cancer and mortality relative to csDMARD users. In this analysis no association with other safety events, including infections, cardiovascular outcomes and malignancy, were identified.

					Overall the results of this study do no suggest any new safety concerns for etanercept and are in line with the known safety profile for etanercept. No changes to the product information are deemed necessary as a consequence of the findings of this study.
WS/1270	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Update of section 4.6 of the SmPC in order to update the current safety information on pregnancy based on the final results from study B1801396, a non-interventional PASS listed as a category 3 study in the RMP. This is a non-interventional, population-based, multi-country, observational cohort register study to evaluate the risk of adverse pregnancy outcomes in patients with rheumatoid arthritis and related inflammatory diseases, who were treated with etanercept compared to patients with the same diseases of interest who were treated with non-biologic systemic drugs, but without etanercept or other biologics during pregnancy, using merged data from Sweden, Denmark and Finland. The Package Leaflet is updated accordingly. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/01/2019	04/02/2020	SmPC and PL	The final report for study B1801396, a non-interventional, population-based, multi-country, observational cohort register study using merged data from Sweden, Denmark and Finland, was submitted as part of this variation application. In this observational multi country registry study comparing the risk of adverse pregnancy outcomes in women exposed to etanercept during the first 90 days of pregnancy (n=425) to those exposed to non-biologic drugs (n=3497), there was no observed increased risk of major birth defects (crude odds ratio [OR]= 1.22, 95% CI: 0.79-1.90; adjusted OR = 0.96, 95% CI: 0.58-1.60 after adjusting for country, maternal disease, parity, maternal age and smoking in early pregnancy). This study also showed no increased risks of minor birth defects, preterm birth, stillbirth, or infections in the first year of life for infants born to women exposed to etanercept during pregnancy. In total the effects of etanercept on pregnancy outcomes have been investigated in two observational cohort studies. Based on all available data, etanercept should only be used during pregnancy if clearly needed. Section 4.6 of the SmPC and section 2 of the PL have been updated accordingly.
T/0017	Transfer of Marketing Authorisation	11/07/2018	23/08/2018	SmPC, Labelling and	

				PL	
WS/1408	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	26/07/2018	n/a		
WS/1362	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report from the study 20050111 listed as category 3 study in the RMP, in order to fulfil Enbrel P46 0134.2. This is a multicentre, open-label extension study to evaluate the long-term safety and efficacy of etanercept in paediatric subjects with moderate to severe plaque psoriasis for up to 264 weeks (or until the quarterly visit after the subject's 18th birthday, whichever comes last) who participated in controlled study 20030211. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/05/2018	n/a		Please refer to Scientific Discussion Enbrel & Lifmior-H-C-WS-1362.
IAIN/0015/G	This was an application for a group of variations.	17/05/2018	23/08/2018	Annex II and	

	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 B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing			PL	
IB/0011	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	12/02/2018	n/a		

WS/1190/G	This was an application for a group of variations following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	25/01/2018	08/05/2018	SmPC and PL	

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

	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits				
IB/0012	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	24/01/2018	08/05/2018	SmPC, Labelling and PL	
WS/1261	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. Submission of the final report for the Anti-Rheumatic Treatment in Sweden Registry-Etanercept Cohort Study listed as a category 3 study in the RMP. It is non-interventional PASS aimed at providing an assessment of a number of pre-specified safety outcomes for Enbrel as used in the treatment of RA in Sweden, using data from the ARTIS system, in total and from 2006. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission	26/10/2017	n/a		The final study report of the Anti-Rheumatic Treatment in Sweden Registry-Etanercept Cohort Study (ARTIS-ETN) Registry provides information on a number of measured outcomes (e.g. primary invasive cancers excluding non-melanoma skin cancers, melanoma, leukaemia, cervical cancer, stroke, fatal cardiovascular event, demyelinating event /MS and all-cause mortality). The results from the ARTIS registry are consistent with the current overall safety profile of etanercept in in the treatment of rheumatoid arthritis. No new safety concerns were identified. Overall, the results presented in this application are consistent with previous reported data and did not warrant amendment to the product information.

	of studies to the competent authority				
IB/0008/G	This was an application for a group of variations. B.II.b.1.f - Replacement or addition of a manufacturing site for part or all of the manufacturing process of the FP - Site where any manufacturing operation(s) take place, except batch release, batch control, and secondary packaging, for sterile medicinal products (including those that are aseptically manufactured) excluding biological/ immunological medicinal products B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size B.II.b.5.b - Change to in-process tests or limits applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits	16/06/2017	n/a		

	applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier B.II.f.1.e - Stability of FP - Change to an approved stability protocol				
IB/0007	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	[illegible]/2017	n/a		
IB/0006/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	16/06/2017	n/a		

	control/testing takes place B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
IB/0001	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	09/06/2017	n/a		
IB/0002	C.I.2.a - Change in the SPC, Labelling or PL of a generic/hybrid/biosimilar products following assessment of the same change for the reference product - Implementation of change(s) for which NO new additional data is required to be submitted by the MAH	01/06/2017	08/05/2018	SmPC, Labelling and PL	
IA/0005/G	This was an application for a group of variations. B.II.b.5.b - Change to in-process tests or limits	29/05/2017	n/a		

	applied during the manufacture of the finished product - Addition of a new test(s) and limits B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test				
IB/0004	B.I.a.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB	24/05/2017	n/a		
IB/0003	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	24/05/2017	n/a		