Benlysta

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0133	Extension of indication to include add-on therapy in paediatric patients from 5 years of age with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g., positive anti dsDNA and low complement) despite standard therapy for Benlysta 200 mg in pre-filled pen (injection), based on final results from study 200908; this is a worldwide population	19/06/2025	18/07/2025	SmPC, Annex II, Labelling and PL	Please refer to Scientific Discussion 'Benlysta-H-C-002015-II-0133'

[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).

	pharmacokinetic (PK) analysis of subcutaneous administered belimumab plus standard therapy to paediatric patients aged 5-17 years with SLE, which was aimed to describe the PK analysis of belimumab to support an appropriate weight-based dosing regimen for subcutaneous administration in paediatric patients aged 5-17 years with SLE. As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC for Benlysta (belimumab, solution for injection in pre-filled syringe, 200 mg) to reflect the paediatric data available for belimumab. Update of sections 4.8 and 5.2 of the SmPC for Benlysta (belimumab powder for solution for infusion 120 mg and 400 mg) to reflect the paediatric data available for the subcutaneous formulation. The Package Leaflet is updated in accordance. Version 46.2 of the RMP is agreed. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives in the Package Leaflet. Furthermore, the PI is brought in line with the latest QRD template version 10.4 and with the excipients guideline. The variation leads to amendments to the Summary of Product Characteristics, Annex II, Labelling and Package Leaflet and to the Risk Management Plan (RMP). C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one				

IB/0138	B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS	10/02/2025	n/a		
IB/0140	B.II.d.z - Change in control of the Finished Product - Other variation	30/01/2025	n/a		
IB/0139	B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	22/01/2025	n/a		
PSUSA/9075/ 202403	Periodic Safety Update EU Single assessment - belimumab	14/11/2024	13/01/2025	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/9075/202403.
IA/0137/G	This was an application for a group of variations. B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method B.I.b.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	09/12/2024	n/a		

	changes to an approved test procedure				
IB/0136	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	12/10/2024	n/a		
IA/0135	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	30/09/2024	13/01/2025	SmPC	
IA/0134	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	23/08/2024	n/a		
II/0130	B.I.e.2 - Introduction of a post approval change management protocol related to the AS	11/07/2024	n/a		
IB/0131	B.II.z - Quality change - Finished product - Other variation	03/06/2024	n/a		
IB/0129	B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	03/05/2024	n/a		
II/0116	Submission of the final report for the Belimumab Pregnancy registry (BEL114256) listed as a category 3 study in the RMP. This is a non-interventional study to evaluate pregnancy and infant outcomes for pregnancies in women with systemic lupus erythematosus (SLE) exposed to commercially supplied belimumab within the 4 months preconception and/or during pregnancy. In addition, the BPR protocol planned to collect pregnancy and	11/04/2024	13/01/2025	SmPC	With this submission, section 4.6 of the SmPC was updated to reflect the presently available data on pregnancy exposure in woman exposed to belimumab. The current data are too limited to confirm a causal relation between belimumab and birth defects. Therefore, the current recommendation in the SmPC that "Benlysta should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus" remains appropriate. However, Section 4.6 of the SmPC was updated to reflect

	infant outcomes for pregnancies in women with SLE and SABLE (Safety and Effectiveness of Belimumab in Systemic Lupus Erythematosus) protocol who were not exposed to belimumab and enrolled in BPR. As a result, Section 4.6 of the SmPC was updated. In addition, RMP version 45.0 has been submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				that formal studies of belimumab in pregnancy have been conducted. For more information, please refer to the Summary of Product Characteristics.
IB/0128	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	10/04/2024	n/a		
IB/0127	B.II.z - Quality change - Finished product - Other variation	19/03/2024	n/a		
IB/0126	B.IV.1.z - Change of a measuring or administration device - Other variation	08/03/2024	n/a		
IB/0125	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	08/03/2024	n/a		
IB/0123	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	15/02/2024	n/a		

IA/0124	B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier	07/02/2024	n/a		
II/0118	Update of section 4.8 of the SmPC in order to change the frequency of urticaria and rash from uncommon to common and to change the frequency of diarrhoea and nausea from very common to common and to update the Summary of the safety profile based on a cumulative review of clinical trials. The Package Leaflet is updated accordingly. In addition, the MAH took this opportunity to introduce editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/01/2024	13/01/2025	SmPC and PL	With this submission, section 4.8 of the SmPC (as well as section 4 of the Package Leaflet), has been updated to change the frequency of urticaria and rash from uncommon to common and to change the frequency of diarrhoea and nausea from very common to common. The Summary of the safety profile is updated as well. These updates are supported by new integration of safety data which includes two additional clinical trials (BEL113750 and BEL115471) not previously included in the primary IV+SC safety population (LBSL02, BEL110751, BEL110752, BEL112341). For more information, please refer to the Summary of Product Characteristics.
II/0117	Update of section 4.4 of the SmPC in order to amend an existing warning and precautions for Progressive multifocal leukoencephalopathy (PML) following the recent review of the wording in the company Core Safety Datasheet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	11/01/2024	13/01/2025	SmPC	SmPC new text 4.4 Progressive multifocal leukoencephalopathy Progressive multifocal leukoencephalopathy (PML) has been reported with Benlysta treatment for SLE. Physicians should be particularly alert to symptoms suggestive of PML that patients may not notice (e.g., cognitive, neurological or psychiatric symptoms or signs). Patients should be monitored for any of these new or worsening symptoms or signs, and if such symptoms/signs occur, referral to a neurologist and appropriate diagnostic measures for PML should be considered as clinically indicated. If PML is suspected, immunosuppressant therapy, including

					Benlysta, must be suspended until PML has been excluded. If PML is confirmed, immunosuppressant therapy, including belimumab, must be discontinued.
IB/0122	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	10/01/2024	n/a		
IB/0120/G	This was an application for a group of variations. B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place	14/12/2023	n/a		
IB/0119	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)	11/12/2023	n/a		
II/0115/G	This was an application for a group of variations. B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	07/09/2023	n/a		

	B.II.b.1.c - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes				
IB/0114	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	16/06/2023	n/a		
IB/0113	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	30/05/2023	n/a		
II/0111	Submission of the final report from year 5 Post-Treatment Follow-Up from study BEL 115467/HGS1006-C113 listed as a category 3 study in the RMP. This is a 52-week, global, multi-center, randomized, placebo-controlled, double-blind study conducted to evaluate mortality and AESI in adults with active, autoantibody-positive SLE treated with belimumab plus standard therapy vs. placebo plus standard therapy. The RMP version 44 was approved. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	12/05/2023	n/a		Study BEL115467, listed as a category 3 in the RMP, was a randomized, double-blind, placebo-controlled, 52-week study to evaluate mortality and adverse events of special interest (AESI) in adult patients with active, autoantibody-positive SLE who were randomised in a 1:1 ratio to belimumab (10 mg/kg IV) plus standard therapy (n=2002) or placebo plus standard therapy (n=2001). Following the 52-week controlled treatment period (Year 1) (please refer to previous assessments as part of procedures EMEA/H/C/002015/II/0065 and EMEA/H/C/002015/II/0076), the study continued to follow up with each participant for a further 4 years (Year 2-5). The objective of this Year 2-5 post-treatment follow-up period was to assess mortality and new primary malignancy, including non-melanoma skin cancer (NMSC), in adult SLE participants who received either belimumab plus standard therapy or placebo plus standard of care

					during the Year 1 treatment period of the study. The safety data presented no new safety concerns for the use of belimumab in adult patients with active, autoantibody positive SLE who are receiving standard therapy. RMP version 44 was updated due to the completion of study BEL115467 (BASE). Some further minor updates were also made (e.g. study 213928 (PASS Belimumab Pregnancy Exposure Study) is updated from planned to ongoing).
IG/1576	A.7 - Administrative change - Deletion of manufacturing sites	02/02/2023	n/a		
IB/0110	B.II.z - Quality change - Finished product - Other variation	09/01/2023	n/a		
IB/0109	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/12/2022	n/a		
II/0107	Update of section 4.4 and 5.1 of the SmPC based on final results from study 205646; this is an interventional Phase III Study to Evaluate the Efficacy and Safety of Belimumab Administered in Combination with Rituximab to Adult Subjects with Systemic Lupus Erythematosus (SLE). In addition, the MAH took the opportunity to implement editorial changes. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/11/2022	05/05/2023	SmPC, Labelling and PL	In study 205646 (BLISS-BELIEVE), the efficacy of belimumab followed by a single cycle of rituximab was not found to be statistically significantly different compared with belimumab alone, while a higher frequency of adverse events was observed in patients from the belimumab and rituximab arm. Therefore section 4.4 of the SmpC is updated to inform prescribers that: co-administration of rituximab with Belimumab in patients with SLE is not supported by available data. A summary of the safety and efficacy data from study 205646 has also been included in section 5.1 of the SmPC. For more information, please refer to the Summary of Product Characteristics.

IB/0108	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	15/09/2022	n/a		
IB/0106	B.II.d.2.z - Change in test procedure for the finished product - Other variation	15/07/2022	n/a		
IB/0105	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	13/06/2022	n/a		
II/0104	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	19/05/2022	05/05/2023	Annex II	
IB/0103	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	04/01/2022	n/a		
IB/0102/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other	08/12/2021	n/a		

	variation				
IB/0101	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	10/11/2021	n/a		
N/0099	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/10/2021	07/06/2022	PL	
PSUSA/9075/ 202103	Periodic Safety Update EU Single assessment - belimumab	30/09/2021	n/a		PRAC Recommendation - maintenance
II/0098	Please refer to the Recommendations section 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	02/09/2021	n/a		
IB/0100	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	19/08/2021	n/a		
IA/0096/G	This was an application for a group of variations. B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the dossier) - Deletion of a supplier B.I.d.1.c - Stability of AS - Change in the re-test	15/06/2021	n/a		

	period/storage period or storage conditions - Change to an approved stability protocol				
IA/0097/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised	07/06/2021	n/a		
II/0094	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	03/06/2021	n/a		
II/0092	Submission of an updated RMP version 40 in order to add an alternative pregnancy exposure study (Study 213928) as a Catergory 3 study for the missing information on limited data in pregnant and lactating patients. The study is to evaluate pregnancy and infant outcomes for pregnancies in women with SLE exposed to belimumab. The RMP includes also completion date and effectiveness for the DHPC in relation to the important identified risk of psychiatric events including depression and suicidality. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing	06/05/2021	n/a		The existing Belimumab Pregnancy Registry (BEL114256) will be terminated because of recruiting difficulties, as it is unable to address its primary objective of estimating the birth defect prevalence with adequate precision. Instead, the MAH will launch an alternative Pregnancy Exposure Study (213928) using the Organization of Teratology Information Specialists (OTIS) Research Center including both a belimumab-exposed and unexposed SLE cohort and using their existing infrastructure to offer adequate and timely enrolment and representativeness of the population. The DHPC in relation to the important identified risk of psychiatric events is removed from the additional risk

	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				minimisation measures.
II/0080	Extension of indication to include treatment of lupus nephritis for belimumab; as a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 38 of the RMP has also been submitted. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	25/03/2021	30/04/2021	SmPC and PL	Please refer to scientific discussion (EMEA/H/C/002015/II/0080).
IB/0093/G	This was an application for a group of variations. B.II.b.z - Change in manufacture of the Finished Product - Other variation B.II.b.z - Change in manufacture of the Finished Product - Other variation	06/04/2021	07/06/2022	Annex II and PL	
II/0090	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	04/02/2021	n/a		
N/0089	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	08/01/2021	30/04/2021	PL	

IB/0091	B.II.z - Quality change - Finished product - Other variation	14/12/2020	n/a		
II/0084	B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	06/11/2020	n/a		
IB/0087/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	15/10/2020	n/a		
IB/0086	B.II.b.z - Change in manufacture of the Finished Product - Other variation	08/10/2020	n/a		
PSUSA/9075/202003	Periodic Safety Update EU Single assessment - belimumab	01/10/2020	n/a		PRAC Recommendation - maintenance
IB/0085	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	30/09/2020	n/a		
II/0081	Update of section 5.1 of the SmPC following the identification of an error in the clinical study report for study BEL114055 conducted in paediatric patients. The results for the other efficacy endpoint 'time to first severe flare over 52 weeks' are corrected. In addition, the MAH took the opportunity	17/09/2020	30/04/2021	SmPC and PL	Section 5.1 of the SmPC is updated as follows: Among patients experiencing a severe flare, the median study day of the first severe flare was Day 150 in the Benlysta group and Day 113 in the placebo group. Severe flares were observed in 17.0% of the Benlysta group compared to 35.0% of the placebo group over the 52 weeks of

	to update the list of local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				observation (observed treatment difference = 18.0%; hazard ratio = 0.36, 95% CI: 0.15, 0.86). The updates are made in accordance with the definitions in the Reporting and Analysis Plan. The revised results show lower proportion of patients experiencing severe flares in both treatment groups than in the originally submitted results. The difference is small and has no impact on the interpretation of the efficacy results.
IA/0082/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation 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	29/07/2020	n/a		
II/0077	Update of section 4.2 and 5.1 of the SmPC in order to update the information on elderly patients based on the interim results from study BEL116559 listed as a category 3 study in the RMP; this is a meta-analysis to assess efficacy and safety in elderly subjects treated in selected belimumab studies. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	28/05/2020	26/06/2020	SmPC	Based on the interim results of the meta-analysis (BEL116559) to assess efficacy and safety in elderly subjects treated in selected Benlysta studies, there were no observed differences in efficacy or safety in patients ≥65 years who received Benlysta intravenously or subcutaneously compared to the overall population in placebo-controlled studies. However, the number of patients aged ≥65 years (63 patients for efficacy and 219 for safety) is not sufficient to determine whether they respond differently to younger patients. Therefore, Benlysta should be used with caution in the elderly. Section 4.2 and

					5.1 of the SmPC were updated accordingly.
II/0076	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information based on the final results from study BEL115467 listed as a imposed PASS in the Annex II; a randomized, double-blind, placebo-controlled 52-Week study to assess adverse events of special interest in adults with active, autoantibody-positive systemic lupus erythematosus receiving belimumab. The Annex II and the Package Leaflet are updated accordingly. The RMP was updated to version 37. In addition, the Marketing authorisation holder took the opportunity make minor editorial changes to the Annex II and the label. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/06/2020	30/04/2021	SmPC, Annex II, Labelling and PL	Results of this study by 31/12/2019 were submitted in line with the marketing authorisation holder's obligation listed in the Annex II of the Product Information. As a result, Annex II has been updated to remove the study. In conclusion, the study results showed that the frequency of infections in total, serious infections, pneumonia and tuberculosis were not reported more frequently for Benlysta than for placebo. Benlysta does not seem to confer an increased risk for infections per se but rather a worse outcome of in case a patient has acquired an infection. It was agreed to strengthen section 4.4 and 4.8 of the SmPC to include information on the increased risk for fatal infections as follows. The PL has been updated accordingly. Section 4.4: "In controlled clinical studies, the incidence of serious infections was similar across the Benlysta and placebo groups; however, fatal infections (e.g. pneumonia and sepsis) occurred more frequently in patients receiving Benlysta compared with placebo (see section 4.8). Pneumococcal vaccination should be considered before initiating Benlysta treatment. Benlysta should not be initiated in patients with active serious infections (including serious chronic infections). Physicians should exercise caution and carefully assess if the benefits are expected to outweigh the risks when considering the use of Benlysta in patients with a history of recurrent infection. Physicians should advise patients to contact their health care provider if they develop symptoms of an infection." Section 4.8: "In a randomised, double-blind, 52-week, post-marketing safety study (BEL115467) which assessed

					mortality and specific adverse events in adults, serious infections occurred in 3.7% of patients receiving Benlysta (10 mg/kg intravenously) vs 4.1% of patients receiving placebo. However, fatal infections (e.g. pneumonia and sepsis) occurred in 0.45% (9/2002) of Benlysta-treated patients vs 0.15% (3/2001) of patients receiving placebo, while the incidence of all-cause mortality was 0.50% (10/2002) vs 0.40% (8/2001), respectively. Most fatal infections were observed during the first 20 weeks of treatment with Benlysta."
IB/0078/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	28/05/2020	n/a		
IB/0074/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	20/12/2019	n/a		
II/0073	Submission of the final report from study BEL116027 listed as a category 3 study in the RMP. This is a multi-centre, open-label, non-randomized, efficacy and safety study to evaluate treatment holidays and	12/12/2019	n/a		BEL116027 was Phase 3b, multi-centre, open-label, non-randomized 52-week study to evaluate treatment holidays and rebound phenomenon in adult subjects with active SLE. Subjects were recruited into three study arms:

	rebound phenomenon after treatment with belimumab 10 mg/kg in subjects with low SLE disease activity. The RMP is updated to version 34 to reflect the study results. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				• a treatment holiday group – 6 months off treatment followed by 6 months re-treatment (TH) • a control group – continuous belimumab treatment (TC) • a long-term discontinuation group (LTD) All subjects had received belimumab for at least 6 months. Subjects eligible for treatment holiday were to be clinically stable as defined as SELENA SLEDAI score ≤3, C3 and C4 complement levels at or above the lower limit of normal and on a stable SLE treatment regimen. The study was non-randomised, i.e. the patients and investigators were free to choose between treatment holiday or continuous treatment. Primary efficacy endpoint was time to any SLE Flare as defined as SELENA SLEDAI SLE Flare Index (SFI). The proportion of subjects experiencing an SFI flare was balanced between the groups (4/12 subjects, 33% in the TH group during the TH phase) and TC group (9/29 subjects, 31%). It should be noted that the follow-up time of the TH phase was only 24 weeks as compared to the treatment control group which was 52 weeks. According to a Kaplan-Meier curve, subjects in the TH group were at higher risk for experiencing flares than the TC group. The primary efficacy analysis, the median time to flare, could not be calculated in the TH or TC groups because fewer than half of the patients flared in these groups. The median time to flare among subjects that flared was substantially shorter in the TH group than in the TC group. In summary, treatment holiday was associated with a higher risk for flare and a shorter time to flare than compared to continuous treatment. No subjects in either group developed anti-drug antibodies. However, due to nature of the study (small sample size, non-randomised,

					only descriptive statistics) no firm conclusion can be made. No increased risk for immunogenicity was observed in this limited study. Therefore, no update to the SmPC was warranted by these data.
IA/0075	A.7 - Administrative change - Deletion of manufacturing sites	29/11/2019	n/a		
II/0062	Extension of indication to include patients aged 5 years and older in the current approved indication for Benlysta (belimumab powder for solution for infusion 120 mg/ml and 400 mg/ml) based on the results of the safety, efficacy and pharmacokinetics study in patients aged 5 years to 17 years (BEL114055). As a consequence, sections 4.1, 4.2, 4.4, 4.8, 5.1, 5.2 and 6.6 of the SmPC are updated with safety and efficacy information. Update of sections 4.2, 4.4, 5.1, 5.2 and 6.4 of the SmPC for Benlysta (belimumab, solution for injection in pre-filled pen and pre-filled syringe, 200 mg) to reflect the paediatric data available for the intravenous formulation. The Annex IIIA and the Package Leaflet is updated accordingly. The RMP version 35.0 has been submitted to support this new indication. In addition, the MAH took the opportunity to make some editorial changes in the product information and bring it in line with the latest QRD template version 10.0. C.I.6.a - Change(s) to therapeutic indication(s) -	19/09/2019	21/10/2019	SmPC, Labelling and PL	Please refer to the Scientific Discussion (EMEA/H/C/002015/II/0062).

	Addition of a new therapeutic indication or modification of an approved one				
PSUSA/9075/ 201903	Periodic Safety Update EU Single assessment - belimumab	03/10/2019	n/a		PRAC Recommendation - maintenance
II/0068	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method	12/09/2019	n/a		
IA/0072	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	13/08/2019	n/a		
II/0065	Update of sections 4.4 and 4.8 of the SmPC in order to add a warning on suicidality and depression based on interim results from study BEL115467 listed in the Annex II; this is a Randomized, Double-Blind, Placebo-Controlled 52-Week Study to Assess Adverse Events of Special Interest in Adults with Active, Autoantibody-Positive Systemic Lupus Erythematosus Receiving Belimumab; the Package Leaflet is updated accordingly. The RMP version 30 has also been endorsed. In addition, a Direct Healthcare Professional Communication (DHPC) and a communication plan were endorsed to increase awareness and provide guidance to Healthcare Professionals.	29/05/2019	01/07/2019	SmPC and PL	The SmPC section 4.4 has been updated to include information on the psychiatric disorders (depression, suicidal ideation and behaviour including suicides) reported more frequently in patients receiving Benlysta. Physicians should assess the risk of depression and suicide considering the patient’s medical history and current psychiatric status before treatment with Benlysta and continue to monitor patients during treatment. Physicians should advise patients (and caregivers where appropriate) to contact their health care provider about new or worsening psychiatric symptoms. In patients who experience such symptoms, treatment discontinuation should be considered. Section 4.8 of the SmPC is updated to add suicidal behaviour and suicidal ideation as uncommon psychiatric disorders and to

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				describe these disorders. The Package Leaflet has been updated accordingly. RMP version 30 has also been submitted.
II/0067	Update of section 5.1 of the SmPC for Benlysta 120 mg and 400mg powder for concentrate for solution for infusion based on final results from study BEL115471/ HGS1006-C1112 listed as a category 3 study in the RMP; this is a Phase 3/4, multicenter, randomized, double-blind, placebo-controlled, 52-week study to evaluate the efficacy and safety of belimumab in African-American/Black subjects with systemic lupus erythematosus. Section 5.1 of the SmPC for Benlsyta 200 mg solution for injection was updated to cross refer to those results. Editorial changes were also brought to the section 5.2 of the SmPC for Benlsyta 200 mg solution for injection and the section 5.1 of the SmPC for Benlysta 120 mg and 400mg powder for concentrate for solution for infusion. The RMP was updated to version 31 with the results from study BEL115471/ HGS1006-C1112. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	27/06/2019	21/10/2019	SmPC	Benlysta was administered intravenously to black patients in a randomised (2:1), double-blind, placebo controlled, 52-week Phase III/IV study (EMBRACE). Efficacy was evaluated in 448 patients. The proportion of black patients achieving an SRI-S2K response was higher in patients receiving Benlysta but the difference was not statistically significant compared with placebo. However, consistent with results from other studies, in black patients with high disease activity (low complement and positive anti-dsDNA at baseline, n=141) the SRI-S2K response was 45.1% for Benlysta 10 mg/kg compared with 24.0% for placebo (odds ratio 3.00; 95% CI: 1.35, 6.68).
II/0069/G	This was an application for a group of variations. B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	26/04/2019	n/a		

	control/testing takes place for a biol/immunol product and any of the test methods at the site is a biol/immunol method B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)				
II/0064/G	This was an application for a group of variations. 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.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	26/04/2019	n/a		
IAIN/0066/G	This was an application for a group of variations. 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	08/04/2019	01/07/2019	Annex II and PL	
IB/0063	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing	11/12/2018	n/a		

	authorisation, including the RMP - Other variation				
IB/0061	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	20/11/2018	n/a		
T/0060	Transfer of Marketing Authorisation	12/10/2018	14/11/2018	SmPC, Labelling and PL	
IB/0059	B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product	11/10/2018	n/a		
PSUSA/9075/ 201803	Periodic Safety Update EU Single assessment - belimumab	04/10/2018	n/a		PRAC Recommendation - maintenance
IB/0058	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	01/10/2018	n/a		
IA/0057	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	27/07/2018	n/a		
IA/0056/G	This was an application for a group of variations. A.z - Administrative change - Other variation A.z - Administrative change - Other variation A.z - Administrative change - Other variation	12/07/2018	n/a		

	A.z - Administrative change - Other variation B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation				
IB/0054	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/04/2018	n/a		
II/0052	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	08/03/2018	n/a		
IA/0053	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	10/11/2017	n/a		
X/0046/G	This was an application for a group of variations. Extension of the marketing authorisation concerning: - a new strength: 200 mg - a new pharmaceutical form: solution for injection - a new route of administration: subcutaneous use Type II variation to update sections 4.2, 4.8, 5.1 and 5.2 of the SmPC as a consequence of the data package submitted to support the new proposed solution for injection subcutaneous presentations. The Package Leaflet is updated accordingly. In	14/09/2017	10/11/2017	SmPC, Annex II, Labelling and PL	

	addition, the Marketing authorisation holder (MAH) took the opportunity to bring the PI in line with the latest QRD template version 10.0 and to introduce some editorial changes. Annex I_2.(c) Change or addition of a new strength/potency Annex I_2.(d) Change or addition of a new pharmaceutical form Annex I_2.(e) Change or addition of a new route of administration C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/9075/ 201703	Periodic Safety Update EU Single assessment - belimumab	28/09/2017	n/a		PRAC Recommendation - maintenance
IB/0051	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	07/07/2017	n/a		
II/0049	Submission of an updated RMP version 23 in order to amend the CSR availability timeline, patient number and the primary and secondary endpoints listed in the EU Risk Management Plan, with regards to study HGS1006-C1121/BEL114054. 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	05/05/2017	n/a		

	by new additional data to be submitted by the MAH where significant assessment is required				
IB/0048/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation	20/04/2017	n/a		
II/0047	Submission of the final report from study LBSL99/BEL112626 listed as a category 3 study in the RMP (MEA010). This is "A Multi-Center, Open Label, Continuation Trial of Monoclonal Anti-Blys Antibody in Subjects with SLE who completed the phase 2 Protocol LBSL02". As a result, an updated RMP (version 20) was submitted. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	23/03/2017	n/a		
PSUSA/9075/ 201603	Periodic Safety Update EU Single assessment - belimumab	29/09/2016	n/a		PRAC Recommendation - maintenance
II/0045	Submission of a revised RMP (finally agreed version: 20) in order to amend the Risk Management Plan concerning the details of the category 3 study	15/09/2016	n/a		

	BEL115471: A Phase 3/4, Multi-Center, Double-Blind, Randomized, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006-C1112/ BEL115471) in Adult Subjects of Black Race with SLE. The final due date of the study is proposed to be changed. 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				
II/0044	Update of sections 6.3 and 6.6 of the SmPC in order to update the product information text in relation to compatibility with reconstitution diluents and container closure system and regarding compatibility with needle gauge. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives for Norway and Iceland in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/09/2016	20/03/2017	SmPC and PL	It is recommended that a 21-25 gauge needle be used when piercing the vial stopper for reconstitution and dilution. The reconstituted medicinal product is diluted to 250 ml with sodium chloride 9 mg/ml (0.9%), sodium chloride 4.5 mg/ml (0.45%), or Lactated Ringer's solution for injection.
II/0043	Update of sections 4.9 of the SmPC in order to update the product information text in relation to overdose.	15/09/2016	20/03/2017	SmPC	There is limited clinical experience with overdose of Benlysta. Adverse reactions reported in association with cases of overdose have been consistent with those

	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				expected for belimumab.
II/0039	Update of section 4.6 of the SmPC in order to update the information relating to pregnancy and lactation following review of all available relevant data. 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	14/07/2016	20/03/2017	SmPC and PL	Benlysta should not be used during pregnancy unless the potential benefit justifies the potential risk to the foetus.
II/0038	Update of sections 4.4 and 4.8 of the SmPC in order to update the safety information on infections in patients receiving immunosuppressant therapy. 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	14/07/2016	20/03/2017	SmPC and PL	The mechanism of action of belimumab could increase the risk for the development of infections, including opportunistic infections. Severe infections, including fatal cases, have been reported in SLE patients receiving immunosuppressant therapy, including belimumab. Physicians should exercise caution when considering the use of Benlysta in patients with severe or chronic infections or a history of recurrent infection. Patients who develop an infection while undergoing treatment with Benlysta should be monitored closely and careful consideration given to interrupting immunosuppressant therapy including belimumab until the infection is resolved. The risk of using Benlysta in patients with active or latent tuberculosis is unknown.
II/0041/G	This was an application for a group of variations. Submission of a revised RMP (final version agreed 19.0) in order to update the following information:	23/06/2016	n/a		

	• changes the scope of the Benlysta Pregnancy registry BEL114256 (category 3 study) • to amend the due dates to Benlysta study HGS1006-C1074 and BEL116559 In addition, the Marketing authorisation holder (MAH) took the opportunity to correctly reflect the status of the Study BEL116027 (treatment Holiday) as ongoing whereas before the status was planned. 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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation				
II/0040	Update of section 4.4 of the SmPC in order to add information on effect of Benlysta on vaccine responses in subjects with systemic lupus erythematosus (SLE) based on results from study BEL115470 (HGS1006-C1117) which fulfils MEA 4.3. The RMP is updated accordingly to version 19. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	23/06/2016	20/03/2017	SmPC	Because of its mechanism of action, belimumab may interfere with the response to immunisations. However, in a small study evaluating the response to a 23-valent pneumococcal vaccine, overall immune responses to the different serotypes were similar in SLE patients receiving Benlysta compared with those receiving standard immunosuppressive treatment at the time of vaccination. There are insufficient data to draw conclusions regarding response to other vaccines.

II/0037	Update of section 5.1 of the SmPC in order to update pharmacodynamic information as a result of the completed efficacy/safety Phase 3 continuation study BEL112233 (HGS1006-C1066) which fulfils MEA 011. The RMP has been updated (version 16.0) to reflect the completed milestone for this study and to update the information on long-term effects of belimumab on B cells which was an element of 'missing information'. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	01/04/2016	20/03/2017	SmPC	Changes in B cells (including naïve, memory and activated B cells, and plasma cells) and IgG levels occurring in patients during ongoing treatment with intravenous belimumab were followed in a long-term uncontrolled extension study. After 7 and a half years of treatment (including the 72-week parent study), a substantial and sustained decrease in various B cell subsets was observed leading to 87% median reduction in naïve B cells, 67% in memory B cells, 99% in activated B cells, and 92% median reduction in plasma cells after more than 7 years of treatment. After about 7 years, a 28% median reduction in IgG levels was observed, with 1.6% of subjects experiencing a decrease in IgG levels to below 400 mg/dl. Over the course of the study, the reported incidence of AEs generally remained stable or declined.
R/0036	Renewal of the marketing authorisation.	17/12/2015	18/02/2016	SmPC, Annex II, Labelling and PL	
PSUSA/9075/ 201503	Periodic Safety Update EU Single assessment - belimumab	08/10/2015	n/a		PRAC Recommendation - maintenance
IA/0035	A.7 - Administrative change - Deletion of manufacturing sites	06/07/2015	n/a		
IB/0033	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	02/06/2015	n/a		
PSUSA/9075/ 201409	Periodic Safety Update EU Single assessment - belimumab	10/04/2015	n/a		PRAC Recommendation - maintenance

II/0031/G	This was an application for a group of variations. 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 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	22/01/2015	n/a		
PSUV/0026	Periodic Safety Update	09/10/2014	n/a		PRAC Recommendation - maintenance
IB/0030/G	This was an application for a group of variations. C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	01/10/2014	24/04/2015	Annex II	

IB/0029	A.7 - Administrative change - Deletion of manufacturing sites	13/08/2014	n/a		
IA/0028/G	This was an application for a group of variations. 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.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	29/07/2014	n/a		
IB/0027	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	27/06/2014	n/a		
IA/0025/G	This was an application for a group of variations. 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.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	25/06/2014	n/a		

IB/0024	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	11/06/2014	n/a		
II/0023	Update of section 4.4 of the SmPC to add a warning regarding Progressive Multifocal Leukoencephalopathy. The Package leaflet is updated accordingly. A clarification has also been added to section 4.8 of the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/04/2014	24/04/2015	SmPC, Labelling and PL	Review of post marketing safety data for Benlysta indicated 2 cases of Progressive Multifocal Leukoencephalopathy. Both patients received other immunosuppressive treatment as well (MMF, steroids, cyclophosphamide). The CHMP concluded that a causal relationship with belimumab is not firmly established and recommended the addition of a warning the product information mentioning that PML has been reported with Benlysta treatment for SLE.
PSUV/0021	Periodic Safety Update	10/04/2014	n/a		PRAC Recommendation - maintenance
II/0022	Changes to 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 substance which may have a significant impact on the medicinal product and is not related to a protocol	20/03/2014	n/a		
IB/0020	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	13/01/2014	n/a		
PSUV/0019	Periodic Safety Update	24/10/2013	17/12/2013	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for

					PSUV/0019.
IB/0018	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	09/08/2013	n/a		
IB/0017	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	14/05/2013	n/a		
IB/0016	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol	14/05/2013	17/12/2013	SmPC	
IG/0279	A.1 - Administrative change - Change in the name and/or address of the MAH	18/04/2013	15/07/2013	SmPC, Labelling and PL	
II/0013	Update, as requested by CHMP after assessment of FUM 005, of section 5.1 of the SmPC to introduce information on Pharmacodynamic effects of Belimumab on Circulating B cells and IgG levels. The MAH updated also the annex II according to the v8.3 of the QRD template. The MAH took also the occasion for revising the contact details of the local representative of Poland and for correcting some minor typographical errors in the PI.	21/03/2013	15/07/2013	SmPC, Annex II and PL	As requested by the CHMP in a post authorisation commitment B cell and B cell subset data were collected in a international Phase 3 Study and in one Phase 3 extension study. The data showed that beyond the first 76 weeks of treatment, B cell reductions either stabilize (as for naïve and plasma B cells), or continue to gradually decrease (as for CD19+ /C20+ B cells, memory cells, plasmacytoid B cells) ultimately leading to net reductions of about 80-90% for naïve as well as CD19/CD20+ B cells and of about 50-

	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				60% for plasma cells after 3 years of continued belimumab dosing. Furthermore a 20% to 30% median reduction in IgG levels after 3 years of treatment were observed. The SmPC of Benlysta was updated accordingly with this information on pharmacodynamic effects.
IG/0275	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	15/03/2013	n/a		
II/0011/G	This was an application for a group of variations. Changes to the control of the active substance and finished product. This was an application for a group of variations. 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.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	21/02/2013	n/a		
II/0010/G	This was an application for a group of variations. Changes to the control of the active substance and finished product. This was an application for a group of variations.	21/02/2013	n/a		

	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.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				
IA/0012	B.II.c.1.a - Change in the specification parameters and/or limits of an excipient - Tightening of specification limits	09/01/2013	n/a		
II/0006	Update of the obligation included in Annex II in order to change the design and the due date of the post-marketing safety study. This variation is submitted following the assessment of FUM 003. Furthermore, the MAH proposed changes related to the implementation of the new QRD template v8.0. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/09/2012	24/10/2012	Annex II	As a condition to approval, the MAH was originally required to provide 5-year data from a randomized, controlled large safety study. In this variation procedure, the MAH proposed a change to the original safety study of long-term belimumab exposure which will be now assessed in a set of two studies: • a 1-year randomized, double-blind, placebo-controlled safety study in 5000 patients investigating the incidence of all-cause mortality and adverse events of special interest including serious infections (including non-serious and serious opportunistic infections and PML) malignancies (including non-melanoma skin cancer), serious infusion and hypersensitivity reactions, and serious psychiatric events including mood disorders, anxiety and suicide. • a large, prospective, controlled, observational registry where 2000 patients receiving commercial belimumab will be followed for 5 years to estimate the

					incidence of all-cause mortality and the incidence of rare events, such as malignancies, selected serious psychiatric events as well as serious infections (including opportunistic infections and PML) as compared with 1000 patients of the control group. The new design and due dates as proposed by the MAH are considered acceptable by the CHMP. The CHMP considers that these two studies will satisfy the need for additional safety data as determined at time of initially requesting the conduct of a large 5-year randomised controlled safety study therefore replacing the previously agreed study against these two studies is accepted.
II/0005	Update of 4.8 of the SmPC regarding frequency of infections. The PIL is being updated accordingly. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	19/04/2012	25/05/2012	SmPC and PL	The changes have been requested by the applicant based on previously available data in consideration of a revised safety primary data for introducing a clearer implication of bacterial infections and their frequency during the use of Benlysta. Following further clarification and the provision of necessary information, the CHMP agreed to the proposed SmPC changes introducing the term bacterial infections with the frequency “very common”.
IG/0150/G	This was an application for a group of variations. C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	05/04/2012	n/a		

II/0004	Update of sections 4.2, 4.4, and 4.8 of the SmPC in order to update the safety information regarding hypersensitivity and infusion reactions. The Package Leaflet is updated in accordance. In addition, the MAH took this opportunity to introduce minor editorial changes in section 5.1 and 6.6 of the SmPC and to update the list of local representatives in the Package Leaflet. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	16/02/2012	19/03/2012	SmPC and PL	Following review of a total of 18 spontaneous post-marketing reports of serious hypersensitivity reactions, an update of the product information was agreed to strengthen the warning regarding potentially serious and life-threatening hypersensitivity and infusion reactions after Benlysta administration. Symptoms may develop or reoccur in a delayed fashion, several hours after completion of the infusion. Currently available data do not seem to indicate a predictive pattern linking infusion reactions to certain characteristics pertaining to, for example, history of allergies, medical history or concomitant medications. Therefore, patients should remain under prolonged clinical supervision following administration of Benlysta. A DHPC and communication plan has been agreed with the CHMP and will be sent to Health Care Professionals to increase awareness about this safety issue and the revised prescriber information.
II/0002	New facility for the manufacture of the finished product B.II.g.2 - Design Space - Introduction of a post approval change management protocol related to the finished product	16/02/2012	16/02/2012		
IB/0008	B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	13/01/2012	n/a		
IB/0003	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	09/01/2012	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0007	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Extension of storage period of a biological/immunological medicinal product in accordance with an approved stability protocol	05/01/2012	19/03/2012	SmPC	Extension of the shelf life of the finished product in unopen vials, at the recommended storage conditions of 2-8°C, from 36 months to 48 months.
II/0001	Changes to the manufacture of the finished product B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	15/12/2011	15/12/2011		