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
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	14/09/2017	10/11/2017	SmPC, Annex II, Labelling and PL	

[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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	- 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 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	05/05/2017	n/a		

	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 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 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	15/09/2016	n/a		
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	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.

	new quality, preclinical, clinical or pharmacovigilance data				
II/0043	Update of sections 4.9 of the SmPC in order to update the product information text in relation to overdose. 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	There is limited clinical experience with overdose of Benlysta. Adverse reactions reported in association with cases of overdose have been consistent with those 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: • 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	23/06/2016	n/a		
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	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

	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				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	01/10/2014	24/04/2015	Annex II	

	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				
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	25/06/2014	n/a		

	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				
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	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.

	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. 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				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 50-60% 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. 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		
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	05/04/2012	n/a		

	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				
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	13/01/2012	n/a		

	re-test period/storage period supported by real time data				
IB/0003	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	09/01/2012	n/a		
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		