Flixabi

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/0077/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	12/01/2023	n/a		

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

	method at the site is a biol/immunol method 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				
IA/0080	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	12/12/2022	n/a		
IB/0076	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	02/12/2022	n/a		
IB/0075	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	30/11/2022	n/a		
N/0079	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/11/2022		PL	
IB/0074	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	07/06/2022		SmPC, Labelling and PL	

IA/0073	A.7 - Administrative change - Deletion of manufacturing sites	08/02/2022	29/04/2022	Annex II and PL	
IB/0071/G	This was an application for a group of variations. 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 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	14/12/2021	29/04/2022	SmPC, Annex II, Labelling and PL	
IA/0072	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)	06/12/2021	n/a		
IAIN/0070	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	13/07/2021	29/04/2022	Annex II and PL	
IB/0068	B.I.b.2.e - Change in test procedure for AS or	01/06/2021	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0069	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	23/04/2021	n/a		
IAIN/0067/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient B.II.b.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 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 A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	12/04/2021	29/04/2022	Annex II and PL	

	A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release)				
R/0064	Renewal of the marketing authorisation.	10/12/2020	11/02/2021	SmPC, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Flixabi in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0066	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	21/12/2020	n/a		
IB/0063	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	23/10/2020	n/a		
IAIN/0065	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	09/10/2020	20/11/2020	SmPC and PL	
II/0062	B.II.b.5.e - Change to in-process tests or limits applied during the manufacture of the finished product - Widening of the approved IPC limits, which may have a significant effect on overall quality of the finished product	24/09/2020	n/a		
IB/0059	B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	02/07/2020	n/a		

IA/0061/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites	22/06/2020	n/a		
IB/0060	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	10/06/2020	n/a		
II/0052	Update of the RMP to replace the prospective observational cohort study of Flixabi in patients with Crohn's disease (CD) (SB2-G42-CD), with real-world data from CREDIT and CEDUR studies. 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	14/05/2020	n/a		Study SB2-G42-CD was included as a category 3 PASS at the time of marketing authorisation of this infliximab biosimilar, in order to monitor the efficacy, safety and immunogenicity (potential risk of loss of efficacy due to ADA development of Flixabi) in CD patients. The MAH argued that the value of SB2-G42-CD study needed to be reconsidered with prudent evaluation of the currently available and future Flixabi study and real-world data. The MAH evaluated data available to date, including 78-week extension phase data from the phase 3 pivotal clinical study (SB2-G31-RA), data from the company safety database, and real-world data from post-approval studies. Results from the 78-week extension phase of SB2-G31-RA demonstrated maintenance of efficacy among the three treatment groups (SB2/SB2 vs Remicade/Remicade vs Remicade/SB2). In addition, analyses on the data from the company safety database regarding immunogenicity did not suggest an increased risk of Flixabi as the frequencies of

					major AEs related to immunogenicity were comparable to those of other infliximab products. From the data from the post-approval studies, there was no evidence indicating increased immunogenicity or decreased efficacy after switching to Flixabi from other infliximab. The quality and quantity of study and real-world data for Flixabi are considered adequate to replace the previously proposed SB2-G42-CD study comparing the immunogenicity and efficacy between Flixabi and Remicade in 200 patients with CD (100 per group) over 104 weeks. CEDUR and CREDIT registries, enrolling IBD patients using TNF alpha inhibitor, recently have been approved to be included in Flixabi RMP as PASS. Even though ADA level is not available in the two registries, immunogenicity-related efficacy and majority of AE/SAEs in IBD patients will be collected and analysed in both registries. Upon completion of CEDUR and CREDIT registries, 5-year or more long-term real-world data of Flixabi in safety and efficacy will be obtainable. Therefore, the CHMP endorsed that SB2-G42-CD study could be replaced by submitting the final reports of the two currently RMP-committed ongoing PASS: CREDIT and CEDUR both conducted in IBD patients.
IB/0058	B.III.2.z - Change to comply with Ph. Eur. or with a national pharmacopoeia of a Member State - Other variation	12/05/2020	n/a		
IB/0055	B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	27/04/2020	n/a		

IB/0056	B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	25/04/2020	20/11/2020	SmPC and PL	
PSUSA/10759 /201908	Periodic Safety Update EU Single assessment - infliximab	17/04/2020	n/a		PRAC Recommendation - maintenance
IB/0057	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	07/04/2020	n/a		
II/0053	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	26/03/2020	n/a		
IB/0050	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	03/12/2019	20/11/2020	SmPC and PL	
IA/0049/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	25/11/2019	n/a		

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.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	12/11/2019	n/a		
II/0039	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	31/10/2019	n/a		
IB/0046	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	10/10/2019	22/11/2019	Annex II and Labelling	
IB/0047	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	16/09/2019	n/a		
II/0034	B.I.a.1.e - Change in the manufacturer of AS or of a	18/07/2019	22/11/2019	Annex II	

	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				
II/0038	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	20/06/2019	n/a		
IB/0045	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	03/05/2019	22/11/2019	SmPC and PL	
II/0031	B.II.b.1.d - Replacement or addition of a manufacturing site for the FP - Site which requires an initial or product specific inspection	26/04/2019	n/a		
IAIN/0044	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/04/2019	22/11/2019	SmPC and PL	
IB/0042	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	08/03/2019	n/a		
IA/0041	B.II.d.2.a - Change in test procedure for the finished	13/02/2019	n/a		

	product - Minor changes to an approved test procedure				
IAIN/0040/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	01/02/2019	22/11/2019	SmPC, Labelling and PL	
IB/0037/G	This was an application for a group of variations. 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 C.I.11.z - Introduction of, or change(s) to, the	29/01/2019	22/11/2019	SmPC, Annex II, Labelling and PL	

	obligations and conditions of a marketing authorisation, including the RMP - Other variation				
IB/0036	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	07/01/2019	22/11/2019	SmPC	
IA/0035	B.II.f.1.e - Stability of FP - Change to an approved stability protocol	20/12/2018	n/a		
IB/0033/G	This was an application for a group of variations. 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 C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	05/12/2018	22/11/2019	SmPC and PL	
T/0032	Transfer of Marketing Authorisation	02/10/2018	08/11/2018	SmPC, Labelling and PL	
PSUSA/10106 /201801	Periodic Safety Update EU Single assessment - infliximab (biosimilars)	06/09/2018	n/a		PRAC Recommendation - maintenance
IB/0030	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other	09/08/2018	n/a		

	changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0028	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	08/08/2018	n/a		
IB/0029/G	This was an application for a group of variations. 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 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	06/08/2018	08/11/2018	SmPC, Labelling and PL	
II/0020	Update of section 6.3 and 6.4 of the SmPC to change the storage condition of Fixabi. The package leaflet is updated accordingly. B.II.f.1.c - Stability of FP - Change in storage conditions for biological medicinal products, when the stability studies have not been performed in accordance with an approved stability protocol	07/06/2018	08/11/2018	SmPC, Labelling and PL	The product information has been amended to reflect that Fixabi can be stored at room temperature (up to a maximum of 25°C) for a single period up to 6 months, but not exceeding the original expiry date. Upon removal from refrigerated storage, Fixabi must not be returned to refrigerated storage.

II/0025	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	17/05/2018	n/a		
IAIN/0024	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	06/03/2018	n/a		
IB/0022	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	21/02/2018	n/a		
IB/0023	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	20/02/2018	08/05/2018	SmPC and PL	
IA/0021	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	15/12/2017	n/a		
II/0013/G	This was an application for a group of variations.	19/10/2017	n/a		

	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.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.b.4.c - Change in the batch size (including batch size ranges) of the finished product - The change requires assessment of the comparability of a biological/immunological medicinal product or a new bioequivalence study B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range				
PSUSA/10106 /201701	Periodic Safety Update EU Single assessment - infliximab (biosimilars)	01/09/2017	n/a		PRAC Recommendation - maintenance
IAIN/0019	A.1 - Administrative change - Change in the name and/or address of the MAH	14/07/2017	08/05/2018	SmPC, Labelling and PL	
IB/0018	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	21/06/2017	n/a		
IB/0016	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a	21/06/2017	n/a		

	biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)				
IB/0017	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	26/05/2017	08/05/2018	SmPC and PL	
IA/0014/G	This was an application for a group of variations. B.II.e.6.b - Change in any part of the (primary) packaging material not in contact with the finished product formulation - Change that does not affect the product information B.II.e.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	26/04/2017	n/a		
II/0009	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	21/04/2017	n/a		Data up to week 54 from study SB2-G31-RA was submitted as part of the initial Marketing Authorisation. The MAH has submitted with this variation data from the extension phase up to week 78. Subjects were enrolled in the transition-extension period for up to 24 weeks after Week 54 of the randomised, double-blind period. At Week 54, subjects receiving Remicade® from the randomised, double-blind period of the SB2-G31-RA study were randomised again in a 1:1 ratio to either continue on Remicade® (Remicade®/Remicade® = 101 patients) or be transitioned

					to SB2 (Remicade®/SB2 = 94) up to Week 70 and this was compared to patients that remained on SB2 (= 201 Patients). The trial was powered for ACR 20 comparison and this measure is of importance when looking at long term therapeutic effect. The observed ACR 20 at 78 weeks of 68.3% (SB2/SB2) vs 68.8% (R/R) vs 63.5% (R/S) values are comparable between the three arms in the per-protocol analyses, and there are still considerable number of patients in follow up with only 15 % attrition, so results were considered relevant. The observed ACR 50 at 78 weeks was 40.6% (SB2/SB2) vs 47.3 (R/R) vs 37.6% (R/S) values are comparable between the three arms. The observed ACR 70 at 78 weeks was 25.6% (SB2/SB2) vs 31.2 (R/R) vs 22.4% (R/S) values are comparable between the three arms with minor differences likely reflecting assay variability in the range of what has been observed before. It is notable that patients who were switched from Remicade to SB2 (R/S) consistently (= ACR 20, 50 and 70) fare somewhat worse in the order of -5 to -10% for week 70 and week 78 data. On the other hand, the R/S patients had better ACR 20,50 and 70 measurements for weeks 54 and 62 in the range of + 2 to + 6%, so variation in the range of up to 10% could also be a chance finding. The ACR 20 time response curves demonstrate maintenance of therapeutic efficacy over the observed time period of 78 weeks which indicates biosimilarity and also no adverse effect of switching. The secondary endpoints ACR-N, EULAR response and also DAS28 all indicate maintained efficacy at week 78 in a similar range for SB2 and Remicade, regardless of

					switching: In the SB2/SB2 treatment group, the mean change in DAS28 score from Week 0 to Week 78 was 2.6189 and from Week 54 to Week 78 was 0.1262.The mean change in DAS28 score from Week 0 to Week 78 was 2.5228 in the Remicade®/SB2 treatment group and 2.5844 in the Remicade®/Remicade® treatment group. The mean change in DAS28 score from Week 54 to Week 78 was −0.1226 in the Remicade®/SB2 treatment group and 0.1238 in the Remicade®/Remicade® treatment group. Regarding immunogenicity, there is still a difference of about 4 to 7% more ADA positive patients at later time points (62, 70, 78 weeks) when treating with SB2 as compared to Remicade only. Up to Week 78, there is no statistically significant or clinically meaningful difference between treatment groups in the proportion of subjects with ADA positive results against SB2. Interestingly, patients who were switched from Remicade to SB2 seem to be less frequently ADA positive, e.g.: at week 78 SB2 (S/S): 47.1% versus R/S:38.5% versus R/R: 40.4% which would support the view that any seemingly negative effects on efficacy parameters are not due to ADAs. However with the lack of any other reasonable explanation on the quality level, this data indicates that differences in ADA positivity observed at the 10% level, may be due to normal variability, which are not considered clinically meaningful. Also, there is no unidirectional trend of therapeutic effect with % patients who are ADA positive, e.g. ACR 50 levels at 78 weeks demonstrate effect for S/S 40.6% vs R/R 47.3% vs R/S 37.6% but the ADA positive rate is 66.2%;

					62.8% vs 61.5%, respectively. In conclusion, up to Week 78, there is no statistically significant or clinically meaningful difference between treatment groups in the proportion of subjects with ADA positive results against SB2:. Furthermore, (a) there is no clear pattern of differences regarding efficacy parameters of switched and unswitched patients (ACR 20, 50,70) and (b) there is no unidirectional trend of therapeutic effect for switched versus unswitched patients who are ADA positive plus (c) the treatment effect is maintained at the overall population level (i.e. all patients, irrespective of ADA positivity). In summary, the efficacy variables for the transition-extension period (ACR20, ACR50 and ACR70 response, continuous ACR-N, change of DAS28 score from Week 0 and EULAR response) were generally comparable between the SB2/SB2, Remicade®/SB2 and Remicade®/Remicade® treatment groups and the observed differences in immunogenicity may likely be viewed as minor and not clinically meaningful. These findings are in support of previous findings observed at week 30 and week 54, regardless of switching.
IAIN/0012	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	21/03/2017	n/a		
IAIN/0011	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	17/02/2017	n/a		

IB/0010	B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS	05/01/2017	n/a		
II/0003	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	10/11/2016	n/a		
IB/0008	B.II.f.1.b.5 - Stability of FP - Extension of the shelf life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol	11/10/2016	23/06/2017	SmPC and Labelling	
IB/0005	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	03/10/2016	n/a		
IB/0006/G	This was an application for a group of variations. 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 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	23/09/2016	n/a		
IB/0007	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	09/09/2016	23/06/2017	SmPC and PL	

	new additional data is required to be submitted by the MAH				
IAIN/0004/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.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.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	24/08/2016	n/a		
IA/0002/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites	19/08/2016	n/a		

	(excluding manufacturer for batch release)				
IB/0001/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	17/06/2016	23/06/2017	SmPC, Labelling and PL	