Strensiq

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
S/0066	8th annual re-assessment	14/12/2023	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Strensiq should be maintained.

[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).

II/0065/G	This was an application for a group of variations. B.I.a.1.e - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The change relates to a biological AS or a starting material [-] used in the manufacture of a biological/immunological product B.I.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	19/10/2023		Annex II	Annex II.A has been updated include the name and address of the manufacturer of the biological active substance: Alexion Pharma International Operations Limited College Business and Technology Park, Blanchardstown Dublin 15 Ireland
IB/0063	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	19/04/2023	n/a		
IB/0062	B.II.e.4.c - Change in shape or dimensions of the container or closure (immediate packaging) - Sterile medicinal products	02/03/2023	n/a		
IAIN/0064/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.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	13/02/2023		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)				
PSUSA/10421 /202207	Periodic Safety Update EU Single assessment - asfotase alfa	09/02/2023	n/a		PRAC Recommendation - maintenance
S/0059	7th annual re-assessment	15/12/2022	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Strensiq should be maintained.
II/0060/G	This was an application for a group of variations. Please refer to the Recommendations section B.II.e.2.a - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Tightening of specification limits A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.b.1.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	24/11/2022	n/a		Not applicable

	B.II.e.2.c - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the finished product, including quality control sites (excluding manufacturer for batch release) B.II.e.3.a - Change in test procedure for the immediate packaging of the finished product - Minor changes to an approved test procedure				
IB/0058	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	26/04/2022	n/a		
PSUSA/10421 /202107	Periodic Safety Update EU Single assessment - asfotase alfa	10/02/2022	n/a		PRAC Recommendation - maintenance
S/0056	6th annual re-assessment	16/12/2021	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Strensiq should be maintained.
IB/0055/G	This was an application for a group of variations. B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure A.7 - Administrative change - Deletion of	15/09/2021	n/a		

	manufacturing sites B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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				
IB/0054	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/06/2021	01/07/2022	SmPC and PL	
IA/0053	A.7 - Administrative change - Deletion of manufacturing sites	15/02/2021	n/a		
PSUSA/10421 /202007	Periodic Safety Update EU Single assessment - asfotase alfa	11/02/2021	n/a		PRAC Recommendation - maintenance
II/0050	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	14/01/2021	n/a		
IB/0052	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	17/12/2020	n/a		
S/0048	5th annual re-assessment	10/12/2020	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data

					submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Strensiq should be maintained.
II/0047	Update of section 5.1 of the SmPC in order to remove the Paediatric Investigation Plan (PIP) compliance statement as per Article 28(3) of Regulation (EC) No 1901/2006, following submission of the results and reports of all the PIP measures, including results of the Extrapolation Study AXN100107PIP ("Extrapolation of Efficacy to Asfotase Alfa Treatment in Paediatric Patients Ages 6 months to <3 years with Juvenile-Onset Hypophosphatasia"). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/10/2020	24/11/2020	SmPC	Please refer to the Scientific Discussion Strensiq EMEA/H/C/003794/II/0047.
IB/0051	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	20/11/2020	n/a		
II/0046	B.I.b.2.d - Change in test procedure for AS or starting material/reagent/intermediate - Substantial change to or replacement of a biological/immunological/immunochemical test method or a method using a biological reagent for a biological AS	03/09/2020	n/a		
IB/0045/G	This was an application for a group of variations. B.I.d.1.z - Stability of AS - Change in the re-test	01/09/2020	24/11/2020	SmPC	

	period/storage period or storage conditions - Other variation B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation				
R/0044	Renewal of the marketing authorisation.	27/02/2020	28/04/2020	SmPC, Annex II, Labelling and PL	
PSUSA/10421 /201907	Periodic Safety Update EU Single assessment - asfotase alfa	16/01/2020	n/a		PRAC Recommendation - maintenance
II/0043/G	This was an application for a group of variations. B.II.f.1.z - Stability of FP - Change in the shelf-life or storage conditions of the finished product - Other variation C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	12/12/2019	28/04/2020	SmPC, Annex II and PL	
S/0041	4th annual re-assessment	12/12/2019	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Strensiq should be maintained.
IB/0039/G	This was an application for a group of variations.	05/09/2019	n/a		

	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.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.i - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Where there is no monograph in the European/National Ph. for the AS, a change in specification from in-house to a non-official/third country Ph.				
IAIN/0040	A.1 - Administrative change - Change in the name and/or address of the MAH	25/07/2019	28/04/2020	SmPC, Labelling and PL	
II/0035/G	This was an application for a group of variations. Update of sections 4.4, 4.6, 4.8 and 5.2 of the SmPC with the results of the integrated safety analysis of pooled asfotase alfa clinical studies, and section 5.1 of the SmPC with the final results of study ENB-002-08/ENB-003-08 (an open-label, non-randomised, non-controlled study) and study ENB-010-10 (a controlled, open label study to evaluate the efficacy, safety, and PK of asfotase alfa in infants and children	25/07/2019	28/04/2020	SmPC and PL	The pooled safety data reflect exposure in 112 patients with perinatal/infantile (n=89), juvenile-onset (n = 22), adult onset (n = 1) HPP (age at enrolment from 1 day to 66.5 years) treated with asfotase alfa, with a treatment duration range from 1 day to 391.9 weeks [7.5 years]). A few case reports of anaphylactoid/hypersensitivity reaction have been received in the clinical trial setting. Localized lipodystrophy, including lipoatrophy and lipohypertrophy, has been reported at injection sites after several months in patients treated with Strensiq in clinical

	≤ 5 years of age with hypophosphatasia (HPP)). The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to implement editorial changes in the SmPC and Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				trials. The majority of patients who experienced an injection site reaction had the first occurrence within the first 12 weeks of treatment with asfotase alfa, and some patients continued to experience injection site reactions until 1 or more years after initiating asfotase alfa dosing. These have been generally assessed as non-serious, mild to moderate in severity and self-limiting. The ADRs Hypocalcaemia and Nephrolithiasis were observed with a frequency of common and have been added to SmPC section 4.8. Study ENB-010-10 was a controlled open-label study in 69 patients, aged 1 day to 72 months, with perinatal/infantile-onset HPP. The mean age at sign/symptom onset was 1.49 months. Patients received Strensiq at 6 mg/kg per week for the first 4 weeks. All patients began the study on a dose of asfotase alfa 6 mg/kg per week. The dose of asfotase alfa was increased for 11 patients during the study. Of these 11 patients, 9 patients had their doses increased specifically to improve clinical response. Thirty-eight patients were treated for at least 2 years (24 months) and 6 patients have been treated for at least 5 years (60 months). At Week 48, 50/69 patients (72.5%) in the full analysis set achieved Radiographic Global Impression of Change scores ≥ 2, and were considered responders. Improvements in median RGI-C were maintained over the course of treatment, which ranged from 0.9 to 302.3 weeks, even if fewer patients were followed after Week 96 (a total of 29 patients were followed after Week 96 and ≤8 patients after Week 192). Height, weight and head circumference were plotted on growth charts (series of percentile curves that illustrate

					distribution) available from the Centers for Disease Control and Prevention (CDC), USA. A total of 24/69 (35%) patients displayed apparent catch-up height-gain and 32/69 (46%) patients displayed apparent catch-up weight-gain, as shown by movement over time to a higher percentile on CDC growth charts. 40/69 patients and 32/69 patients did not show apparent catch-up gain in height and in weight, respectively. 4 patients did not have enough data to permit judgement and 1 patient could not be determined with certainty. Please refer to the updated section 5.1 of the SmPC for the final results of study ENB-002-08/ENB-003-08. SmPC section 5.2 has been updated to reflect the fact that in adult patients with pediatric-onset HPP, the pharmacokinetics of asfotase alfa at doses of 0.5, 2 and 3 mg/kg administered three times per week was consistent with those observed in pediatric patients with pediatric-onset HPP, and thus supported the approved dose of 6 mg/kg per week in treating adult patients with pediatric-onset HPP.
PSUSA/10421 /201901	Periodic Safety Update EU Single assessment - asfotase alfa	11/07/2019	n/a		PRAC Recommendation - maintenance
IB/0038	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	03/06/2019	n/a		
PSUSA/10421 /201807	Periodic Safety Update EU Single assessment - asfotase alfa	31/01/2019	28/03/2019	SmPC and PL	Please refer to asfotase alfa Strensiq PSUSA-10421-201807 EPAR:

					Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IB/0036	B.I.e.5.b - Implementation of changes foreseen in an approved change management protocol - Requires further supportive data	21/01/2019	n/a		
S/0032	3rd annual re-assessment	13/12/2018	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Strensiq should be maintained.
IA/0034/G	This was an application for a group of variations. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	21/11/2018	n/a		
II/0029	Update of annex II after submission of the final report from study AA-HPP-208 listed as a category 1 study in the RMP (ANX001.2). This is a multicentre, randomised, open-label, phase 2a study of Strensiq in patients with hypophosphatasia. The MAH took also the occasion to update the PI to QRD version	13/09/2018	07/01/2019	Annex II and Labelling	

	10.0. 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/0031/G	This was an application for a group of variations. B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation 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	10/08/2018	n/a		
II/0030/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 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	12/07/2018	n/a		

	material/intermediate				
PSUSA/10421 /201801	Periodic Safety Update EU Single assessment - asfotase alfa	12/07/2018	n/a		PRAC Recommendation - maintenance
II/0027/G	This was an application for a group of variations. 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 B.II.e.4.b - Change in shape or dimensions of the container or closure (immediate packaging) - The change in shape or dimensions concerns a fundamental part, which may have a significant impact on the delivery, use, safety or stability of the FP	03/05/2018	07/01/2019	SmPC	
II/0019/G	This was an application for a group of variations. Update of section 5.1 of the SmPC in order to update information following final results from studies ENB-006-09 (and its extension ENB-008-10) and ENB-009-10 listed as an obligation in the Annex II (ANX002). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	25/01/2018	07/01/2019	SmPC and Annex II	The description of studies ENB-006-09 (and its extension ENB-008-10) and ENB-009-10 in section 5.1 of the SmPC was updated to include information on the final composition of patients who completed the studies. Efficacy and safety results were in line with the ones previously reported. For more information please refer to the Summary of Product Characteristics.

	data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
PSUSA/10421 /201707	Periodic Safety Update EU Single assessment - asfotase alfa	11/01/2018	n/a		PRAC Recommendation - maintenance
S/0024	2nd annual re-assessment	14/12/2017	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Strensiq should be maintained.
II/0026/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.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.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting	23/11/2017	n/a		

	material/intermediate/reagent - Tightening of specification limits				
II/0023	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	19/10/2017	n/a		
PSUSA/10421 /201701	Periodic Safety Update EU Single assessment - asfotase alfa	01/09/2017	n/a		PRAC Recommendation - maintenance
IB/0021	B.II.e.1.z - Change in immediate packaging of the finished product - Other variation	30/06/2017	n/a		
II/0018	Update of section 4.5 of the SmPC in order to update the information on Asfotase alfa interaction with the Alkaline Phosphatase (ALP), used as the detection reagent in many routine laboratory assays, which may leading to abnormal values reports. 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	09/06/2017	11/12/2017	SmPC and PL	Alkaline Phosphatase (ALP) is used as the detection reagent in many routine laboratory assays. If asfotase alfa is present in clinical laboratory samples, aberrant values could be reported. The treating physician should inform the testing lab that the patient is treated with medication affecting the ALP levels. Alternative assays (i.e. not utilizing an ALP-conjugated reporter system) may be considered in patients treated with Strensiq.
IB/0014	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	20/04/2017	11/12/2017	SmPC and Annex II	

IAIN/0017/G	This was an application for a group of variations. A.z - Administrative change - Other variation A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release B.II.e.1.z - Change in immediate packaging of the finished product - Other variation	11/04/2017	11/12/2017	Annex II and PL	
IB/0015	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	28/03/2017	11/12/2017	Annex II	
PSUSA/10421 /201607	Periodic Safety Update EU Single assessment - asfotase alfa	12/01/2017	n/a		PRAC Recommendation - maintenance
S/0011	1st Annual Re-assessment	15/12/2016	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Strensiq should be maintained.
II/0008	Update of sections 4.3, 4.4 and 4.8 of the SmPC in order to reinforce the wording on the risk of anaphylaxis. The Package Leaflet is updated accordingly. The MAH took the opportunity to include the Pharmacotherapeutic group in section 5.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	15/12/2016	11/12/2017	SmPC, Annex II and PL	The contra-indications section of the product information has been updated to include that: "severe or life-threatening hypersensitivity to the active substance or to any of the excipients is a contraindication to re-challenge, if hypersensitivity is not controllable". In addition, the existing warning on hypersensitivity has been expanded to include that: "Hypersensitivity reactions including signs and symptoms consistent with anaphylaxis have been reported in patients treated with asfotase alfa (see section 4.8). These symptoms included difficulty

					breathing, choking sensation, nausea, periorbital edema, and dizziness. The reactions have occurred within minutes after subcutaneous administration of Strensiq and can occur in patients on treatment for more than one year. Other hypersensitivity reactions included vomiting, fever, headache, flushing, irritability, chills, skin erythema, rash, pruritus, and oral hypaesthesia. (…) Consider the risks and benefits of re-administering Strensiq to individual patients following a severe reaction, taking other factors into account that may contribute to the risk of a hypersensitivity reaction, such as concurrent infection and/ or use of antibiotics. If the decision is made to re-administer the product, the re-challenge should be made under medical supervision and consideration may be given to use appropriate pre-medication. Patients should be monitored for recurrence of signs and symptoms of a severe hypersensitivity reaction. The need for supervision for subsequent administrations and need for emergency treatment for home care should be at the discretion of the treating physician. Severe or potentially life-threatening hypersensitivity is a contraindication to re-challenge, if hypersensitivity is not controllable (see section 4.3)" In addition, "Anaphylactoid reactions" has been included in the product information as a common adverse reaction.
IAIN/0013	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	14/11/2016	n/a		
II/0009/G	This was an application for a group of variations.	15/09/2016	n/a		

	B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method B.II.b.2.c.3 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing for a biol/immunol product and any of the test methods is a biol/immunol/immunochemical method				
PSUSA/10421 /201601	Periodic Safety Update EU Single assessment - asfotase alfa	02/09/2016	n/a		PRAC Recommendation - maintenance
IB/0010	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	22/08/2016	n/a		
IB/0007	B.I.b.2.e - Change in test procedure for AS or	08/04/2016	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate				
II/0005	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	01/04/2016	n/a		
IAIN/0004	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	12/01/2016	11/11/2016	Annex II and PL	
IB/0001/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.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	18/11/2015	11/11/2016	SmPC and Labelling	
IB/0002	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	13/11/2015	n/a		

	material/intermediate				