EMA/176801/2021

NeuroBloc

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
IAIN/0107	C.I.3.a - Change(s) in the SPC, Labelling or PL intended to implement the outcome of a procedure concerning PSUR or PASS or the outcome of the assessment done under A 45/46 - Implementation of wording agreed by the competent authority	04/03/2021		SmPC 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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PSUSA/428/202006	Periodic Safety Update EU Single assessment - botulinum toxin b	11/02/2021	n/a		PRAC Recommendation - maintenance
IA/0105	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	29/05/2020	n/a		
II/0104/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.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.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.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.2.a - Change to importer, batch release arrangements and quality control testing of the FP - Replacement/addition of a site where batch	16/01/2020	28/04/2020	Annex II	

	control/testing takes place 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				
IAIN/0103	B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing	28/05/2019	28/04/2020	Annex II and PL	
IAIN/0102/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.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	28/05/2019	28/04/2020	Annex II and PL	
T/0101	Transfer of Marketing Authorisation	27/07/2018	20/09/2018	SmPC, Labelling and PL	
PSUSA/428/201706	Periodic Safety Update EU Single assessment - botulinum toxin b	22/02/2018	23/04/2018	SmPC, Annex II, Labelling and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/428/201706.
N/0100	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/11/2017	23/04/2018	PL	

IB/0098/G	This was an application for a group of variations. 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.e - Stability of FP - Change to an approved stability protocol	07/04/2017	23/04/2018	SmPC	
PSUSA/428/201406	Periodic Safety Update EU Single assessment - botulinum toxin b	12/02/2015	n/a		PRAC Recommendation - maintenance
IAIN/0096	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	06/06/2014	n/a		
IAIN/0095	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	05/03/2014	n/a		
IB/0094	Update of Product Information in line with the most recent version of the QRD template (Version 9, 03/2013). Linguistic corrections required to align the Product Information with the national language templates have also been included in the updates besides a few additional minor changes. The MAH has also taken this opportunity to update the representative information in the Patient Information	26/02/2014	19/02/2015	SmPC, Annex II and PL	

	Leaflet for Belgium, Luxembourg, Hungary and Iceland as well as introducing details for Croatia in accordance with QRD template Version 9. Removal of the wording concerning 'An updated RMP shall be submitted annually until renewal' in Annex II, Section D, as a renewal was granted in 2010 with unlimited validity. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation				
II/0092	To add an alternative source of an excipient used in the manufacturing of Neurobloc. B.II.a.3.b.3 - Changes in the composition (excipients) of the finished product - Other excipients - Change that relates to a biological/immunological product	23/01/2014	n/a		
IA/0093	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	20/12/2013	n/a		
IB/0090	B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	26/09/2013	n/a		
IA/0089/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	19/09/2013	n/a		

	or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient 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				
IAIN/0091	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	18/09/2013	n/a		
IG/0345	C.I.8.a - Introduction of or changes to a summary of Pharmacovigilance system - Changes in QPPV (including contact details) and/or changes in the PSMF location	03/09/2013	n/a		
IAIN/0087	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	31/07/2013	n/a		
N/0086	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/07/2013	21/02/2014	Labelling and PL	
IAIN/0084	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	06/05/2013	n/a		

IAIN/0083/G	This was an application for a group of variations. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	31/01/2013	n/a		
IB/0082/G	This was an application for a group of variations. B.V.a.1.b - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - First-time inclusion of a new PMF NOT affecting the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier	17/01/2013	n/a		

	of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP				
II/0078	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	17/01/2013	21/02/2014	SmPC, Annex II, Labelling and PL	

IB/0080	B.II.b.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing takes place	14/12/2012	n/a		
IB/0079/G	This was an application for a group of variations. 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.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	06/11/2012	n/a		
IB/0076/G	This was an application for a group of variations. B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue B.I.a.4.f - Change to in-process tests or limits applied during the manufacture of the AS - Addition or replacement of an in-process test as a result of a safety or quality issue	06/06/2012	n/a		
II/0075	B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	24/05/2012	n/a		
IA/0077	B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting	16/05/2012	n/a		

	material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter)				
II/0071/G	This was an application for a group of variations. Replacement of a manufacturing site for the finished product. Change in immediate packaging of the finished product. Change in source of an excipient with TSE risk. Change in the supplier of packaging components. 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, batch control, and secondary packaging, for biological/immunological medicinal products. B.II.e.1.z - Change in immediate packaging of the finished product - Other variation B.II.c.3.z - Change in source of an excipient or reagent with TSE risk, other change B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier	22/09/2011	22/09/2011		
IB/0073	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	22/07/2011	n/a		
IB/0072	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a	22/07/2011	n/a		

	test procedure (including replacement or addition) for the AS or a starting material/intermediate				
IB/0070	Type IB Variation to update Annex IIB to include the key messages of the additional risk minimisation activities described in the Risk Minimisation Plan. C.I.3.a - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Changes with NO new additional data are submitted by the MAH	31/01/2011	n/a	Annex II	
R/0067	Renewal of the marketing authorisation.	23/09/2010	29/11/2010	SmPC, Annex II, Labelling and PL	Based on the review of the available information the CHMP is of the opinion that the quality, safety and efficacy of this medicinal product continues to be adequately and sufficiently demonstrated and considers that the benefit/risk profile of Neurobloc continues to be favourable. The CHMP therefore recommended that a renewal can be granted with unlimited validity. Within the renewal procedure the MAH provided the results of an analysis of hypersensitivity type reactions. Based on these results the CHMP recommended the inclusion of the terms angioedema, rash, urticaria and pruritus in the paragraph on post-marketing experience in section 4.8 of the SPC. The Product Information was further updated to be in line with the current QRD requirements and SmPC guideline.
IB/0069	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	08/09/2010	n/a		

IA/0068	B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	20/07/2010	n/a		
IA/0066	To amend the marketing authorisation dossier for Neurobloc with an approved 2nd step PMF re-certification procedure regarding human Serum Albumin excipient. B.V.a.1.d - PMF - Inclusion of a new, updated or amended PMF in the marketing authorisation dossier of a medicinal product. (PMF 2nd step procedure) - Inclusion of an updated/amended PMF when changes do not affect the properties of the FP	30/03/2010	n/a		
II/0064	Replacement of reference standards for the active substance and for the finished product. Update of or change(s) to the pharmaceutical documentation	21/01/2010	02/02/2010		
II/0063	Changes in test procedure for active substance and finished product. Update of or change(s) to the pharmaceutical documentation	21/01/2010	02/02/2010		
N/0065	Update of local representatives in Bulgaria, Czech Republic, Cyprus, Finland, France, Greece, Hungary, Latvia, Malta and Slovak Republic together with minor	11/01/2010	n/a	Labelling and PL	

	grammatical/typographical corrections in the Danish labelling. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
II/0062	Change in one of the chromatographic steps in the purification of the drug substance. Change(s) to the manufacturing process for the active substance	24/09/2009	30/09/2009		
II/0061	Update of Summary of Product Characteristics (SPC) and Package Leaflet (PL). To update sections 4.2, 4.4 and 5.1 of the SPC to reflect immunological data from two clinical studies in patients with cervical dystonia. Section 3 of the PL has been updated accordingly. This variation also fulfils FUM2 019.4 and FUM2 003.2. The MAH took the opportunity to correct the list of local representatives from Austria and Portugal in section 6 of the PL. In addition, the MAH made editing correction to section 4 of the PL. Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	23/07/2009	SmPC and PL	The SPC of NeuroBloc has been updated with immunological information from two completed Phase IV post-marketing studies that evaluate the safety and immunogenicity of NeuroBloc (Botulinum Toxin Type B) in patients with cervical dystonia. In the first study (AN 072-401 CD-EU), 130 patients were enrolled, including 67 patients resistant and 63 responders to Botulinum Toxin Type A respectively. The objective of this study was to evaluate the safety and evaluate immunogenicity of repeat doses of NeuroBloc in subjects with cervical dystonia (CD) by assessing clinical safety parameters, laboratory tests, and adverse events (AEs). The second study (AN072-402CD-EU) compared effectiveness, safety and duration of action of Botulinum Toxin Types A and B in subjects who had never previously received a botulinum toxin. Both studies suggest that the presence of antibodies was not synonymous with a loss of clinical response with impact on the overall safety profile. The Product Information was therefore updated to reflect the

					mentioned findings.
2PMF/0059	Inclusion of the updated or amended Plasma Master File (Grifols EMEA/H/PMF/000002/04) in the marketing authorisation dossier	02/04/2009	n/a		
II/0053	The Marketing Authorisation Holder applied to add an additional storage period of 3 months when stored below 25 C, to facilitate holding of the product prior to use. Change(s) to shelf-life or storage conditions	19/02/2009	25/03/2009	SmPC, Labelling and PL	
IB/0058	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	12/03/2009	n/a		
IA/0060	IA_01_Change in the name and/or address of the marketing authorisation holder	12/03/2009	n/a	SmPC, Labelling and PL	
IA/0057	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	13/02/2009	n/a	Annex II and PL	
IB/0056	IB_20_c_Change in test procedure for an excipient - other changes	02/02/2009	n/a		
II/0055	Update of section 4.8 of the Summary SPC to include the adverse event 'dyspnoea' based on data from PSUR 8 (covering the period from 20.07.05 to 30.06.08). Section 4 of the PL was updated accordingly. In addition, section 4 of the PL was updated with the adverse event 'headache', in line with the SPC.	18/12/2008	30/01/2009	SmPC, Labelling and PL	A cumulative review of the MAH's safety database up to 30 June 2008 identified 25 reports of dyspnoea. Seventeen (17) of these reports were related to off-label use (3 reports involving children or adolescents, 16 reports involving non approved indications, 8 involving patients with underlying neurological disease). Four (4) of the patients with dyspnoea had symptoms suggestive of allergic reaction. Not all cases

	The MAH also took the opportunity to remove the warning on albumin from section 4.4 of the SPC and section 3 of the PL, as recommended by the CHMP in April 2008. The MAH also made minor corrections to the labelling for Bulgaria, Czech Republic, Estonia, Denmark, Finland, Germany, Hungary, Iceland, Lithuania, Latvia, Poland, Norway, Slovakia, Slovenia and Sweden. Update of Summary of Product Characteristics, Labelling and Package Leaflet				of dyspnoea appeared to be related to NeuroBloc administration and other morbidities may be more likely etiologies; however it is not possible to exclude a role of NeuroBloc in these events. Some patients also experienced other events of possible toxin spread. Based on this review, 'dyspnoea' has been added to the SPC among the side effects related to spread of toxin distant from the site of administration.
II/0054	Change(s) to the manufacturing process for the active substance	18/12/2008	05/01/2009		
II/0049	The Marketing Authorisation Holder applied to introduce a new reference standard used for analyses of the concentrated product. Change(s) to the manufacturing process for the finished product	25/09/2008	01/10/2008		
N/0050	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/09/2008	n/a	PL	
IA/0051	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	05/09/2008	n/a	Annex II and PL	
IA/0052	IA_25_b_02_Change to comply with Ph. - compliance with EU Ph. update - excipient	04/09/2008	n/a		

II/0047	Change(s) to the manufacturing process for the finished product	24/07/2008	31/07/2008		
MF/0048	2PMF (2nd step of PMF certification procedure)	16/06/2008	n/a		
II/0044	Update of Summary of Product Characteristics and Labelling. Update of section 5.1 of the SPC to reflect final data from an open label safety and immunogenicity study of NeuroBloc in patients with cervical dystonia. The MAH also took the opportunity to make a minor correction in section 4.8. In addition, section 9 of the SPC and section 16 of the Labelling have been updated in line with the EMEA QRD template version 7.2. Update of Summary of Product Characteristics and Labelling	24/01/2008	26/02/2008	SmPC and Labelling	A post-marketing open label clinical study was performed by the MAH as a post-authorisation commitment to evaluate the safety and immunogenicity of NeuroBloc (Botulinum Toxin Type B) in patients with cervical dystonia previously treated with Botulinum Toxin Type A. Interim results of this study were already reflected in the SPC. The study has now been completed and its description has been updated in the SPC. A total of 130 patients were enrolled, including 67 patients resistant to Botulinum Toxin Type A and 63 patients responsive to Botulinum Toxin Type A. The final results showed that the safety profile of NeuroBloc was similar in both types of patients and no new safety concerns were identified. The immunogenicity results will be submitted at a later stage.
IA/0046	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	05/02/2008	n/a		
IA/0045	IA_05_Change in the name and/or address of a manufacturer of the finished product	10/01/2008	n/a		
T/0043	Transfer of Marketing Authorisation	23/08/2007	25/09/2007	SmPC, Labelling and PL	Transfer of the Marketing Authorisation from Solstice Neurosciences Ltd. to Eisai Limited.
II/0041	Update of Summary of Product Characteristics, Annex II, Labelling and Package Leaflet	19/07/2007	21/08/2007	SmPC, Annex II, Labelling	Final results of a post-marketing clinical study comparing the safety and efficacy of botulinum toxin type B (NeuroBloc) with botulinum toxin type A (Botox) in patients with cervical

	Update of sections 4.8 and 5.1 of the SPC to reflect the final results from a Phase IV clinical study designed to compare the safety and efficacy of NeuroBloc (botulinum toxin type B) with botulinum toxin type A in patients with cervical dystonia who have never received previously a botulinum toxin product. Section 4 of the PL was updated accordingly. The MAH also took the opportunity to update the product information according to the latest EMEA/QRD template (version 7.2). Update of Summary of Product Characteristics, Labelling and Package Leaflet			and PL	dystonia (torticollis) never previously treated with botulinum toxin products showed that NeuroBloc is not inferior to Botox in terms of efficacy. In terms of safety, the most common undesirable effects in patients treated with NeuroBloc were dry mouth and dysphagia, which were reported at a frequency of 44% and 35% respectively, which was significantly higher than the rates observed with botulinum toxin type A.
II/0042	Change(s) to the test method(s) and/or specifications for the active substance	19/07/2007	10/08/2007		
MF/0040	2PMF (2nd step of PMF certification procedure)	26/04/2007	n/a		
II/0039	Update of sections 4.4 and 4.8 of the SPC to include information on adverse spread reactions as requested by the CHMP in November 2006. Sections 2 and 4 of the PL were updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	22/02/2007	28/03/2007	SmPC and PL	Distant reactions including muscle weakness, dysphagia and aspiration represent a significant proportion of all reported serious events associated with the use of botulinum toxin containing products. These adverse effects are temporary and usually disappear within a few weeks. However, fatal cases have been reported and the botulinum toxin is likely to have contributed to some of those cases. The majority of the fatal cases reported also had underlying medical conditions such as neurological disorders and prior histories of dysphagia or aspiration. Although dysphagia and aspiration pneumonia were already mentioned in the SPC, the CHMP considered that the issue of distant spread of the toxin as well as the need for caution in vulnerable patients,

					particularly those with underlying neurological disorders should also be adequately addressed in the product information.
II/0036	Change(s) to the manufacturing process for the active substance	16/11/2006	27/11/2006		
IA/0038	IA_05_Change in the name and/or address of a manufacturer of the finished product	30/10/2006	n/a	Annex II and PL	
IA/0037	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	21/07/2006	n/a		
II/0035	Change(s) to the test method(s) and/or specifications for the finished product	28/06/2006	06/07/2006		
R/0033	Renewal of the marketing authorisation.	14/12/2005	06/04/2006	SmPC, Annex II, Labelling and PL	There are no major differences on the efficacy and safety evaluations of Neurobloc after 5 years on the Market. Although it is worth noting that a number of studies were conducted and their data made the benefit risk assessment more robust. It should be mentioned that there is an overall concern on the class of botulinum toxins regarding dysphagia and fatal outcomes. This is not specific of Neurobloc but of the whole class. Final reports of the studies that will be concluded in 2006 should be delivered when ready as per commitment timetables. Based on the re-evaluation of the benefit/risk balance, the

					Marketing Authorisation of the medicinal product can be considered for renewal. However, due to the above-mentioned safety concern and waiting for final reports of studies being conducted, the CHMP recommended the MAH should submit one additional renewal in 5 years time.
II/0034	Update of section 4.4 of the SPC to include a warning about aspiration pneumonia and/or potentially fatal respiratory disease in patients with respiratory distress or difficulty in swallowing following the assessment of a clinical follow-up measure (from PSUR 5 covering the period 01/01/03 - 31/12/03) and the assessment of PSUR 6 covering the period 01/01/04 - 31/12/04. Update of Summary of Product Characteristics	13/10/2005	15/11/2005	SmPC	Following the assessment of PSUR 5 the CHMP requested clarification on the analyses of all fatal cases associated with the use of NeuroBloc. The data submitted showed that the 3 cases presented only reinforced the need to closely monitor the cases of death and stroke and the need to evaluate the inclusion of aspiration pneumonia in the safety information of Neurobloc. In PSUR 6 a cumulative analysis of all fatal cases associated with the use of Botulinum Toxin type B was presented. During the covered period 17 fatal cases from a total of 693 cases were reported. Of those, 7 originated from post marketing sources, 5 cases from clinical trials, and 5 from the Medical Index for Neuromuscular Data (MIND) registry. Aspiration pneumonia and death related to respiratory distress/aspiration pneumonia accounted for 6 in 17, that is to say, 35% of all fatal cases. This variation addresses the request of the CHMP to include a warning about aspiration pneumonia in patients with respiratory distress or difficulty in swallowing.
II/0031	Change(s) to shelf-life or storage conditions	15/09/2005	19/10/2005	SmPC	
II/0032	Change(s) to the test method(s) and/or specifications for the finished product	15/09/2005	22/09/2005		

T/0030	Transfer of Marketing Authorisation	04/08/2005	26/08/2005	SmPC, Labelling and PL	The Marketing Authorisation for Neurobloc was transfered from Elan Pharma International Ltd to Solstice Neurosciences Ltd.
II/0029	Update of section 5.1 "Pharmacodynamic Properties" of the Summary of Product Characteristics to reflect the results of an interim report of the Study AN072-401 on immunogenicity of NeuroBloc in Botulinum Toxin Type A resistant patients. Update of Summary of Product Characteristics	23/06/2005	16/08/2005	SmPC	An interim analysis of the development of neutralising antibodies to NeuroBloc was performed in 67 Botulinum Toxin Type A-resistant subjects after at least 50 subjects had completed four cycles of NeuroBloc (Botulinum Toxin Type B) treatment. On the first year of treatment the number of patients that developed antibodies to Botulinum Toxin Type B was low, about 5%. It should be born in mind that presence of antibodies does not necessarily equal resistance to treatment, i.e. the number of truly resistant patients could be lower than the number of patients who develop antibodies. On the second year, the rate of patients with antibodies increased. However, the overall number of patients treated was small. So far, these data suggest that, at least during one year, resistant patients to Botulinum Toxin Type A may benefit from Botulinum Toxin Type B, which is of importance. These results have been incorporated into the SPC Section 5.1. "Pharmacodynamic Properties".
S/0025	Fourth annual reassessment.	21/04/2005	08/07/2005	Annex II	On the basis of the data submitted, the benefit/risk in the treatment of cervical dystonia (torticollis) in patients responsive and resistant to Botulinum toxin type A preparations remains positive. No amendments of Annexes I and III of the Marketing Authorisation were necessary. However, it was necessary to update the Annex II.C of the CHMP Opinion as the remaining

					Specific Obligation (to conduct a Phase IV clinical study to demonstrate the non-inferiority of NeuroBloc (Botulinum Toxin Type B) to Botulinum Toxin Type A (Botox) in patients with cervical dystonia who have never previously received a Botulinum toxin product) could be considered finalised. The primary results of this study were previously reflected in the Type II variation II/0024. The MAH has commited to provide the final report by 2Q2006. The CHMP finally agreed that there are no grounds for the Marketing Authorisation to remain under exceptional circumstances.
II/0027	Change(s) to the test method(s) and/or specifications for the active substance	23/06/2005	27/06/2005		
II/0028	Change(s) to the manufacturing process for the active substance	26/05/2005	02/06/2005		
II/0023	Further to post-marketing surveillance. Update of Summary of Product Characteristics and Package Leaflet	17/02/2005	29/03/2005	SmPC and PL	The SPC was updated in its sections: - 4.8 "Undesirable effects" to reflect that 70% of the dysphagia cases reported were serious and required medical intervention. This update was requested following PSUR 5 (01.01.2003 - 31.12.2003) where four cases were identified where dysphagia occurred with unexpected severity. - 5.2 "Pharmacokinetic Properties" to reflect that on a total of 552 cases reported from January 2001 to December 2003, 165 (30%) were serious cases, of which 66 were serious cases with possible systemic effects, meaning 12% of the total cases. These reports during the post-marketing experience included the following adverse events: dry mouth, dysphagia and blurred vision.

II/0024	Further to results of a phase IV clinical study. Update of Summary of Product Characteristics	20/01/2005	28/02/2005	SmPC	The SPC was updated in its section 5.1 "Pharmacodynamic Properties" to reflect the results of a Phase IV study conducted to demonstrate the non-inferiority of NeuroBloc to botulinum toxin type A in patients with cervical dystonia who have never previously received a botulinum toxin product. An interim analysis was carried out on the total of 111 enrolled botulinum naive enrolled patients (56 in the NeuroBloc group) following a single injection, into 2 of 4 predetermined muscles, of NeuroBloc 10,000 units or botulinum toxin type A 150 units. The analysis showed that there were no clinically relevant differences between these two treatments. The primary analysis of non-inferiority with the per-protocol population was not proven (90% CI of difference -2.66, 4.01 compared with an upper limit of <4.00), however, a sensitivity analysis for robustness and a confirmatory ITT population analysis (90% CI of difference -3.4, 3.2 and -3.23, 2.98 respectively) demonstrated non-inferiority.
IA/0026	IA_04_Change in name and/or address of a manuf. of the active substance (no Ph. Eur. cert. avail.)	09/02/2005	n/a	Annex II	
S/0019	Third Annual Reassessment.	22/04/2004	17/12/2004	SmPC, Annex II and PL	On the basis of the data submitted since the Marketing Authorisation, the benefit/risk in the symptomatic treatment of cervical dystonia in patients responsive and resistant to Botulinum toxin type A preparations remains positive. There was however the necessity to update the Annexes of the opinion as follows: a. the Annex I, according to the latest EMEA/QRD template, b. the Annex II, according to the latest EMEA/QRD

					template and to revise Annex II.C to the Commission Decision, in order to update the remaining Specific Obligation, c. the Annex III, to revise the list of local representatives in the Package Leaflet. The CPMP agreed that the Marketing Authorisation should remain under exceptional circumstances.
II/0022	Quality changes	16/09/2004	21/09/2004		Quality change to site of product manufacture.
II/0021	Quality changes	16/09/2004	21/09/2004		Quality changes to amend the analytical test methods.
IA/0020	IA_05_Change in the name and/or address of a manufacturer of the finished product	24/03/2004	n/a	Annex II and PL	
II/0016	The MAH applied for changes to the sections 4.8 "Undesirable effects" and 5.2 "Pharmacokinetics properties" of the SPC further to the evaluation of PSUR4 covering the period from 1 July 2002 to 31 December 2002. In addition, an amendment to section 5.3 "Preclinical Safety Data" is proposed to remove an inconsistency remaining from the previous variation. The Package Leaflet has been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	20/11/2003	29/01/2004	SmPC and PL	
IB/0017	IB_19_b_Change in specification of an excipient - addition of new test parameter	11/12/2003	n/a		
I/0018	IB_19_b_Change in specification of an excipient - addition of new test parameter	11/12/2003	n/a		

II/0014	sections 4.6 and 5.3 Update of Summary of Product Characteristics	22/05/2003	16/09/2003	SmPC	Following the evaluation of the PSUR covering the period from 1 January 2002 to 30 June 2002 and based on new published information, the sections 4.6 "Pregnancy and lactation" and 5.3 "Preclinical Safety Data" of the SPC have been updated, and consequently the section 4.3 "Contraindications".
I/0015	24_Change in test procedure of active substance	29/08/2003	05/09/2003		
S/0013	Annual re-assessment.	25/04/2003	15/07/2003	Annex II	
II/0009	Update of Summary of Product Characteristics and Package Leaflet	18/12/2002	07/03/2003	SmPC and PL	
I/0012	12_Minor change of manufacturing process of the active substance	18/12/2002	19/12/2002		
II/0010	Change(s) to the test method(s) and/or specifications for the finished product	21/11/2002	26/11/2002		
I/0011	01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	08/11/2002	n/a		
S/0008	Annual re-assessment.	25/04/2002	25/04/2002		
I/0007	15_Minor changes in manufacture of the medicinal product	08/03/2002	18/03/2002		
I/0006	16_Change in the batch size of finished product	15/02/2002	28/02/2002		
N/0005	Minor change in labelling or package leaflet not	12/09/2001	29/10/2001	PL	

	connected with the SPC (Art. 61.3 Notification)				
I/0001	20_Extension of shelf-life as foreseen at time of authorisation	18/05/2001	04/07/2001	SmPC	
I/0002	17_Change in specification of the medicinal product	31/05/2001	21/06/2001		
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	23/05/2001	02/07/2001	PL	
I/0004	12_Minor change of manufacturing process of the active substance	18/05/2001	n/a		