Naglazyme

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
IB/0097	B.II.g.5.c - Implementation of changes foreseen in an approved change management protocol - For a biological/immunological medicinal product	12/12/2024		SmPC	
IA/0096	A.7 - Administrative change - Deletion of manufacturing sites	06/09/2024	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).

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IB/0094	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	11/03/2024	n/a		
IA/0093	A.7 - Administrative change - Deletion of manufacturing sites	08/08/2023	n/a		
IB/0091/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 B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	06/07/2023	n/a		
II/0090	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	12/05/2023	n/a		
PSUSA/1515/202205	Periodic Safety Update EU Single assessment - galsulfase	12/01/2023	n/a		PRAC Recommendation - maintenance
II/0086	Update of section 4.1 of the SmPC to remove information on limited safety data in children under 5 years of age, based on the results from the final	27/01/2022	01/04/2022	SmPC, Annex II and PL	The wording of the therapeutic indication in section 4.1 of the SmPC was amended to remove the following statements regarding safety in children aged below 5

	study report from the Mucopolysaccharidosis (MPS) VI Clinical Surveillance Program (CSP) listed as a Specific Obligation (SOB 002) in the Annex II of the Product Information. This observational CSP was undertaken to characterise the natural progression of MPS VI, to evaluate the long-term safety and efficacy data from Naglazyme treatment, to collect information on the effect of Naglazyme treatment on lactation, growth and development of infants of Naglazyme treated mothers, and to evaluate the effects of Naglazyme treatment on children under 5 years of age. Further, section 5.1 of the SmPC was updated to remove reference to marketing authorisation under exceptional circumstances and Annex II was updated in order to remove SOB 002. In addition, the statement on additional monitoring and corresponding black triangle were removed from the SmPC and the Package leaflet, and the Annex II was aligned with the latest QRD template version 10.2. The revised RMP version 7 was submitted in order to remove gastrointestinal haemorrhage, hepatic impairment and thrombocytopenia from the list of important potential risks, spinal cord compression and neutralising antibodies as important potential risks and pregnant or lactating women as missing information. As a consequence of the RMP updates, specific adverse reaction follow-up questionnaires for spinal cord compression were removed in Annex 4 of the RMP. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing				years: A key issue is to treat children aged <5 years suffering from a severe form of the disease, even though children <5 years were not included in the pivotal phase 3 study. Limited data are available in patients < 1 year of age (see section 5.1) The final wording of the indication: Naglazyme is indicated for long-term enzyme replacement therapy in patients with a confirmed diagnosis of Mucopolysaccharidosis VI (MPS VI; N-acetylgalactosamine 4-sulfatase deficiency; Maroteaux-Lamy syndrome) (see section 5.1). For more information, please refer to the Summary of Product Characteristics.

	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				
PSUSA/1515/ 202105	Periodic Safety Update EU Single assessment - galsulfase	13/01/2022	n/a		PRAC Recommendation - maintenance
S/0087	Annual re-assessment.	11/11/2021	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 Naglazyme should be maintained.
PSUSA/1515/ 202005	Periodic Safety Update EU Single assessment - galsulfase	14/01/2021	n/a		PRAC Recommendation - maintenance
S/0083	Annual re-assessment.	12/11/2020	11/01/2021	Annex II	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 Naglazyme should be varied, as SOB 003 is considered fulfilled and thus is removed from the list of specific obligations to be completed.
IB/0085	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	14/12/2020	03/12/2021	SmPC and Annex II	
IB/0082	C.I.11.z - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Other variation	27/08/2020	11/01/2021	Annex II	

II/0081	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		
S/0078	Annual re-assessment.	27/02/2020	05/05/2020	SmPC and PL	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 Naglazyme should be maintained.
PSUSA/1515/ 201905	Periodic Safety Update EU Single assessment - galsulfase	30/01/2020	03/04/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/1515/201905.
IG/1141	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	12/12/2019	n/a		
IA/0077	A.7 - Administrative change - Deletion of manufacturing sites	10/05/2019	03/04/2020	Annex II and PL	
IG/1083	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	08/04/2019	n/a		

IA/0075/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 A.7 - Administrative change - Deletion of manufacturing sites	11/03/2019	n/a		
S/0073	11th annual re-assessment	28/02/2019	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 Naglazyme should be maintained.
PSUSA/1515/ 201805	Periodic Safety Update EU Single assessment - galsulfase	17/01/2019	n/a		PRAC Recommendation - maintenance
II/0070	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	26/07/2018	n/a		
T/0072	Transfer of Marketing Authorisation	02/07/2018	13/07/2018	SmPC, Labelling and PL	
N/0071	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	10/04/2018	13/07/2018	Labelling	
PSUSA/1515/ 201705	Periodic Safety Update EU Single assessment - galsulfase	11/01/2018	n/a		PRAC Recommendation - maintenance

S/0067	Annual re-assessment.	09/11/2017	n/a		
IB/0069	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	24/10/2017	n/a		
PSUSA/1515/201605	Periodic Safety Update EU Single assessment - galsulfase	12/01/2017	n/a		PRAC Recommendation - maintenance
S/0065	Annual re-assessment.	15/12/2016	n/a		
IG/0658	A.1 - Administrative change - Change in the name and/or address of the MAH	02/02/2016	09/01/2017	SmPC, Labelling and PL	
PSUSA/1515/201505	Periodic Safety Update EU Single assessment - galsulfase	14/01/2016	n/a		PRAC Recommendation - maintenance
IA/0063	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)	10/12/2015	n/a		
S/0060	Annual re-assessment.	19/11/2015	n/a		
IG/0629	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	05/11/2015	n/a		
II/0059	B.II.b.2.b - Change to importer, batch release arrangements and quality control testing of the FP -	17/09/2015	n/a		

	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				
IB/0058	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	28/05/2015	n/a		
IB/0057/G	This was an application for a group of variations. 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 B.I.d.1.b.3 - Stability of AS - Change in the storage conditions - Change in storage conditions of the AS B.I.d.1.z - Stability of AS - Change in the re-test period/storage period or storage conditions - Other variation	14/04/2015	n/a		
IB/0055	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	26/01/2015	n/a		
PSUV/0054	Periodic Safety Update	09/01/2015	n/a		PRAC Recommendation - maintenance
IB/0056	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	12/12/2014	n/a		

S/0053	7thAnnual Re-assessment.	20/11/2014	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 Naglazyme should be maintained.
IG/0471	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	04/08/2014	n/a		
IG/0458	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	09/07/2014	15/12/2014	Annex II and PL	
PSUV/0046	Periodic Safety Update	09/01/2014	n/a		PRAC Recommendation - maintenance
IAIN/0049	C.I.12 - Inclusion or deletion of black symbol and explanatory statements for medicinal products in the list of medicinal products that are subject to additional monitoring	08/01/2014	15/12/2014	SmPC and PL	
IB/0047/G	This was an application for a group of variations. 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 control/testing takes place 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	19/12/2013	15/12/2014	Annex II and PL	

	manufacturing site for the FP - Secondary 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 control/testing takes place 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				
IB/0048	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	05/12/2013	n/a		
S/0043	Annual re-assessment.	21/11/2013	n/a		
IB/0044	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	09/09/2013	n/a		
IA/0042/G	This was an application for a group of variations. 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 B.II.e.7.b - Change in supplier of packaging components or devices (when mentioned in the dossier) - Replacement or addition of a supplier A.7 - Administrative change - Deletion of manufacturing sites	11/06/2013	n/a		

IB/0041	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	26/04/2013	n/a		
IA/0040/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 supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished product, including quality control sites (excluding manufacturer for batch release)	26/04/2013	n/a		
IAIN/0039	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	26/02/2013	n/a		
S/0034	Annual re-assessment.	20/09/2012	15/11/2012	SmPC and PL	
IG/0207	C.I.9.a - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the QPPV	03/08/2012	n/a		
IG/0177	C.I.9.c - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the back-up procedure of the QPPV	25/05/2012	n/a		
II/0033/G	This was an application for a group of variations. Changes to the manufacture of the active substance	15/12/2011	15/12/2011		

	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 medicinal product and is not related to a protocol B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits				
II/0030	Update of sections 4.3, 4.4 and 4.8 of the SmPC to reflect the conclusions of a cumulative review of all post-marketing adverse events. This review was requested by the CHMP, following review of PSUR-7. The MAH also took this opportunity to update the MedDRA terms used to describe adverse events collected during clinical studies involving Naglazyme. The Package Leaflet has been updated accordingly and Annex II has been updated with a minor linguistic correction. 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	22/09/2011	20/10/2011	SmPC and PL	The MAH has conducted two through reviews; one using clinical trial data from 5 studies and the second using post-marketing spontaneous data. Following these reviews a number of updates have been proposed to the Naglazyme product information. The re-analysis of the 5 clinical trials (ASB-00-001, ASB-04-01, ASB-03-05, ASB-03-06 and ASB-008) identified a total 59 patients who had received at least one dose of Naglazyme. No treatment related deaths were identified from these clinical studies. Following the re-analysis of data set from study ASB-03-05, the MAH has proposed the deletion of face oedema and the addition of arthralgia, rash, and hearing impaired to Table 1 in section 4.8 of the SmPC. The MAH proposal to remove Apnoea from Table 1 to the post-marketing section was not endorsed as this ADR was only identified in a clinical study setting.

					The cumulative review of post-marketing spontaneous reports revealed a number of ADRs that were reported more frequently in Naglazyme-treated subjects. Most of these were hypersensitivity type reactions that occurred during Naglazyme infusion. The MAH proposed to strengthen the wording relating to hypersensitivity reactions and management in section 4.4. of the Naglazyme SmPC. Five cases of CCF were identified however, 3 patients had worsening of pre-existing CCF, and it is not known whether such patients were included in clinical trials. The MAH will continue to monitor cases of CCF as part of routine Pharmacovigilance, and will update the Risk Management Plan should this term become a more clearly identified risk. According to the data presented, the hypersensitivity reactions in association with Naglazyme therapy were of different degrees of severity ranging from very severe, life-threatening to mild symptoms. Whilst the CHMP acknowledge that other treatment options for MPS VI patients are limited, rechallenge in patients who have experienced a severe or life-threatening hypersensitivity to Naglazyme is not considered to be acceptable. Therefore, the CHMP was of the view that Naglazyme should be contraindicated in cases of severe or life-threatening hypersensitivity, if hypersensitivity is not controllable. This variation does not change the benefit/risk balance for Naglazyme which remains positive.
IB/0032/G	This was an application for a group of variations.	13/10/2011	n/a		

	C.I.9.z - Changes to an existing pharmacovigilance system as described in the DDPS - Other variation C.I.9.d - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the safety database C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD				
R/0028	Renewal of the marketing authorisation.	18/11/2010	26/01/2011	SmPC, Annex II and PL	
II/0031	Update of Summary of Product Characteristics and Package Leaflet to reflect the results of study ASB-008 (infant study), as requested by the CHMP following evaluation of this study report as part of the latest Annual Reassessment. Additionally the MAH took the opportunity to update Annex II to reflect the completion of a commitment as per the 4th Annual Reassessment. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	18/11/2010	20/10/2010	SmPC, Annex II and PL	The infant study (ASB-008) is a Phase IV, multi-center, multi-national, open-label, randomized, two-dose level study designed to evaluate the safety and efficacy of two dose levels (1 mg/kg/week and 2 mg/kg/week) of Naglazyme in preventing the progression of skeletal dysplasia in infants under the age of one who have MPS VI. The study started in May 2006 and was completed in April 2009. Four patients completed the study. Although limited by the very small number of patients that could be enrolled and their short follow-up, the conclusions that can be drawn from this study are the following: " Treatment with Naglazyme did not prevent the progression of skeletal dysplasia and development of hernias in infants less than 2 years of age and, as expected, did not prevent the progression of corneal

					clouding. " However, it prevented development or worsening of facial dysmorphism and improved hearing loss to some extent. " High urinary GAG levels decreased by more than 70%, as was observed with older patients. " Growth remained essentially normal over this limited follow-up period. " Some level of improvement in hearing was observed in all subjects. " The dose of 2 mg/kg/week was not more effective than the current recommended dose of 1 mg/kg/week. Of note, the randomisation allocated the higher dose to the oldest children (aged > 1 year). The overall safety profile of the higher dose of 2 mg/kg/week did not seem different in a clinically meaningful manner from that of the 1 mg/kg/week dose. They were consistent with the safety profile of Naglazyme in previous clinical trials involving older children. No new safety signal emerged in this small group of infants.
II/0027	Change in the manufacture of the drug substance B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs	23/09/2010	29/09/2010		
S/0026	Annual re-assessment.	20/05/2010	06/08/2010	SmPC and Annex II	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concludes that, overall, the benefit/risk balance for

					the product remains unchanged.
II/0025	Additional sites for the manufacture of the drug product and for the control of the drug substance and drug product. Change(s) to the manufacturing process for the finished product	24/09/2009	05/10/2009		
S/0021	Annual Reassessment	23/04/2009	01/07/2009	Annex II	"The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the MAH and having re-assessed the benefit/risk profile of the medicinal product, concluded that the benefit/risk balance for the product remains favourable. The CHMP agreed that the Marketing Authorisation for Naglazyme should remain under exceptional circumstances and agreed on a revised list of Specific Obligations. The following Specific Obligation has been fulfilled with the annual re-assessment: SOB-4: "All clinical trial patients are currently receiving the product manufactured by the commercial process. GAG and antibody samples continue to be collected at protocol-specified intervals. A change in nature or frequency of the adverse events and serious adverse events that are collected in an ongoing fashion within these studies will be evaluated to investigate a potential relationship between an observed change in safety parameters and the transition to commercial material and reported in the annual CSP reports and PSURs as appropriate.

					The MAH commits to analysing the data from patients who have received clinical and then commercial process product to determine if there was any change to safety (antibody formation) or efficacy parameters stemming from the transition to commercial material and will provide this analysis in the clinical study reports for each of these studies when complete. The Clinical Study Reports for all studies are targeted for submission no later than January 2007".
IB/0023	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening IB_37_a_Change in the specification of the finished product - tightening of specification limits	23/06/2009	n/a		
IB/0024	IB_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening IB_37_a_Change in the specification of the finished product - tightening of specification limits	18/05/2009	n/a		
IA/0020	IA_01_Change in the name and/or address of the marketing authorisation holder	13/02/2009	n/a	SmPC, Labelling and PL	
IA/0019	IA_31_a_Change to in-process tests/limits during manufacture - tightening of in-process limits	11/08/2008	n/a		
S/0015	Annual re-assessment.	24/04/2008	30/07/2008	Annex II	The CHMP, having reviewed the evidence of compliance with the Specific Obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile for Naglazyme, concluded that the benefit/risk ratio for the product remains favourable in the approved indication.

					The CHMP agreed that the Marketing Authorisation should be kept under exceptional circumstances and agreed on a revised list of Specific Obligations, which can be found in Annex II.C of the product information.
II/0018	Change(s) to the test method(s) and/or specifications for the active substance	26/06/2008	16/07/2008		
II/0017	Change(s) to the manufacturing process for the active substance	30/05/2008	11/06/2008		
IB/0016	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	23/04/2008	23/04/2008	SmPC, Labelling and PL	
IA/0014	IA_05_Change in the name and/or address of a manufacturer of the finished product	04/10/2007	n/a	Annex II, Labelling and PL	
II/0013	Change(s) to the manufacturing process for the active substance	20/09/2007	01/10/2007		
IB/0012	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	05/07/2007	n/a	SmPC	
S/0011	Annual re-assessment.	26/04/2007	02/07/2007	SmPC and PL	The CHMP, having reviewed the evidence of compliance with the Specific Obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile for Naglazyme, concluded that the benefit/risk ratio for the product remains favourable in the approved indication. The CHMP agreed that the Marketing Authorisation should be kept under exceptional circumstances and agreed on a

					revised list of Specific Obligations, which can be found in Annex II.C of the product information.
II/0010	Change(s) to the manufacturing process for the active substance	22/02/2007	26/02/2007		
II/0009	Change(s) to the manufacturing process for the finished product	24/01/2007	29/01/2007		
II/0007	Change(s) to the test method(s) and/or specifications for the finished product	18/10/2006	23/10/2006		
IB/0006	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	18/09/2006	n/a	SmPC	
N/0004	The Marketing Authorisation Holder (MAH) applied for the addition of the term "5 mg/5 ml" in section 4 "Pharmaceutical form and contents" of the outer packaging. The MAH also applied for the update of the local representative list of the Package Leaflet to include contact details for all Member States. Additionally corrections were made in section 6 of to the German and French package leaflets. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/07/2006	n/a	Labelling and PL	
II/0001	Change(s) to the manufacturing process for the active substance	27/04/2006	04/05/2006		
IB/0003	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	11/04/2006	n/a	SmPC	

IA/0002	IA_01_Change in the name and/or address of the marketing authorisation holder	31/03/2006	n/a	SmPC, Labelling and PL	