Fabrazyme

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
II/0129	Update of section 4.6 of the SmPC in order to update the safety information on pregnancy and breast-feeding based on results from AGAL02603/MSC12868: "A Multicenter, Multinational Study of the Effects of Fabrazyme (agalsidase beta) Treatment on Lactation and Infants", listed as a	14/03/2024		SmPC and PL	Based on the review of the available data, the CHMP recommended to update the information on pregnancy and lactation for Fabrazyme about the limited experience with the use of Fabrazyme in pregnant women. The CHMP recommended as a precaution to avoid the use of Fabrazyme during pregnancy. Fabrazyme gets into breast

[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).

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
Send us a question Go to www.ema.europa.eu/contact **Telephone** +31 (0)88 781 6000

	category 3 study in the RMP, MAH safety database and literature search; the Package Leaflet is updated accordingly. In addition, the MAH took this opportunity to introduce minor editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				milk. Discuss with your doctor the risks and benefits of breastfeeding versus continuing Fabrazyme therapy. Studies have not been performed to examine the effects of Fabrazyme on fertility.
IAIN/0128	A.1 - Administrative change - Change in the name and/or address of the MAH	03/04/2023	13/06/2023	SmPC, Labelling and PL	
PSUSA/70/20 2207	Periodic Safety Update EU Single assessment - agalsidase beta	16/03/2023	n/a		PRAC Recommendation - maintenance
IB/0126	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	01/08/2022	n/a		
II/0123	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	19/05/2022	13/06/2023	SmPC and PL	
IB/0125	B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method	11/04/2022	n/a		

IA/0124	A.7 - Administrative change - Deletion of manufacturing sites	21/02/2022	n/a		
N/0122	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/11/2021	13/06/2023	PL	
IA/0121	B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits	06/10/2021	n/a		
X/0118/G	This was an application for a group of variations. Annex I_1.(c) Replacement of a biological AS with one of a slightly different molecular structure 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.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological substance which may have a significant impact on the medicinal product and is not related to a protocol B.I.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its	22/04/2021	17/06/2021	Annex II	

	corresponding test method B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP 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 B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method B.II.d.1.f - Change in the specification parameters and/or limits of the finished product - Deletion of a specification parameter which may have a significant effect on the overall quality of the finished product B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.1.c - Change in the specification parameters and/or limits of the finished product - Addition of a new specification parameter to the specification with its corresponding test method 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				

II/0119	Update of section 5.1 of the SmPC following submission of the final report following CHMP conclusions on the related postauthorisation measure (MEA 57.12) from the Fabry registry, a global, observational and voluntary program designed to collect uniform and meaningful clinical data related to the onset, progression, and treated course of patients with Fabry disease . This is a long term effectiveness study to enhance the understanding of long-term severe events and clinical continuous outcomes of Fabrazyme among 5 subgroups identified by modified Arends criteria, estimate the disease progression after Fabrazyme treatment among Classic male patients with sustained anti-agalsidase beta immunoglobulin G (IgG) antibodies (ADA); and compare the long-term effectiveness of Fabrazyme between Classic patients with lower-dose regimen and those with standard-dose regimen. C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	25/03/2021	17/06/2021	SmPC	The dataset contained in this registry did not allow to confirm the relevant clinical benefits expected in long term treatment with Fabrazyme. However, information relevant to the prescribers were added regarding the observed relationship between the incidence rate of the composite of severe clinical events and the peak of drug antibodies concentration.
II/0120	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	14/01/2021	n/a		
II/0116	Update of sections 4.2 and 5.1 of the SmPC in order to change posology recommendations in adults, children and adolescents aged 8 years and older by	17/09/2020	27/10/2020	SmPC and PL	After reviewing the observational published data, the CHMP recommended to remove the information on the lower dose regimen of 0.3 mg/kg every 2 weeks in the posology

	removing the information on the lower dosing regimens that have been used in clinical studies and update the clinical information based on the review of published scientific literature including two observational studies in patients remaining on standard dose of Fabrazyme or switching to lower dose regimens. In addition, the MAH took the opportunity to propose changes in the Product Information according to the QRD templates and current guidelines, including new warnings related to sodium excipient and traceability of biological medicinal products. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				section of the SmPC. The existing information on the short term data of the AGAL-017-01 dose maintenance (0.3 mg/kg every 2 weeks) study was subsequently removed from section 5.1 of the SmPC and replace by the long term data of two main observational studies in patients remaining on standard dose of Fabrazyme or switching to lower dose regimens, noting that comparison between different observational groups should be cautiously interpreted due to the study designs.
II/0113	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority	17/04/2020	27/10/2020	Annex II	
IA/0117	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	10/04/2020	n/a		
PSUSA/70/20 1907	Periodic Safety Update EU Single assessment - agalsidase beta	12/03/2020	n/a		PRAC Recommendation - maintenance
IB/0115	B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is	21/01/2020	n/a		

	increased/decreased without process change (e.g. duplication of line)				
IA/0114/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.7 - Administrative change - Deletion of manufacturing sites	11/12/2019	27/10/2020	Annex II and PL	
IA/0111/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	30/08/2019	n/a		
IG/1003	A.1 - Administrative change - Change in the name and/or address of the MAH	20/12/2018	28/11/2019	SmPC, Labelling and PL	
IB/0109	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	20/12/2018	n/a		
II/0108/G	This was an application for a group of variations. B.I.b.1.e - Change in the specification parameters and/or limits of an AS, starting	15/11/2018	n/a		

	material/intermediate/reagent - Deletion of a specification parameter which may have a significant effect on the overall quality of the AS and/or the FP B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
II/0107	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	18/10/2018	n/a		
II/0106	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	13/09/2018	n/a		
IB/0105/G	This was an application for a group of variations. B.I.a.4.z - Change to in-process tests or limits applied during the manufacture 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	17/05/2018	n/a		
N/0104	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/02/2018	28/11/2019	Labelling	

WS/1262	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. 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	14/12/2017	n/a		
IB/0103	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	17/11/2017	n/a		
N/0102	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	26/10/2017	20/12/2017	PL	
II/0099/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site 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	06/07/2017	n/a		

	release/control, and secondary packaging, for biol/immunol medicinal products or pharmaceutical forms manufactured by complex manufacturing processes B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.c - Change in the manufacturing process of the finished or intermediate product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability B.II.b.4.f - Change in the batch size (including batch size ranges) of the finished product - The scale for a biological/immunological medicinal product is increased/decreased without process change (e.g. duplication of line)				
IA/0100/G	This was an application for a group of variations. B.II.b.5.c - Change to in-process tests or limits applied during the manufacture of the finished product - Deletion of a non-significant in-process test B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	16/06/2017	n/a		
IA/0097/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	16/03/2017	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
PSUSA/70/20 1607	Periodic Safety Update EU Single assessment - agalsidase beta	09/03/2017	n/a		PRAC Recommendation - maintenance
II/0093	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	23/02/2017	n/a		
II/0094	Update of sections 4.2, 4.8, 5.1 and 5.2 of the SmPC with information from paediatric study AGAL06207/EFC12821/FIELD, a Randomized, Multicenter, Multinational, Phase 3B, Open- Label, Parallel-Group Study of Fabrazyme (agalsidase beta) in Treatment-Naive Male Paediatric Patients with Fabry Disease Without Severe Symptoms, after its assessment in procedure EMEA/H/C/000370/P46/063. The Package Leaflet is updated accordingly. In addition, the Marketing authorisation holder (MAH) took the opportunity to update the list of local representatives for Bulgaria, Romania, Spain, Greece, Cyprus and France in the Package Leaflet and to bring the PI in line with the latest QRD template version 10.0.	26/01/2017	20/12/2017	SmPC, Annex II, Labelling and PL	The safety and efficacy of Fabrazyme in children aged 0 to7 years have not yet been established. No recommendation on posology can be made in children aged 5 to 7 years. No data are available in children 0 to 4 years. Limited information from clinical trials suggests that the safety profile of Fabrazyme treatment in paediatric patients ages 5-7, treated with either 0.5 mg/kg every 2 weeks or 1.0 mg/kg every 4 weeks is similar to that of patients (above the age of 7) treated at 1.0 mg/kg every 2 weeks. For more information, please refer to the Summary of Product Characteristics.

	C.I.3.b - 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 - Change(s) with new additional data submitted by the MAH				
IB/0095/G	This was an application for a group of variations. 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.1.k - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - New storage site of MCB and/or WCB B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	20/12/2016	n/a		
II/0091	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	15/09/2016	n/a		

IB/0090	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	03/05/2016	n/a		
IB/0089	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	12/04/2016	n/a		
IB/0086/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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/01/2016	n/a		
IA/0088/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 B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	04/01/2016	n/a		
IA/0087/G	This was an application for a group of variations.	04/01/2016	n/a		

	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure				
IB/0085/G	This was an application for a group of variations. B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	21/12/2015	n/a		
IB/0084	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	10/12/2015	n/a		

	control/testing takes place				
IB/0083	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	11/09/2015	n/a		
IB/0082	To delete a bioburden specification of ethylene glycol; yhe MAH take his opportunity to make minor typographical correction in 3.2.S.2.3 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	09/07/2015	n/a		
II/0081	B.II.e.1.b.2 - Change in immediate packaging of the finished product - Change in type/addition of a new container - Sterile medicinal products and biological/immunological medicinal products	21/05/2015	n/a		
IA/0080	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	19/12/2014	n/a		
IA/0079/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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test	12/12/2014	n/a		

	procedure B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0078	B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased without process change (e.g. duplication of line)	16/09/2014	n/a		
IB/0077	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	11/07/2014	n/a		
II/0074/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.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP -	26/06/2014	19/06/2015	SmPC, Annex II, Labelling and PL	

	Including batch control/testing				
IB/0076	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	20/05/2014	n/a		
IB/0075	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	20/05/2014	n/a		
IG/0418	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	11/04/2014	n/a		
IA/0072/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.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	27/03/2014	n/a		

	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				
PSUV/0070	Periodic Safety Update	06/03/2014	n/a		PRAC Recommendation - maintenance
IB/0071/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.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	06/02/2014	n/a		
N/0069	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	07/11/2013	23/07/2014	PL	
IB/0068	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	23/10/2013	n/a		
IA/0067	A.7 - Administrative change - Deletion of manufacturing sites	25/07/2013	23/07/2014	Annex II	
IB/0066	B.I.a.3.e - Change in batch size (including batch size ranges) of AS or intermediate - The scale for a biological/immunological AS is increased/decreased	03/05/2013	n/a		

	without process change (e.g. duplication of line)				
IB/0064	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition)	17/04/2013	n/a		
IG/0283	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/03/2013	n/a		
IB/0062	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	20/03/2013	n/a		
IA/0063	B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	14/03/2013	n/a		
IB/0059	B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate	21/02/2013	n/a		
IB/0061	B.I.a.3.z - Change in batch size (including batch size ranges) of AS or intermediate - Other variation	12/02/2013	n/a		
IB/0060/G	This was an application for a group of variations. B.I.a.4.f - Change to in-process tests or limits	03/01/2013	n/a		

	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.b.1.c - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Addition of a new specification parameter to the specification with its corresponding test method				
IB/0056	To register a new primary reference standard 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	13/09/2012	n/a		
N/0057	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/07/2012	23/07/2014	PL	
N/0055	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	13/04/2012	23/07/2014	PL	
IB/0054	B.V.c.1.c - Change management protocol - Update of the quality dossier to implement changes, requested by the EMA/NCA, following assessment of a change management protocol - Implementation of a change for a biological/immunological medicinal product	12/01/2012	n/a		
II/0049	Inclusion of a statement in section 4.2 (Posology and Method of Administration) of the SmPC about the	22/09/2011	22/11/2011	SmPC, Annex II, Labelling	Based on the assessment of the submitted Healthcare Professional Guidance and the Patient Manual and on the

	possibility for the patients to be treated by home infusion with Fabrazyme. Consequently, section 3 of the Package Leaflet and Annex II and Annex 127a have been modified. In addition, the Product Information has been revised to comply with the current QRD Human Product Information Template and information on the local representatives has been updated. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data			and PL	evaluation of identified and potential risks of home infusion, the CHMP accepted the proposal for the MAH to include the possibility of home infusion in the PI. Section 4.2 of the SmPC and section 3 of the Package Leaflet have been updated, and the conditions of use were included in Annex II and Annex 127a.
II/0051	Active substance Post Approval Change Management Protocol B.I.e.2 - Design Space - Introduction of a post approval change management protocol related to the AS	20/10/2011	20/10/2011		
IG/0104	A.7 - Administrative change - Deletion of manufacturing sites	27/09/2011	n/a		
IG/0103/G	This was an application for a group of variations. B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate from an already approved manufacturer	21/09/2011	n/a		

II/0050	Change to in-process limits applied during the manufacturer of the active substance. B.I.a.4.d - Change to in-process tests or limits applied during the manufacture of the AS - Widening of the approved in-process test limits, which may have a significant effect on the overall quality of the AS	23/06/2011	23/06/2011		
II/0048	Update of Summary of Product Characteristics and Package Leaflet C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	14/04/2011	07/06/2011	SmPC and PL	This type II variation concerns an update of section 5.1 to include postmarketing information on the long term low dosage use. Section 4.7 was updated in line with the adverse events and safety profile of the medicinal product. The PIL is amended accordingly. In addition, the Product Information has been updated with the wording in line with the current QRD Human Product Information Template. Information on the local representatives has been updated. In the CHMP 'Assessment report on the shortage of Fabrazyme' Overview of Shortage Period: Spontaneous Reports from June 2009 through 15 September 2010 and Registry Data from June 2009 through 05 August 2010' of January 2011, the CHMP requested the MAH the following: "The MAH should include the important safety data on long-term low dosage use that has become available during the shortage of Fabrazyme in the SPC in section 5.1." This resulted in the addition of relevant information in section 5.1 of the SmPC, stating that in patients who initiated treatment at a Fabrazyme dose of 1 mg/kg every 2 weeks and subsequently received a reduced dose for an extended period, an increase of some of the following

					symptoms such as pain, paraesthesia and diarrhoea, as well as cardiac, central nervous system and renal manifestations was spontaneously reported. These reported symptoms resemble the natural course of Fabry disease. The Package Leaflet was updated accordingly. In addition, section 4.7 was updated in line with the adverse events and safety profile of the medicinal product. The benefit-risk ratio of the medicinal products remains favourable.
II/0047/G	This was an application for a group of variations. Add sites for the manufacture and control of the drug product. 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.b.2.b.2 - Change to batch release arrangements and quality control testing of the FP - Including batch control/testing	17/03/2011	29/03/2011		
IA/0046	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	28/06/2010	n/a		
IA/0045	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	28/06/2010	n/a	Annex II	

	in the manufacture of the AS				
IB/0044	To extend of 14 days the testing period of the In Vitro assay for viral contaminants. Testing will now occur at day 14 (as previously) and also at day 28. The test is only carried out on the harvest material this method is then removed from 3.2.P.5.2 and 3.2.P.5.3 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	25/06/2010	n/a		
IA/0043	To tighten the in-process pre-filtration bioburden specification from =< 2 CFU/10 ml to =< 10 CFU/100 ml, for the formulated bulk drug substance. An alert limit for bioburden is set at >0 CFU/100ml (previously 1 CFU/ml) B.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	21/05/2010	n/a		
II/0042	Change in the manufacturing process of the active substance B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal	22/04/2010	27/04/2010		

	product and is not related to a protocol				
IA/0041	To group Genzyme Corporation 45, 51, 74, 76 and 80, New York Avenue Framingham, MA 01701-9322, USA in one manufacturing facility Genzyme Corporation New York Avenue Framingham, MA 01701-9322, USA. 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	09/02/2010	n/a		
II/0039	Update of section 4.8 of the Summary of Product Characteristics (SPC) with the terms "oxygen saturation decreased" and "hypoxia". Section 4 of the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to correct minor linguistic errors in the SPC and to update Annex II to be inline with the current QRD requirements. Update of Summary of Product Characteristics and Package Leaflet	17/12/2009	25/01/2010	SmPC, Annex II and PL	Based on an annual cumulative review of the adverse event (AE) data from the AE database of the MAH, two additional terms, "oxygen saturation decreased" and "hypoxia" were identified. The CHMP accepted the MAH proposal to include the two terms with the frequency "unknown" in section 4.8 of the SPC. Section 4 of the Package Leaflet was updated accordingly.
IA/0040	To change an in-process control test. IA_31_a_Change to in-process tests/limits during manufacture - tightening of in-process limits	01/12/2009	n/a		
II/0037	Update of the descriptions of analytical methods for	24/09/2009	05/10/2009		

	the active substance and the finished product. Update of or change(s) to the pharmaceutical documentation				
II/0038	Changes in the active substance manufacturing process. Change(s) to the manufacturing process for the active substance	24/09/2009	01/10/2009		
IA/0036	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	16/07/2009	n/a		
N/0035	Update of the list of local representatives in section of 6 of the Package Leaflet (PL). Additionally the MAH corrected a typing mistake in the Danish and Swedish PL for Fabrazyme 5mg. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	15/07/2009	n/a	PL	
IB/0034	IB_31_a_Change to in-process tests/limits during manufacture - tightening of in-process limits	12/05/2009	n/a		
II/0033	Change in controls for manufacture of active substance Change(s) to the manufacturing process for the active substance	19/02/2009	27/02/2009		

II/0031	The Marketing Authorisation Holder applier to include an additional type of (chlorobutyl) stopper for the finished product. Change(s) to the manufacturing process for the finished product	25/09/2008	01/10/2008		
IB/0032	IB_12_b_02_Change in spec. of active subst./agent in manuf. of active subst. - test parameter	16/09/2008	n/a		
N/0030	Update of section 2 of the Package Leaflet (PL) to reword the paragraph on how to act in case of a infusion-associated reaction. In addition sections 3, 4 and 6 of the PL have been updated and minor linguistic amendments have been introduced throughout the PL. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	12/08/2008	n/a	PL	
IB/0029	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	29/04/2008	n/a		
IB/0028	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	29/04/2008	n/a		
S/0027	Annual re-assessment.	13/12/2007	06/02/2008	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having reassessed the benefit-risk profile of Fabrazyme concluded that the benefit risk remains favourable since all specific obligations have been

					fulfilled (las specific obligation was submitted and assessed as part of variation type II EMEA/H/C/0370/II/25), there are no remaining grounds for the Marketing Authorisations to remain under exceptional circumstances. Section 4.8 "Undesirable effects" of the SPC has been amended to include editorial restructuring on the adverse events section. This information was also reflected in the Package Leaflet of the product. Furthermore following the user readability testing the PL was restructured. The contact details of the local representative for Romania have been amended.
II/0026	Change(s) to the manufacturing process for the active substance	18/10/2007	24/10/2007		
II/0025	Update of the sections 4.2 and 5.1 of the Summary of Product Characteristics to reflect the results of the clinical study AGAL-017-01(Dose Maintenance Study). Update of Summary of Product Characteristics, Labelling and Package Leaflet	19/07/2007	22/10/2007	SmPC, Labelling and PL	The CHMP reviewed the results from the dose maintenance study AGAL-017-01 and considered that although no definitive conclusion regarding the dose maintenance regimen can be drawn due to the limitations of the study design (small number of patients, post hoc analysis), a dose regimen of 0.3 mg/kg of Fabrazyme every 2 weeks for 18 months was able to maintain the clearance of cellular GL-3 in the capillary endothelium of the kidney, other kidney cell types and skin (superficial skin capillary endothelium) in some patients following treatment with 1 mg/kg of Fabrazyme every other week for 24 weeks. These findings suggested that, after an initial debulking dose of 1.0 mg/kg of Fabrazyme every 2 weeks, 0.3 mg/kg of Fabrazyme every 2 weeks may be sufficient in some patients to maintain clearance of GL-3, the long term

					clinical relevance of these findings not being established.
S/0024	Annual re-assessment.	14/12/2006	15/02/2007	SmPC, Annex II and PL	
II/0023	Based on the results of three clinical studies (AGAL-008-00, AGAL-005-99 and AGAL-019-01), the Marketing Authorisation Holder (MAH) has applied for an update of sections 4.4, 4.8, 5.1 of the Summary of Product Characteristics (SPC) to include information on the long-term efficacy and safety of Fabrazyme. In addition, change to section 6.6 of the SPC has been made according to QRD templates. Sections 2 and 4 of the Package Leaflet have been amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	14/12/2006	24/01/2007	SmPC and PL	The CHMP reviewed the study AGAL-008-00 as part of type II variation (EMEA/H/C/370/II/16) and studies AGAL-005-99 and AGAL-019-01 at the time of the fourth annual reassessment (EMEA/H/C/370/S/18). Based on these three clinical studies, changes in section 4.4 of the SPC to update the information on development of antibodies and infusion-associated reactions (IAR) with the most recent figures. Results from the rechallenge study AGAL-019-01 were also reflected in section 4.4 of the SPC. In addition, further to CHMP's recommendations, the MAH updated section 4.8 of the SPC to include all adverse events with corresponding frequencies in accordance with the SPC guideline and presented adverse events using the MedDRA terminology. Finally, changes in section 5.1 of the SPC were also made to reflect the efficacy data obtained up to a total of 5 years of treatment. All these changes were considered acceptable by the CHMP.
II/0022	Based on the evaluation of Specific Obligation 2 (paediatric clinical study AGAL-016-01), the Marketing Authorisation Holder has applied for an update of sections 4.2, 4.8, 5.1 and 5.2 of the Summary of Product Characteristics. Section 3 of the Package Leaflet has been amended accordingly. In addition, contact details of Bulgaria and Romania local representatives were also included. Update of Summary of Product Characteristics and	14/12/2006	24/01/2007	SmPC, Annex II and PL	The CHMP reviewed results from the paediatric study AGAL-016-01 and considered that although the trial was not powered to demonstrate clinical benefit, the results show consistent trend for clinical improvements, including improvement of early disease manifestations in major organs such as the kidney and heart in children (8-16 years). The CHMP concluded that the overall safety and efficacy profile of Fabrazyme treatment administered at 1 mg/kg every 2 weeks in paediatric patients (8-16 years) was consistent with the one observed in adults. The CHMP

	Package Leaflet				considered the proposed changes to the product information to reflect information on this paediatric study to be acceptable.
II/0019	Change(s) to shelf-life or storage conditions	27/07/2006	01/09/2006	SmPC and PL	
N/0021	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/08/2006	n/a	PL	
R/0020	Renewal of the marketing authorisation.	01/06/2006	28/07/2006	SmPC, Annex II, Labelling and PL	
S/0018	Fourth annual re-assessment.	14/12/2005	13/02/2006	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 of the medicinal product, concluded that, overall, the benefit/risk balance for the product remains unchanged and recommends that no amendment of Annexes I and III of the Commission Decision is necessary. The list of Specific obligations is set out in Annex II.C and has been revised according to the conclusions of the CHMP discussion. The CHMP considered that the Marketing Authorisation for Fabrazyme should remain under exceptional circumstances in view of the pending Specific Obligations.
II/0017	Change(s) to the manufacturing process for the active substance	15/09/2005	23/09/2005		

II/0016	Update of the Summary of Product Characteristics (section 5.1) and Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	23/06/2005	01/08/2005	SmPC and PL	Section 5.1 of the Summary of Product Characteristics (SPC) was updated to incorporate newly available data. In addtion, the Package Leaflet was also updated with new contact details of local representatives.
S/0014	Third annual re-assessment.	15/12/2004	03/03/2005	SmPC, Annex II, Labelling 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 of the medicinal product, concludes that, overall, the benefit/risk balance for the product remains unchanged. Section 4.8 of Annex I of the Commission Decision (SPC), was changed. Annex IIIB (Package leaflet) of the Commission Decision was amended accordingly in its section 4. The Marketing Authorisation for Fabrazyme should remain under exceptional circumstances in view of the pending Specific Obligations.
IB/0015	IB_30_b_Change in supplier of packaging components - replacement/addition	22/02/2005	n/a		
IB/0013	IB_38_c_Change in test procedure of finished product - other changes	13/10/2004	n/a		
II/0012	This variation concerns updates to the SPC and section the PIL further to the conclusions of the assessment of the fourth PSUR.	23/06/2004	09/08/2004	SmPC and PL	Further to the conclusions of the assessment of the fourth PSUR, section 4.4 and 4.8 of the Summary of Product Characteristics (SPC) and section 4 of the Package Leaflet

	Update of Summary of Product Characteristics and Package Leaflet				(PL) were updated.
S/0010	Second annual re-assessment	22/10/2003	16/01/2004	SmPC, Annex II and PL	The CPMP, having reviewed the evidence of compliance with the specific obligations submitted by the Marketing Authorisation Holder and having re-assessed the benefit/risk profile of the medicinal product, concludes that, overall, the benefit/risk balance for the product remains unchanged. Annex I of the Commission Decision (SPC), was changed to include a statement in section 4.4). Annex IIIB (Package leaflet) of the Commission Decision has been amended accordingly. The Marketing Authorisation for Fabrazyme should remain under exceptional circumstances in view of the pending Specific Obligations.
I/0011	24_Change in test procedure of active substance 24a_Change in test procedure for starting material/intermediate used in manuf. of active substance	17/12/2003	15/01/2004		
I/0009	20_Extension of shelf-life as foreseen at time of authorisation	09/07/2003	05/08/2003	SmPC	
II/0008	Update of section 4.8 of the SPC and the corresponding section 4 of the Package Leaflet (PIL) as requested by CPMP following the assessment of the second PSUR. Update of Summary of Product Characteristics and Package Leaflet	25/04/2003	22/07/2003	SmPC and PL	

II/0007	Update of Summary of Product Characteristics and Package Leaflet	20/02/2003	19/05/2003	SmPC, Labelling and PL	
II/0005	Change(s) to the manufacturing process for the active substance Change(s) to the manufacturing process for the finished product	23/01/2003	20/02/2003	Annex II	
S/0006	Annual re-assessment.	17/10/2002	24/01/2003	Annex II	
II/0004	New presentation(s)	19/09/2002	02/12/2002	SmPC, Labelling and PL	
I/0002	24_Change in test procedure of active substance	09/08/2002	17/09/2002		
II/0003	Change(s) to the test method(s) and/or specifications for the active substance	25/07/2002	29/07/2002		
I/0001	03_Change in the name and/or address of the marketing authorisation holder	14/12/2001	07/03/2002	SmPC, Labelling and PL	