Replagal

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/0120/G	This was an application for a group of variations. 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)	12/05/2022		Annex II 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).

	B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing A.7 - Administrative change - Deletion of manufacturing sites				
T/0118	Transfer of Marketing Authorisation	01/03/2022	01/04/2022	SmPC, Labelling and PL	
PSUSA/69/202108	Periodic Safety Update EU Single assessment - agalsidase alpha	10/03/2022	n/a		PRAC Recommendation - maintenance
IAIN/0119	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	25/02/2022	n/a		
IB/0116/G	This was an application for a group of variations. B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) 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	25/02/2022	n/a		
II/0112/G	This was an application for a group of variations.	09/09/2021	n/a		

	B.I.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.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				
IAIN/0114	A.1 - Administrative change - Change in the name and/or address of the MAH	26/07/2021	26/11/2021	SmPC, Labelling and PL	
IA/0113	A.7 - Administrative change - Deletion of manufacturing sites	29/06/2021	n/a		
IB/0111	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	20/01/2021	n/a		
II/0106	Update of sections 4.8 and 4.4 of the Summary of Product Characteristics (SmPC) in order to update the list of adverse drug reactions (ADRs) information based on the final results from study HGT-REP-081 " a Multicenter Open-label Treatment Protocol to Observe the Safety of Replagal (agalsidase alfa) Enzyme Replacement Therapy in Canadian Patients with Fabry Disease" and the safety information reported in clinical trials. In addition, the MAH took the opportunity to introduce editorial and QRD	26/11/2020	26/11/2021	SmPC and PL	Following review of the submitted data, the list of adverse drug reactions (including frequencies) have been updated in the corresponding SmPC table, taking into account the pooled data of relevant individual clinical studies. In addition, safety information related to clinical trials has also been updated accordingly. For more information, please refer to the Summary of Product Characteristics.

	changes in sections throughout the Product Information according to the QRD templates and current guidelines, including new warnings related to sodium excipient and traceability of biological medicinal products. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				
IB/0110	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	30/09/2020	n/a		
IAIN/0109/G	This was an application for a group of variations. 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) A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	06/07/2020	n/a		
IB/0108	B.I.d.1.a.4 - Stability of AS - Change in the re-test	11/06/2020	n/a		

	period/storage period - Extension or introduction of a re-test period/storage period supported by real time data				
IA/0107	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)	17/03/2020	n/a		
IAIN/0105	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	28/01/2020	n/a		
IAIN/0104	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	22/10/2019	n/a		
IB/0103/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.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	18/06/2019	n/a		
IB/0102/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of	27/03/2019	n/a		

	manufacturing sites A.7 - Administrative change - Deletion of manufacturing sites 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				
PSUSA/69/201808	Periodic Safety Update EU Single assessment - agalsidase alpha	14/03/2019	n/a		PRAC Recommendation - maintenance
IB/0100	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	22/11/2018	n/a		
IB/0101/G	This was an application for a group of variations. B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.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	21/11/2018	n/a		
IA/0098/G	This was an application for a group of variations. A.5.b - Administrative change - Change in the name and/or address of a manufacturer/importer of the	17/08/2018	n/a		

	finished product, including quality control sites (excluding manufacturer for batch release) A.7 - Administrative change - Deletion of manufacturing sites				
IA/0097/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.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	17/01/2018	n/a		
IAIN/0096	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	21/11/2017	25/10/2018	Annex II and PL	
IA/0095	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)	11/11/2016	n/a		
IA/0094/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	15/09/2016	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.7 - Administrative change - Deletion of manufacturing sites				
IAIN/0093	A.1 - Administrative change - Change in the name and/or address of the MAH	14/07/2016	06/10/2016	SmPC, Labelling and PL	
PSUSA/69/20 1508	Periodic Safety Update EU Single assessment - agalsidase alpha	11/02/2016	n/a		PRAC Recommendation - maintenance
IB/0092/G	This was an application for a group of variations. 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 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.II.b.5.a - Change to in-process tests or limits applied during the manufacture of the finished product - Tightening of in-process limits	14/01/2016	n/a		
IAIN/0091	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	21/10/2015	06/10/2016	Annex II and PL	

	responsible for importation and/or batch release - Not including batch control/testing				
IG/0621	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	16/10/2015	n/a		
IB/0088	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	10/08/2015	n/a		
S/0086	13th Annual Re-assessment	21/05/2015	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and having reassessed the impact of data submitted as part of this annual re-assessment, considers that the benefit/risk balance of Replagal remains positive and therefore, recommends by consensus the variation to the terms of the Marketing Authorisation for the medicinal product. In addition, the CHMP considers that all specific obligations have now been fulfilled and there are no remaining grounds for the Marketing Authorisation to remain under exceptional circumstances. The data provided by the LTER 5 year outcome study are considered robust and reliable. They provide further long term efficacy and safety data on the use of Replagal in patients with Fabry disease treated with a 0.2 mg EOW regimen. Therefore the specific obligation 041.6 1a is now considered fulfilled. It is agreed that a further a Low-Dose Maintenance Clinical Study would be difficult to perform and would not add

					further value, to the current knowledge gathered through literature and registry since initial approval. Amendments are introduced in the SmPC section 5.1 reflect the current knowledge with the use of a lower maintenance dose (0.1 mg/kg/body weight).
PSUSA/69/201408	Periodic Safety Update EU Single assessment - agalsidase alpha	12/02/2015	n/a		PRAC Recommendation - maintenance
II/0084/G	This was an application for a group of variations. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/07/2014	10/02/2015	SmPC, Annex II and PL	
IB/0085/G	This was an application for a group of variations. B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits	13/06/2014	n/a		

	B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits B.I.b.1.b - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Tightening of specification limits 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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
S/0080	Annual re-assessment.	23/01/2014	21/03/2014	Annex II	
II/0083	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	10/02/2015	SmPC, Annex II, Labelling and PL	
PSUV/0081	Periodic Safety Update	06/02/2014	n/a		PRAC Recommendation - maintenance

IB/0082/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.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised A.7 - Administrative change - Deletion of manufacturing sites	03/01/2014	n/a		
II/0078	Update of section 5.1 of the SmPC as requested by the CHMP after assessment of specific obligation SO2 041.5 1b (final analysis of data in patients enrolled in study TKT028) in order to add information on various dosing regimen. The Package Leaflet is updated accordingly. Furthermore, the PI is being brought in line with the latest QRD template version 9.0 and to update Annex II in order to reflect the fulfilment of two specific obligations. The requested variation proposed amendments to the Summary of Product Characteristics, Annex II, Labelling 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	21/11/2013	21/03/2014	SmPC, Annex II, Labelling and PL	With the submission of final study report from the clinical study on the use of various dosing regiments of Replagal, important clinical data became available and the CHMP requested the update of section 5.1 of the SmPC and Patient Leaflet. This study was submitted in fulfilment of a specific obligation. The benefit-risk balance of Replagal remains positive.
IA/0077	B.II.e.5.b - Change in pack size of the finished	14/08/2013	21/03/2014	SmPC,	

	product - Deletion of a pack size(s)			Labelling and PL	
S/0075	Annual Reassessment.	25/04/2013	n/a		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.
WS/0291	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.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	21/02/2013	n/a		
II/0076	Update of section 5.1 of the SmPC in order to add safety information from the interim report of study HGT-REP-059, summarising the results from this prospectively defined interim analysis of the 12 month experience of open-label Replagal AF (Animal Free process) treatment in US patients with Fabry disease and to include information on patients switched from Fabrazyme to Replagal. Minor formatting changes have been implemented in sections, 4.8, 5.1, 5.2 and 6.5 of the SmPC. The requested variation proposed amendments to the Summary of Product Characteristics.	17/01/2013	01/07/2013	SmPC	Based on the preliminary results available from the on-going clinical study HGT-REP-059, the MAH proposed to update section 5.1 of the SmPC of Replagal. This information is of interest for patients and treating physician as it indicates that (short-term) safety is not compromised by the switch from Fabrazyme to Replagal.

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				
IA/0073/G	This was an application for a group of variations. B.I.a.4.a - Change to in-process tests or limits applied during the manufacture of the AS - Tightening of in-process limits B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits	19/09/2012	n/a		
IG/0216	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/09/2012	n/a		
IB/0072	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	14/09/2012	n/a		
IG/0175/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)	04/06/2012	17/09/2012	Annex II	

S/0068	Annual reassessment	15/12/2011	17/02/2012	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.
IB/0067	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	07/12/2011	17/02/2012	SmPC and PL	
II/0066	Change in the manufacturer of the active substance. 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	23/06/2011	23/06/2011		
II/0064	Change in the specification parameters of the finished product. B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	19/05/2011	19/05/2011		
II/0063/G	This was an application for a group of variations. Addition of manufacturing sites responsible for the manufacturing process of the finished product.	17/03/2011	29/03/2011		

	Change in the batch size of the finished 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.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) 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.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site 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.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.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				

IB/0062	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)	14/03/2011	n/a		
S/0060	Annual re-assessment.	16/12/2010	07/01/2011		
IG/0029	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)	02/12/2010	n/a		
II/0058	Addition of alternative storage of cell banks and GMP storage facility. 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	23/09/2010	29/09/2010		
II/0056	Addition of a manufacturer responsible for batch release testing of the finished product. 01_Change in or addition of manufacturing site(s) for part or all of the manufacturing process	24/06/2010	01/07/2010		
IA/0059	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	24/06/2010	n/a	Annex II and PL	

IB/0057	Extension of the long term storage period of the unpurified bulk active substance intermediate. B.I.d.1.a.4 - Stability of AS - Change in the re-test period/storage period - Extension or introduction of a re-test period/storage period supported by real time data	16/02/2010	n/a		
II/0054	Update of sections 4.2, 4.4, 4.8 and 5.1 of the Summary of Product Characteristics to include details emerging from study TKT-029. Additionally, sections 4.4 and 4.8 were updated to include relevant information from a cumulative review of cardiac events up to August 2008. Section 2 of the Package Leaflet have been updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	19/11/2009	22/12/2009	SmPC and PL	The MAH has performed a long term paediatric extension study (TKT 029) in 17 children aged 8.5 to 18 years to assess the safety of enzyme replacement therapy (ERT) with Replagal in Fabry disease. The results of study TKT029 indicate that the effects of Replagal treatment on manifestations of Fabry disease in children 7-18 years of age are consistent with those reported in adults. The pharmacokinetic results were as expected, and it was concluded that Replagal is cleared faster from circulation in children (7-18) then in adults. Although the data interpretation of the renal efficacy endpoint (eGFR) and the pain endpoint is limited by the small sample size, the observed effects suggest an improvement over time for both variables. The adverse drug reactions (ADRs) reported in the study were similar to those seen in the adult population and represent symptoms commonly seen in patients with Fabry disease. Based on the observations in the study the CHMP recommended an update of sections 4.2, 4.4, 4.8 and 5.1 of the SPC. The MAH also performed a review on cardiac events and Replagal infusions. The review did not reveal any causal

					association of cardiac events with Replagal. However, it was noted than that in patients with pre-existing cardiac manifestations of Fabry disease, infusion reactions may be associated with hemodynamic stress triggering a cardiac event. The CHMP therefore recommended an update of sections 4.4 and 4.8 to include a relevant warning.
S/0055	Annual re-assessment.	17/12/2009	n/a		
IA/0053	IA_05_Change in the name and/or address of a manufacturer of the finished product	04/09/2009	n/a		
IA/0052	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	24/06/2009	n/a		
II/0050	Change in drug substance manufacturing process. Change(s) to the manufacturing process for the active substance	23/04/2009	28/04/2009		
II/0051	Addition of new quality control laboratory and change in name of an existing manufacturer. Change(s) to the manufacturing process for the active substance Change(s) to the manufacturing process for the finished product	19/12/2008	23/03/2009		
S/0048	Annual re-assessment.	18/12/2008	n/a		
IA/0049	IA_01_Change in the name and/or address of the marketing authorisation holder	31/10/2008	n/a	SmPC, Labelling and	

				PL	
IB/0047	IB_36_a_Change in shape or dimensions of the container/closure - sterile ph. forms/biologicals	17/10/2008	n/a		
IA/0046	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	11/04/2008	n/a		
II/0045	Change(s) to the manufacturing process for the active substance	19/03/2008	26/03/2008		
S/0043	Annual re-assessment.	13/12/2007	05/03/2008	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 of the medicinal product, concludes that overall, the benefit/risk ratio for the product remains unchanged. The CHMP considered that the Marketing Authorisation for Replagal should remain under exceptional circumstances in view of the pending specific obligations. Additionally, the section 4.4 "Special warnings and precautions for use" of the SPC has been amended to include "dizziness" and "hyperhidrosis" as an Infusion related reaction. The relevant section in the Package Leaflet has been updated.
II/0044	Change(s) to the manufacturing process for the finished product	13/12/2007	21/12/2007		
II/0041	Change(s) to the test method(s) and/or specifications for the active substance	18/10/2007	24/10/2007		

IA/0042	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	17/09/2007	n/a	Annex II and PL	
S/0037	Fifth annual re-assessment	14/12/2006	12/02/2007	SmPC, 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 ratio for the product remains unchanged. The CHMP considered that the Marketing Authorisation for Replagal should remain under exceptional circumstances in view of the pending specific obligations. Additionally, an update of the number of pregnancies exposed to Replagal (n=4) in section 4.6 of the Summary Product Characteristics and corresponding section of the Package Leaflet was made.
II/0035	This variation relates to an update of sections 4.2 and 5.1 of the Summary of Product Characteristics to include long term efficacy data with regards to renal function, cardiac function and life quality enhancement based on several studies summarized in the 3rd Annual Reassessment. EMEA/H/C/369/S/25. Update of Summary of Product Characteristics	18/10/2006	24/11/2006	SmPC	Changes in the SPC section 4.2 Posology and method of administration and section 5.1 Pharmacodynamic properties. These changes are based on data accumulated since the granting of the Marketing Authorisation and that have previously been reported in clinical study reports submitted to the CHMP or in analyses that were summarized in the 3rd Annual Reassessment EMEA/H/C/369/S/25. The following information included in the Replagal SPC is based on the combined analysis of the effect of long-term Replagal therapy on renal function in adult Fabry patients enrolled in the studies submitted to the EMEA as part of the initial application and the clinical study reports for studies were submitted and assessed post marketing.

					Changes related to the renal function Update of section 4.2 Posology and method of administration of the Replagal SPC for end-stage renal disease (ESRD) and section 5.1 as follows. 4.2 Posology and method of administration Patients with renal impairment No dose adjustment is necessary in patients with renal impairment. The presence of extensive renal damage (eGFR <60mL/min) may limit the renal response to enzyme replacement therapy. Limited data are available in patients on dialysis or post-kidney transplantation, no dose adjustment is recommended. And section 5.1 Pharmacodynamic properties "Longer term therapy (48-54 months) resulted in stabilisation of GFR in male patients with normal baseline GFR (= 90 mL/min/1.73 m2) and with mild to moderate renal dysfunction (GFR 60 to < 90 mL/min/1.73 m2), and in slowing of the rate of decline in renal function and progression to end-stage renal disease in male Fabry patients with more severe renal dysfunction (GFR 30 to < 60 mL/min/1.73 m2)." Changes related to cardiac function The MAH proposed changes to section 5.1 based on the combined analysis of Left Ventricular (LV) mass changes with long-term Replagal therapy in adult Fabry patients.

					The following information is included in sect
IA/0036	IA_01_Change in the name and/or address of the marketing authorisation holder	13/09/2006	n/a	SmPC, Annex II, Labelling and PL	
II/0034	This variation refers to an update of relevant sections of the Summary Product Characteristics (SPC) to include information on paediatric patients further to the fourth annual reassessment. Corresponding section of the Package Leaflet (PL) was amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	01/09/2006	SmPC and PL	During the fourth annual reassessment, the CHMP reviewed data on the use of Replagal in paediatric patients (7-18 years) and recommended to reflect this information into the Summary Product Characteristics (SPC). Therefore, the Marketing Authorisation Holder (MAH) submitted this type II variation to update relevant sections of the SPC and also proposed to amend section 2 of the Package Leaflet (PL) accordingly. The CHMP considered these changes to be acceptable.
II/0033	This variation refers to an update of section 4.6 of the Summary Product Characteristics (SPC) to include information on pregnancy further to the fourth annual reassessment. Section 2 of the Package Leaflet (PL) was amended accordingly. Update of Summary of Product Characteristics and Package Leaflet	27/07/2006	01/09/2006	SmPC and PL	During the fourth annual reassessment, the CHMP reviewed data on pregnancy exposure to Replagal and recommended to include these data into the SPC. Therefore, the MAH submitted this type II variation to mention in section 4.6 of the SPC that very limited clinical data on pregnancies exposed to Replagal (n=3) have shown no adverse effects on the mother or newborn child. Section 2 of the PL was amended accordingly.The CHMP considered these changes to be acceptable.
R/0030	Renewal of the marketing authorisation.	01/06/2006	28/07/2006	SmPC, Annex II, Labelling and PL	
II/0031	Change(s) to the manufacturing process for the active substance	28/06/2006	03/07/2006		

S/0029	Annual reassessment: Fourth annual re-assessment.	14/12/2005	09/02/2006	Annex II 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, concluded that, overall, the benefit/risk ratio 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 Replagal should remain under exceptional circumstances in view of the pending Specific Obligations.
II/0028	Change(s) to the manufacturing process for the active substance	17/11/2005	22/11/2005		
II/0027	Revision of the Summary of Product Characteristics, section 4.4 and 4.8, and corresponding update of Package Leaflet, sections 2 and 4. Update of Summary of Product Characteristics and Package Leaflet	23/06/2005	27/07/2005	SmPC and PL	Following the assessment of the 5th PSUR and the 3rd Annual Re-assessment, the MAH revised the wordings of sections 4.4 and 4.8 of the Summary of Product Characteristics (SPC) and sections 2 and 4 of the Package Leaflet (PL). The sections were also revised in general to reflect current available data.
S/0025	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, concluded that, overall, the benefit/risk ratio for the product remains

					unchanged and recommends that no amendment of Annexes I and III of the Commission Decision is necessary. The CHMP considered that the Marketing Authorisation for Replagal should remain under exceptional circumstances in view of the pending Specific Obligations.
IA/0026	IA_01_Change in the name and/or address of the marketing authorisation holder	18/11/2004	n/a	SmPC, Labelling and PL	
II/0022	New presentation(s)	24/03/2004	29/07/2004	SmPC, Labelling and PL	The CPMP considered this Type II variation on the addition of a new 1.0ml presentation (1.0mg/ml) in pack sizes of 1, 4 and 10 vials to be acceptable .
II/0023	Update of section 4.4 of the Summary of Product Characteristics, concerning the effects of renal function in patients with extensive renal damage. QRD editorial changes were introduced in section 6.4 of SPC. The Labelling and the Package Leaflet were updated. Update of Summary of Product Characteristics, Labelling and Package Leaflet	26/02/2004	20/07/2004	SmPC, Labelling and PL	As a result of the second annual re-assessment for Replagal in October 2003 the MAH was requested to submit a type II variation in order to adjust the SPC to include reference to therapy being probably less effective in patients with extensive renal damage. The new text was considered a warning and therefore included in section 4.4. Additionally, the section 6.4 was revised to take account of the most recent changes to the QRD. The Labelling and the Package leaflet were consequently updated.
II/0024	Change(s) to shelf-life or storage conditions	24/03/2004	31/03/2004		
II/0021	Change(s) to the manufacturing process for the finished product Change(s) to the test method(s) and/or specifications for the active substance	24/03/2004	31/03/2004		

S/0019	Annual re-assessment.	22/10/2003	16/01/2004	Annex II	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, concluded that, overall, the benefit/risk ratio for the product remained unchanged and recommended that no amendment of Annexes I and III of the Commission Decision was necessary. The Marketing Authorisation for Replagal should remain under exceptional circumstances in view of the pending Specific Obligations.
IB/0020	IB_37_b_Change in the specification of the finished product - add. of new test parameter	10/11/2003	n/a		
II/0018	Inclusion of severe infusion reactions in the SPC, and changes resulting from changing the WHOART 98.3 dictionary to MedDRA 5.1. Update of Summary of Product Characteristics	26/06/2003	03/10/2003	SmPC	
II/0017	Change(s) to the manufacturing process for the active substance Change(s) to the manufacturing process for the finished product	25/04/2003	22/07/2003	Annex II	
I/0016	16_Change in the batch size of finished product	19/03/2003	01/04/2003		
I/0015	20_Extension of shelf-life as foreseen at time of authorisation	19/12/2002	17/02/2003	SmPC	
I/0013	11a_Change in the name of a manufacturer of the active substance	19/12/2002	17/02/2003	Annex II	

I/0014	12_Minor change of manufacturing process of the active substance	23/01/2003	06/02/2003		
S/0012	Annual re-assessment.	17/10/2002	28/01/2003	Annex II	
II/0011	Change(s) to the manufacturing process for the active substance	17/10/2002	21/10/2002		
II/0008	Update of Summary of Product Characteristics	27/06/2002	03/10/2002	SmPC	
II/0007	Update of or change(s) to the pharmaceutical documentation	26/08/2002	12/09/2002		
I/0010	30_Change in pack size for a medicinal product	26/07/2002	10/09/2002	SmPC, Labelling and PL	
I/0009	30_Change in pack size for a medicinal product	26/07/2002	10/09/2002	SmPC, Labelling and PL	
II/0006	Update of or change(s) to the pharmaceutical documentation	25/04/2002	24/05/2002		
I/0001	11a_Change in the name of a manufacturer of the active substance	24/10/2001	28/02/2002	Annex II	
I/0004	12_Minor change of manufacturing process of the active substance	17/01/2002	07/02/2002		
I/0003	14_Change in specifications of active substance	17/01/2002	07/02/2002		

	24_Change in test procedure of active substance				
I/0002	14_Change in specifications of active substance 17_Change in specification of the medicinal product 24_Change in test procedure of active substance	13/12/2001	07/01/2002		
N/0005	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/12/2001	10/04/2002	Labelling and PL	