Elaprase

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/0108/G	This was an application for a group of variations. A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release A.1 - Administrative change - Change in the name	14/12/2022		SmPC, Annex II, Labelling and PL	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

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	and/or address of the MAH				
IB/0107	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	23/11/2022	n/a		
S/0099	Annual re-assessment.	15/09/2022	09/11/2022	Annex II	
IB/0106	B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	18/10/2022	n/a		
II/0095	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	22/09/2022	n/a		
IA/0105/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 A.4 - Administrative change - Change in the name	02/09/2022	n/a		

	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 B.I.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation				
II/0101	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	01/09/2022	n/a		
N/0104	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	03/08/2022	09/11/2022	PL	
IB/0102	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	26/07/2022	n/a		
II/0098/G	This was an application for a group of variations. Please refer to the Recommendations section 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.f.1.e - Stability of FP - Change to an approved stability protocol B.I.d.1.c - Stability of AS - Change in the re-test period/storage period or storage conditions - Change to an approved stability protocol	21/07/2022	n/a		Not applicable

	B.I.b.2.b - Change in test procedure for AS or starting material/reagent/intermediate - Deletion of a test procedure for the AS or a starting material/reagent/intermediate, if an alternative test procedure is already authorised 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				
IA/0103	A.7 - Administrative change - Deletion of manufacturing sites	19/07/2022	n/a		
IAIN/0100	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	17/05/2022	09/11/2022	SmPC, Annex II and PL	
T/0097	Transfer of Marketing Authorisation	25/02/2022	04/04/2022	SmPC, Labelling and PL	
IB/0096	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	12/03/2022	n/a		
PSUSA/1722/202107	Periodic Safety Update EU Single assessment - idursulfase	10/02/2022	n/a		PRAC Recommendation - maintenance

IAIN/0093	A.1 - Administrative change - Change in the name and/or address of the MAH	28/07/2021	04/04/2022	SmPC, Labelling and PL	
S/0092	Annual re-assessment.	22/07/2021	n/a		
PSUSA/1722/ 202007	Periodic Safety Update EU Single assessment - idursulfase	11/02/2021	n/a		PRAC Recommendation - maintenance
IA/0091	A.7 - Administrative change - Deletion of manufacturing sites	26/11/2020	n/a		
S/0087	13th annual re-assessment	23/07/2020	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that marketing authorisation of Elaprase should be maintained.
II/0086	Update of section 4.9 of the SmPC in order to include a warning on the risk of anaphylactoid reaction following overdose with Elaprase. 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	28/05/2020	05/11/2020	SmPC	Some patients may experience an anaphylactoid reaction following an overdose with Elaprase.
IB/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	11/05/2020	n/a		

	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				
IA/0089	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)	07/05/2020	n/a		
II/0082	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	20/02/2020	n/a		
PSUSA/1722/ 201907	Periodic Safety Update EU Single assessment - idursulfase	13/02/2020	n/a		PRAC Recommendation - maintenance
IB/0084	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/11/2019	05/11/2020	SmPC, Annex II and PL	
IAIN/0085	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site	30/10/2019	n/a		
IB/0081/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 -	17/09/2019	n/a		

	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.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS 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.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition of a new in-process test and limits B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test B.I.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test 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				
S/0080	Annual re-assessment.	25/07/2019	n/a		
IB/0079/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites	11/04/2019	n/a		

	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.1.a - Change in the specification parameters and/or limits of the finished product - 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				
PSUSA/1722/ 201807	Periodic Safety Update EU Single assessment - idursulfase	14/02/2019	n/a		PRAC Recommendation - maintenance
S/0075	11th annual re-assessment	26/07/2018	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation under exceptional circumstances of Elaprase should be maintained.
II/0077/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.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised	21/06/2018	n/a		

	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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation				
II/0076	Update of section 4.8 of the SmPC to update the frequency category of the following adverse drug reactions: hypertension, tachypnoea, dyspepsia, erythema and infusion-site swelling, following a review of the frequencies and incidence categories for adverse drug reactions reported with Elaprase, based on integrated data from all relevant completed studies (i.e. studies TKT024, TKT024EXT and HGT-ELA-038). The Package Leaflet is updated accordingly. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to implement some minor corrections to the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/06/2018	17/12/2018	SmPC and PL	Following a review of the frequencies and incidence categories for adverse drug reactions reported with Elaprase, based on integrated data from all relevant completed studies (i.e. studies TKT024, TKT024EXT and HGT-ELA-038), the safety information in section 4.8 of the SmPC was updated. In the summary of safety profile, the list of most common infusion-related reactions has been updated to include 'erythema', 'wheezing', 'dyspnoea', 'vomiting', 'abdominal pain', 'nausea' and 'chest pain' and to delete 'hypertension'. The frequency category for 'Hypertension', 'dyspepsia', 'infusion site swelling' was also amended from 'very common' to 'common', for 'erythema' from 'common' to 'very common' and for 'tachypnoea' from 'common' to 'uncommon'.
IA/0074/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	16/03/2018	n/a		

	intermediate used in the manufacture of the AS or manufacturer of a novel excipient A.7 - Administrative change - Deletion of manufacturing sites 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				
PSUSA/1722/201707	Periodic Safety Update EU Single assessment - idursulfase	08/02/2018	n/a		PRAC Recommendation - maintenance
IAIN/0073	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	16/01/2018	17/12/2018	Annex II and PL	
II/0071/G	This was an application for a group of variations. 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.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.b.2.e - Change in test procedure for AS or	07/12/2017	n/a		

	starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.II.d.2.c - Change in test procedure for the finished product - Substantial change to or replacement of a biol/immunol/immunochemical test method or a method using a biol. reagent or replacement of a biol. reference preparation not covered by an approved protocol 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 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				
S/0070	10th Annual Re-assessment	20/07/2017	n/a		The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that Marketing Authorisation of Elaprase should be maintained.
PSUSA/1722/201607	Periodic Safety Update EU Single assessment - idursulfase	09/02/2017	n/a		PRAC Recommendation - maintenance

IB/0069	B.II.c.3.a.2 - Change in source of an excipient or reagent with TSE risk - From TSE risk material to vegetable or synthetic origin - For excipients or reagents USED in the manufacture of a biol/immunol AS or in a biol/immunol medicinal product	16/01/2017	n/a		
IB/0068/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.a.4.z - Change to in-process tests or limits applied during the manufacture of the AS - Other variation	18/10/2016	n/a		
R/0065	Renewal of the marketing authorisation.	21/07/2016	09/09/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Elaprase in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IAIN/0066	A.1 - Administrative change - Change in the name and/or address of the MAH	22/07/2016	09/09/2016	SmPC, Labelling and PL	
S/0064	Annual re-assessment.	21/07/2016	n/a		
IB/0063	B.II.f.1.b.5 - Stability of FP - Extension of the shelf	31/03/2016	09/09/2016	SmPC	

	life of the finished product - Biological/immunological medicinal product in accordance with an approved stability protocol				
PSUSA/1722/ 201507	Periodic Safety Update EU Single assessment - idursulfase	11/02/2016	n/a		PRAC Recommendation - maintenance
IA/0062/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.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure 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	22/12/2015	n/a		
II/0058	Update of section 6.6 of the SmPC in order to align with the general physicians' practices and specifies that total volume of infusion should be delivered using a 0.2 µm in line filter. Section 4.2 is updated to cross-refer to section 6.6. 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	22/10/2015	09/09/2016	SmPC and PL	

IAIN/0061	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	16/10/2015	09/09/2016	Annex II and PL	
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		
II/0057	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	06/08/2015	n/a		
S/0055	8th Annual Re-assessment	23/07/2015	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 Elaprase should be maintained.
IB/0056/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.II.d.2.b - Change in test procedure for the finished product - Deletion of a test procedure if an alternative method is already authorised	19/06/2015	n/a		

II/0054	Update of sections 5.1 of the SmPC with clinical efficacy information after revision of the clinical report for study TKT024EXT "An open-label extension of Study TKT024 evaluating long-term safety and clinical outcomes in patients with Hunter syndrome receiving iduronate-2-sulfatase enzyme replacement therapy. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	26/03/2015	14/09/2015	SmPC	Introduction of clarifications of pharmacological data in the product information for Elaprase after clinical study report review for study TKT024EXT.
PSUSA/1722/ 201407	Periodic Safety Update EU Single assessment - idursulfase	12/02/2015	n/a		PRAC Recommendation - maintenance
II/0051	Update of sections 4.4 and 4.8 of the SmPC to reflect outcomes of the ongoing surveillance of anaphylactic reaction in patients treated with idursulfase. Section 4.3 is also updated regarding the contraindication on hypersensitivity. Section 2 of the Package Leaflet is amended accordingly. In addition, minor editorial changes are made in the Product Information (PI). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	25/09/2014	14/09/2015	SmPC and PL	Following the outcomes of the ongoing surveillance of anaphylactic reaction in patients treated with idursulfase, the CHMP recommended the inclusion of the term "anaphylactic" in the existing warning on hypersensitivity reaction. A statement was also added that these reactions may occur up to several years after initiating treatment. Additional amendments to section 4.3 and 4.4 were also agreed to reflect the fact that severe or life-threatening hypersensitivity to idursulfase or any of the excipients is a contraindication, if hypersensitivity is not controllable.
IB/0052/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of	06/08/2014	n/a		

	manufacturing sites 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.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.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.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				
S/0050	Annual re-assessment.	24/07/2014	n/a		
PSUV/0047	Periodic Safety Update	20/02/2014	23/04/2014		Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUV/0047.
IB/0048	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	11/12/2013	n/a		

IA/0049	A.7 - Administrative change - Deletion of manufacturing sites	06/12/2013	n/a		
II/0045	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	24/10/2013	25/11/2013	Annex II	
S/0044	Annual re-assessment.	25/07/2013	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 Elaprase should be varied. The product information for Elaprase was updated to reflect the latest EMA/QRD template and the revised list of specific obligations.
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/0040	Update of sections 4.4, 4.8 and 5.1 of the SmPC in order to include information on a post-hoc immunogenicity analysis of the data collected from the treatment-naïve patients in the TKT024 and TKT024EXT studies. In addition, the MAH took the opportunity to correct an address in Annex II.A.	17/01/2013	19/09/2013	SmPC and Annex II	The MAH has carried out a post-hoc analysis of immunogenicity results of use of Elaprase in treatment-naïve patients with Hunter syndrome who received 0.5 mg/kg intravenous Elaprase weekly enzyme replacement therapy whilst enrolled in studies TKT024 and TKT024EXT. Studies TKT024 and TKT024EXT have been previously assessed by the CHMP. Patients were classified according to

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				antibody status: 32/63 patients treated with 0.5mg/kg weekly Elaprase had at least 1 blood sample that tested positive for anti-Elaprase antibodies, and 23/63 tested positive for antibodies on at least 3 consecutive study visits. Patients were also classified by genotype (patients had either a mis-sense, frameshift or nonsense mutation or were considered "unclassifiable"). With regards to efficacy: after 105 weeks of exposure to Elaprase, neither antibody status nor genotype were shown to affect reductions in liver and spleen size or distance walked in the 6-minute walk test or forced vital capacity measurements. Patients who tested antibody-positive displayed less reduction in urinary output of glycosaminoglycans than antibody-negative patients: the longer-term effects of antibody development on clinical outcomes (efficacy and safety) have yet to be established. With regards to safety: although patients with the nonsense / frameshift genotype mutation may develop adverse events sooner than other patients, the differences described are only statistically significant for treatment-emergent adverse events. Patients displayed adverse events irrespective of their underlying genotype and with no apparent differences of risk in doing so. The MAH has presented argument that the relationship between antibodies and adverse events may not be directly causal, but parallel. In conclusion, the current procedure has added to the knowledge of clinical efficacy and safety of Elaprase in the management of patients with Hunter syndrome in relation to antibody status and genotype and has not raised any new concerns on clinical safety. The benefit / risk balance of Elaprase at the approved posology in the management of

					patients with Hunter syndrome is considered to be unchanged and still positive.
S/0036	Annual re-assessment.	15/11/2012	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.
II/0035	Update of sections 4.2, 4.4, 4.8, 5.1 and 5.2 of the SmPC in order to add information about Elaprase use in children of 5 years of age or younger in view of the results of study HGT-ELA-038. The Package Leaflet was updated accordingly. Annex II.C was updated to reflect that Specific Obligation 3 has been fulfilled. The Labelling was updated with a minor correction. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/11/2012	19/09/2013	SmPC, Annex II, Labelling and PL	At the time of approval of the Initial Marketing Authorisation, the Marketing Authorisation Holder (MAH) committed to conduct several Specific Obligations. Specific Obligation 3 was a commitment to conduct a study of the use of Elaprase on patients with Hunter syndrome and who are under 5 years of age: this age group had not been addressed in studies submitted for initial authorisation. Patients under 5 years of age are considered to have a more severe form of Hunter syndrome. To comply with this Specific Obligation, the MAH has submitted study HGT-ELA-038, a study of use of weekly infusion of 0.5mg/kg Elaprase in 28 patients with Hunter syndrome and who are 16 months to 6.5 years of age. Patients were followed over the course of 1 year exposure to Elaprase. Results submitted by the MAH suggest that, for patients with Hunter syndrome in the age range 16 months to 6.5 years of age as described in study HGT-ELA-038, glycosaminoglycan excretion, liver index size and spleen size decrease in response to weekly infusion of idursulfase. Overall, results are similar to those described for subjects over 5 years of age in study TKT024, submitted for the initial MA of Elaprase in 2007.

					The CHMP was concerned, however, that there is a subpopulation of patients who develop antibodies against idursulfase and that these antibodies have in vivo activity thereby reducing clinical efficacy benefit. The MAH has confirmed that the clinical efficacy of Elaprase for patients in study HGT-ELA-038 may be subdivided according to antibody development against Elaprase. Patients with high antibody titre and undetectable idursulfase immediately after infusion of the current product display a reduced response to Elaprase as assessed by urinary output of glycosaminoglycans, liver size and spleen size. The MAH has further demonstrated a relationship between antibody response and underlying genotype: patients with idursulfase protein detectable after infusion of the current product at week 27 had mostly either missense or frameshift genotypes whereas patients with no detectable idursulfase protein after infusion of the current product had mostly the complete deletion/large rearrangement genotype. It was not possible, however, to predict individual efficacy response on the basis of genotype. Overall, the safety profile of subjects in study HGT-ELA-038 is similar to that described for subjects in previously reported studies where patients with Hunter syndrome were over 5 years of age. Adverse events were apparently more common in subjects who developed antibodies to idursulfase. The MAH has now identified "vomiting" as an additional adverse event. The MAH will carry out pharmacovigilance activity for the important identified risk “immunogenicity” by means of safety data monitoring via the Hunter Outcome Survey. For subjects with Hunter syndrome who are under 6.5

					years of age and who have missense or frameshift genotypes, the benefit/risk balance may be considered to be positive and in accord with the already-described benefit/risk balance for patients with Hunter syndrome and who are over 5 years of age. Although subjects with Hunter syndrome who have the complete deletion/large rearrangement genotype may display an apparent reduced clinical efficacy response as assessed by the reductions in urinary output of glycosaminoglycans and change in liver size and spleen size, it was not possible to predict individual efficacy response on the basis of genotype. Overall, the clinical benefit of exposure to Elaprase in the sub-group of subjects with Hunter syndrome caused by the complete deletion/large rearrangement genotype is considered to outweigh the clinical risk and so the benefit/risk balance in this group is also positive. The CHMP was of the opinion that Specific Obligation 3 has been fulfilled and agreed to introduce information on the use of Elaprase on patients under the age of 5 years in the product information.
IG/0216	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	14/09/2012	n/a		
IB/0042	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	11/09/2012	n/a		
IA/0041	B.I.a.4.b - Change to in-process tests or limits applied during the manufacture of the AS - Addition	17/08/2012	n/a		

	of a new in-process test and limits				
IA/0038/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.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 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.a.4.c - Change to in-process tests or limits applied during the manufacture of the AS - Deletion of a non-significant in-process test	19/07/2012	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	24/09/2012	Annex II	

R/0032	Renewal of the marketing authorisation.	21/07/2011	03/10/2011	SmPC, Annex II, Labelling and PL	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP considers that the benefit-risk balance of Elaprase remains positive, but considers that its safety profile is to be closely monitored for the following reasons: Additional data is required to further characterise and assesses the long-term effectiveness and safety profile of Elaprase in the treatment of Hunter Syndrome. This includes data on long term pulmonary and cardiovascular morbidity and mortality, long term urinary GAG excretion patterns, dosing information, long term antibody levels and information on longer duration infusions. Therefore, based upon the safety profile of Elaprase, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time. Furthermore, since there are remaining Specific Obligations, the CHMP is of the opinion that the Marketing Authorisation should remain under exceptional circumstances.
II/0033/G	This was an application for a group of variations. To register new facilities for the manufacture and quality control 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.2.a - Change to batch release arrangements and quality control testing of the FP - Replacement or addition of a site where batch control/testing	21/07/2011	21/07/2011		

	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.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				
IB/0031	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	15/03/2011	n/a		
II/0030	Changes to the manufacture of the finished product B.II.b.3.c - Change in the manufacturing process of the finished product - The product is a biological/immunological medicinal product and the change requires an assessment of comparability	17/02/2011	28/02/2011		
IG/0029	A.5.b - Administrative change - Change in the name and/or address of a manufacturer of the finished	02/12/2010	n/a		

	product, including quality control sites (excluding manufacturer for batch release)				
II/0028	New facility for the manufacture of the drug 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	24/06/2010	06/07/2010		
S/0027	3rd Annual Re-Assesment	24/06/2010	29/06/2010		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. However the Marketing Authorisation for Elaprase should remain under exceptional circumstances in view of the pending Specific Obligations
IA/0029	B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	18/06/2010	n/a	Annex II and PL	
II/0026	Update of section 5.1 of the Summary of Product Characteristics to include the potential use of the product at home. Update of Summary of Product Characteristics	21/01/2010	15/03/2010	SmPC	Data from Hunter Outcome Survey on safety of home therapy with Elaparase in selected patients who have tolerated infusions in the clinic well has been provided. The results show low incidence of infusion-related reactions and no treatment-related serious adverse events. Moreover, home therapy has the advantage of convenience for patients and their carers and the potential for improving compliance. Considering importance of these results MAH

					submitted a type II variation to update section 5.1 of the SPC. However, as per CHMP request appropriate information on home therapy was included in section 4.2. of SPC.
II/0024	Additional site and changes of responsibilities for exisiting sites regarding the manufacture and Quality Control testing of the drug substance. Change(s) to the manufacturing process for the active substance	17/12/2009	20/01/2010	Annex II	
II/0023	Update to sections 4.6 and 5.3 of the Summary of Product Characteristics to include new non-clinical data on a segment III study (pre and post-development) and an utero/lacteal excretion biodistribution study and consequential changes to the Package Leaflet. Update of Summary of Product Characteristics and Package Leaflet	17/12/2009	20/01/2010	SmPC and PL	Three new non-clinical studies (SHGT-1I1-06-007, SHGT-1I1-06-008 and SHGT-1I1-06-009) were submitted in this variation application. These studies related to the potential effect of idursulfase on pre- and postnatal development, and exposure of offspring in utero or through lactation due to maternal treatment. These new data indicate that idursulfase is transferred to the foetal circulation in utero when administered by the intravenous route to pregnant rats. Idursulfase is also excreted in breast milk.
II/0022	Update to sections 4.8 and 5.1 of the Summary of Product Characteristics to include information on the extension trial TXT024EXT and consequential changes to the Package Leaflet. The MAH has also taken the opportunity to amend the Package Leaflet to align it with the QRD template version 7.3. Update of Summary of Product Characteristics and Package Leaflet	17/12/2009	20/01/2010	SmPC and PL	Study TXT024EXT, an extension of TXT024, a randomised placebo-controlled trial of idursulfase, was submitted in this variation application. The primary objective of this extension study was to collect long-term safety and clinical outcome data in patients with Hunter syndrome who were receiving idursulfase enzyme replacement therapy. Long-term treatment with weekly infusions of 0.5 mg/kg idursulfase was safe and well tolerated. The overall clinical experience during the extension study TXT024EXT was similar to that reported during Study TKT024 and supports

					the long-term administration of idursulfase.
II/0025	Change to the specifications of the drug substance Quality changes	17/12/2009	12/01/2010		
S/0019	2nd Annual Reassessment	25/06/2009	21/09/2009	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. However the Marketing Authorisation for Elaprase should remain under exceptional circumstances in view of the pending Specific Obligations.
IA/0021	IA_05_Change in the name and/or address of a manufacturer of the finished product	07/09/2009	n/a		
II/0018	Changes to the purification process of the drug substance Change(s) to the manufacturing process for the active substance	29/05/2009	16/06/2009		
IA/0020	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	27/05/2009	n/a		
II/0017	Changes to the purification process of the drug substance Change(s) to the manufacturing process for the active substance	23/04/2009	05/05/2009		

II/0015	Changes to the release and shelf life specifications for the drug substance and drug product Change(s) to the test method(s) and/or specifications for the active substance	23/04/2009	05/05/2009		
II/0016	Additional Quality Control testing facility for the drug substance and drug product. Name changes of facilities responsible for the control of the drug substance and manufacture of the drug product. Change(s) to the manufacturing process for the active substance	19/03/2009	25/03/2009		
II/0013	Update of the Detailed Description of the Pharmacovigilance System (DDPS). Update of DDPS (Pharmacovigilance)	18/12/2008	04/02/2009	Annex II and Labelling	With this variation the MAH submitted an updated DDPS (version 3.0). After assessing the documentation the CHMP concluded that the submitted DDPS contained all required elements. The CHMP accepted an update of Annex II to include an updated wording of the section "other conditions" comprising the version numbers of the current DDPS and Risk Management Plan.
II/0012	Additional storage facility for the cell banks. Change to the control and specifications for the drug substance (release) and drug product (stability). Change(s) to the test method(s) and/or specifications for the active substance	20/11/2008	28/11/2008		
IA/0014	IA_01_Change in the name and/or address of the marketing authorisation holder	30/10/2008	n/a	SmPC, Labelling and	

				PL	
S/0008	Annual reassessment.	26/06/2008	02/09/2008	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 Elaprase, concludes that the benefit /risk ratio for the product remains unchanged. The list of Specific Obligations was revised according to the conclusions of the CHMP discussion. The CHMP considered that the Marketing Authorisation for Elaprase should remain under exceptional circumstances in view of the pending Specific Obligations.
II/0007	Change(s) to the test method(s) and/or specifications for the finished product	24/04/2008	30/04/2008		
IA/0011	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	11/04/2008	n/a		
IA/0010	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	11/04/2008	n/a		
IA/0009	IA_22_a_Submission of TSE Ph. Eur. certificate for exc. - Approved/new manufacturer	11/04/2008	n/a		
IA/0006	IA_08_b_01_Change in BR/QC testing - repl./add. manuf. responsible for BR - not incl. BC/testing	26/11/2007	n/a	Annex II and PL	
II/0001	Update of Section 4.2, 4.4 and 4.8 of the SPC and section 2 of the PL to include additional safety information regarding infusion-related reactions resulting from post-approval experience with	19/07/2007	15/10/2007	SmPC and PL	During post-marketing use of Elaprase, two patients experienced symptoms and signs suggestive of late-emergent anaphylactoid reactions.

	Elaprase. Update of Summary of Product Characteristics and Package Leaflet				For each of these 2 patients, onset of symptoms occurred approximately 24 hours after the Elaprase infusion and recovery from an initial anaphylactoid reaction to the Elaprase. Both patients were negative for anti-idursulfase antibody isotypes IgG, IgA, IgM and IgE, based on analysis of serum samples obtained prior to their subsequent infusion. For one patient, the symptoms were treated with inhaled beta-adrenergic antagonists, adrenaline, anti-histamines, and corticosteroids as well as hospitalization, while the second patient required corticosteroids only. With appropriate pre-treatment and clinical monitoring prior to and during subsequent infusions, both patients continue to receive weekly Elaprase treatment. No anaphylactic reactions to Elaprase have been reported to date and no patient is known to have developed IgE antibodies to Elaprase. Given the relative infrequency of such events together with evidence that infusion-related adverse events decline over time, and the fact that both patients continue to receive weekly Elaprase infusions, the CHMP believed that Elaprase remains a safe and effective treatment for patients with Hunter syndrome. However, it was considered appropriate to update Section 4.2 (Posology and method of administration), 4.4 (Special warnings and precautions for use) and 4.8 (Underisable effects) of the SPC and section 2 of the PL to include additional safety information.
II/0002	Change to the test procedure and/or specification of a raw material	19/07/2007	24/07/2007		