Aldurazyme

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion/ Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IB/0088	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	13/02/2024	n/a		
II/0085	To update section 4.2 of the SmPC in order to add home infusion upon request by PRAC following the assessment of procedure PSUSA/00001830/202104 based on literature review. The Package Leaflet and Annex II are updated accordingly. The RMP version 1.3 has also been submitted.	25/01/2024		SmPC, Annex II and PL	SmPC new text Section 4.2 Home Infusion Infusion of Aldurazyme at home may be considered for patients who are tolerating their infusions well and have no history of moderate or severe IARs for a few months. The

[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).

	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				decision to have a patient move to home infusion should be made after evaluation and upon recommendation by the treating physician. Home infusion infrastructure, resources, and procedures, including training, must be established and available to the healthcare professional. Home infusion should be supervised by a healthcare professional who should be always available during the home infusion and for a specified time after infusion. Appropriate information should be given by the treating physician and/or nurse to the patient and/or caregiver prior to initiation of home infusion. Dose and infusion rate should remain constant while at home, and not be changed without supervision of a healthcare professional. If the patient experiences adverse reactions during the home infusion, the infusion process should be stopped immediately, and appropriate medical treatment should be initiated (see section 4.4). Subsequent infusions may need to occur in a hospital or in an appropriate setting of outpatient care until no such adverse reaction is present. For more information, please refer to the Summary of Product Characteristics.
IB/0086	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	30/03/2023		SmPC and PL	

IAIN/0087	A.1 - Administrative change - Change in the name and/or address of the MAH	29/03/2023		SmPC, Labelling and PL	
IB/0084/G	This was an application for a group of variations. B.I.b.2.e - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure (including replacement or addition) for the AS or a starting material/intermediate B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	29/11/2022	n/a		
IA/0083	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	08/08/2022	n/a		
IB/0082	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	12/04/2022	n/a		
PSUSA/1830/ 202104	Periodic Safety Update EU Single assessment - laronidase	02/12/2021	n/a		PRAC Recommendation - maintenance
N/0081	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	09/11/2021		PL	

IB/0079	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	12/07/2021	n/a		
IA/0078/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	06/05/2021	15/11/2021	Annex II and PL	
IB/0077/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.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	22/12/2020	n/a		
WS/1829	This was an application for a variation following a worksharing procedure according to Article 20 of Commission Regulation (EC) No 1234/2008. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	12/11/2020	15/11/2021	SmPC, Annex II and PL	
IB/0075	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	22/06/2020	n/a		

N/0074	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/02/2020	15/11/2021	PL	
IB/0073	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	20/11/2019	n/a		
II/0071/G	This was an application for a group of variations. 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 B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	17/01/2019	n/a		
IG/1003	A.1 - Administrative change - Change in the name and/or address of the MAH	20/12/2018	04/10/2019	SmPC, Labelling and PL	
IB/0069/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	11/12/2018	n/a		

	changes to an approved test procedure B.I.b.2.z - Change in test procedure for AS or starting material/reagent/intermediate - Other variation 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.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				
PSUSA/1830/201804	Periodic Safety Update EU Single assessment - laronidase	29/11/2018	n/a		PRAC Recommendation - maintenance
IAIN/0070/G	This was an application for a group of variations. B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.2.c.1 - Change to importer, batch release arrangements and quality control testing of the FP - Replacement or addition of a manufacturer responsible for importation and/or batch release - Not including batch control/testing	08/10/2018	04/10/2019	Annex II and PL	
N/0066	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	02/03/2018	04/10/2019	Labelling	
IA/0067	B.I.b.2.a - Change in test procedure for AS or	21/02/2018	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0064/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.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 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 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 B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting	05/02/2018	n/a		

	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 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				
IA/0065	A.7 - Administrative change - Deletion of manufacturing sites	19/12/2017	n/a		
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/09/2017	04/10/2019	PL	
N/0062	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	22/02/2017	04/10/2019	PL	
IB/0061/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 procedure	10/01/2017	n/a		
II/0060	B.III.1.b.5 - Submission of a new/updated or deletion of Ph. Eur. TSE Certificate of Suitability -	19/05/2016	n/a		

	New/updated certificate from an already approved/new manufacturer using materials of human/animal origin for which a risk assessment on potential contamination with adventitious agents is required				
IA/0059	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	22/12/2015	n/a		
II/0057	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	17/12/2015	n/a		
IB/0058/G	This was an application for a group of variations. B.II.b.1.z - Replacement or addition of a manufacturing site for the FP - Other variation 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	16/12/2015	n/a		
S/0054	12th Annual Re-assessment	22/10/2015	16/12/2015	SmPC, Annex II and PL	The CHMP, having reviewed the evidence of compliance with the specific obligations and the impact of the data submitted by the MAH on the benefit/risk profile of the medicinal product, concluded that the Marketing Authorisation of Aldurazyme should be maintained. In addition, as all Specific Obligations have been fulfilled,

					the CHMP considered that there were no remaining grounds for the Marketing Authorisation to remain under exceptional circumstances.
PSUSA/1830/ 201504	Periodic Safety Update EU Single assessment - laronidase	06/11/2015	n/a		PRAC Recommendation - maintenance
IB/0055	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	14/07/2015	n/a		
IA/0053	A.7 - Administrative change - Deletion of manufacturing sites	27/03/2015	n/a		
PSUV/0052	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
S/0051	Annual re-assessment.	25/09/2014	n/a		
II/0049/G	This was an application for a group of variations. to replace an analytical method used in control of the active substance and to amend the active substance specification. 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.1.z - Change in the specification parameters and/or limits of an AS, starting	25/04/2014	n/a		

	material/intermediate/reagent - Other variation				
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/0048	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	27/11/2013	n/a		
S/0047	Annual re-assessment.	24/10/2013	n/a		
II/0046	Changes to the active substance manufacturing process. B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol	19/09/2013	n/a		
IA/0043/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 B.III.1.b.3 - Submission of a new or updated Ph. Eur. TSE Certificate of suitability - Updated certificate	26/03/2013	n/a		

	from an already approved manufacturer				
IG/0283	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	22/03/2013	n/a		
IA/0044	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	20/03/2013	n/a		
S/0041	Annual re-assessment.	17/01/2013	18/02/2013	SmPC, Annex II, Labelling and PL	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/0042	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	07/12/2012	n/a		
N/0040	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	27/04/2012	18/02/2013	PL	
S/0037	Annual Re-assessment	22/09/2011	21/11/2011	SmPC, Annex II, Labelling and PL	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/0039	B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation	09/11/2011	n/a		
II/0038	Changes to the manufacture of the active substance	22/09/2011	22/09/2011		

	B.I.a.2.c - Changes in the manufacturing process of the AS - The change refers to a [-] substance in the manufacture of a biological/immunological medicinal product and is not related to a protocol				
IA/0036	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)	19/05/2011	n/a		
IA/0033/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 procedure	29/03/2011	n/a		
N/0035	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/03/2011	n/a	PL	
IA/0034	B.III.1.a.2 - Submission of a new or updated Ph. Eur. Certificate of Suitability to the relevant Ph. Eur. Monograph - Updated certificate from an already approved manufacturer	25/03/2011	n/a		
S/0031	Annual re-assessment.	23/09/2010	28/09/2010		
II/0030	Changes to the manufacture of the drug substance	24/06/2010	06/07/2010		

	B.I.c.1.b - Change in immediate packaging of the AS - Qualitative and/or quantitative composition for sterile and non-frozen biological/immunological ASs				
II/0028	To update the SPC and the PL with adverse event "erythema" and to include minor adjustments to bring SPC labelling and leaflet in line with QRD template version 7.3 10/2009 Update of Summary of Product Characteristics and Package Leaflet	18/03/2010	27/04/2010	SmPC and PL	As a result of PSUR assessment MAH proposed to update the Section 4.8 of the SmPC with the term 'erythema' and with corresponding changes in PL. Proposed changes were accepted by CHMP.
IA/0029	A.7 - Administrative change - Deletion of manufacturing sites	19/03/2010	n/a		
II/0026	Additional sites for the manufacture and control of the drug product. Change(s) to the manufacturing process for the finished product	24/09/2009	06/10/2009		
S/0025	Annual re-assessment.	24/09/2009	01/10/2009		
IA/0027	IA_16_b_Submission of new TSE certificate relating to active substance - other substances	30/09/2009	n/a		
II/0024	Update of section 4.8 of the Summary of Product Characteristics (SPC) and relevant section of the Package Leaflet (PL) with regard to the adverse reactions, tachypnoea, cyanosis and extravasation.	29/05/2009	02/07/2009	SmPC and PL	Following the CHMP requirement after the evaluation of the 7th Periodic Safety Update Report (PSUR) to review all cases of cyanosis, tachypnoea and extravasation, the MAH has performed a revision of these three adverse events in

	Additionally, local representative details have been updated in the PL. Update of Summary of Product Characteristics and Package Leaflet				their global safety database. The results of this revision support the addition of information on extravasation, tachycardia and cyanosis to the product information.
II/0023	Additional Quality Control testing facility. New reference standard with change to its storage conditions. Change(s) to the manufacturing process for the active substance	23/10/2008	28/10/2008		
S/0022	Annual re-assessment.	25/09/2008	01/10/2008		
R/0021	Renewal of the marketing authorisation.	19/03/2008	20/05/2008	PL	Based on the review of the available information, the CHMP considers that the benefit-risk balance of Aldurazyme remains positive. Due to inconsistencies in the PSURs submitted and the relatively low patient exposure, the PSUR should remain on a yearly cycle. Furthermore, Aldurazyme remains under exceptional circumstances due to one pending specific obligation regarding the MPS I Registry, by which the MAH commits to collect long term safety and efficacy data in patients treated with Aldurazyme as well as data on natural disease progression in untreated patients. Annual updates will be provided at the time of the annual reassessment. The benefit-risk balance of the product will continue to be reviewed annually as part of the Annual Re-assessments. The CHMP concluded that the renewal can be granted with unlimited validity.

					Changes were made to the product information to bring it in line with the current EMEA/QRD template. In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Romania.
S/0018	Annual re-assessment.	18/10/2007	20/12/2007	SmPC, Annex II and PL	
IB/0020	IB_38_b_Change in test procedure of finished product - minor change, biol. active subst./excipient	18/12/2007	n/a		
II/0017	Update of section 4.4, 4.8 and 5.1 of the Summary of Product Characteristics (SPC) and section 1, 2, 3 and 4 of the Package Leaflet (PL) to include the long term safety and efficacy results of the open label Extension Study ALID-006-01 which was completed and assessed during the third Annual Re-assessment (EMEA/H/C/0477/S/14). Furthermore, the PL has been amended to reflect the recommendation made during readability testing. Update of Summary of Product Characteristics and Package Leaflet	20/09/2007	30/10/2007	SmPC and PL	Update of section 4.4 'Special warnings and precautions for use', 4.8 'Undesirable effects' and 5.1 'Pharmacodynamic properties' of the SPC and section 1 'What Aldurazyme is and what it is used for', 2 'Before you use Aldurazyme', 3 'How to use Aldurazyme' and 4 'Possible side effects' of the Package Leaflet (PL) to include the long term safety and efficacy results of the open label Extension Study ALID-006-01 which was completed and assessed during the third Annual Re-assessment (EMEA/H/C/0477/S/14). Furthermore, the PL has been amended to reflect the recommendation made during the readability testing exercise.
II/0019	Change(s) to the manufacturing process for the active substance	20/09/2007	27/09/2007		
II/0016	Change(s) to the manufacturing process for the active substance	26/04/2007	02/05/2007		

II/0015	Change(s) to the manufacturing process for the finished product	22/02/2007	28/02/2007		
S/0014	Annual re-assessment.	16/11/2006	05/02/2007	SmPC, Annex II, Labelling and PL	
II/0012	This variation relates to an application for an update of section 4.2 (Posology and method of administration), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties) and 5.2 (Pharmacokinetic properties) of the Summary of Product Characteristics (SPC) to include changes from the completion of the final study report (open label study in patients less than 5 years of age with MPS I). Additionally section 4.6 (Pregnancy and lactation) was updated to improve linguistics. In addition, the term "rigors" has being substituted in the SPC by "chills" as per the latest MedDRA version, as requested after the evaluation of the latest PSUR. Annex II was updated to reflect the finalisation of the mentioned study. Finally the package leaflet has been revised in accordance to the SPC changes and the list of the local representatives has been updated. Update of Summary of Product Characteristics and Package Leaflet	27/04/2006	31/05/2006	SmPC, Annex II and PL	At the time of the initial Marketing Authorisation approval, the CHMP requested that the MAH should determine whether patients under 5 years of age would benefit from Aldurazyme treatment and the Marketing Authorisation Holder (MAH) undertook the commitment of submitting the clinical report of a phase II, open-label study conducted in children under the age of 5 years, which was ongoing at the time of the Marketing Authorisation Application (MAA). The MAH submitted the clinical study repot of the mentioned study and applied for an update of section 4.2 (Posology and method of administration), 4.8 (Undesirable effects), 5.1 (Pharmacodynamic properties) and 5.2 (Pharmacokinetic properties) of the Summary of Product Characteristics (SPC) to include changes from the completion of the study. Annex II (list of specific obligations) was updated to reflect the finalization of the mentioned study. The package leaflet was revised in accordance to the SPC changes and the list of the local representatives was updated.
II/0013	Change(s) to the manufacturing process for the active substance	27/04/2006	03/05/2006		

S/0010	Annual re-assessment.	13/10/2005	19/01/2006	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 Aldurazyme, concluded that the benefit/risk of the product remains favourable in the approved indication.The CHMP agreed that the Marketing Authorisation should be kept under exceptional circumstances and agreed on a revised list of Specific Obligations.
II/0011	Change(s) to the manufacturing process for the finished product	17/11/2005	25/11/2005		
II/0009	Change(s) to the manufacturing process for the active substance	23/06/2005	30/06/2005		
II/0008	The Marketing Authorisation Holder applied for changes to section 4.4 (Special warnings and special precautions for use) and section 4.8 (Undesirable effects) of the Summary of Product Characteristics (SPC) to include safety information as a result of the 2nd PSUR assessment covering the period from 31 October 2003 to 30 April 2004. The Package Leaflet (PL) was revised accordingly. In addition, minor linguistic corrections were made in Annex II. Update of Summary of Product Characteristics and Package Leaflet	17/02/2005	22/03/2005	SmPC, Annex II and PL	This variation concerned the update of sections 4.4 and 4.8 of the SPC and relevant sections of the PL to include safety information, following the assessment of the 2nd PSUR. The change to section 4.4 of the SPC was the addition of a warning regarding the monitor of patients with severe underlying upper airway involvement. The adverse events pyrexia, vomiting and rigors were added to section 4.8 of the SPC and the wording regarding the severe infusion related events in patients with underlying airway involvement was updated . This information was also reflected in the PL. In addition, minor linguistic corrections were made in Annex II.
S/0005	Annual re-assessment.	21/10/2004	12/01/2005	SmPC and Annex II	The CHMP having reviewed the evidence of compliance with the Specific Obligations submitted by the MAH and having re-assessed the benefit/risk profile of Aldurazyme, concluded that the benefit/risk of the product remains

					favourable in the approved indication. Minor changes were made to the SPC and PL.The CHMP agreed that the Marketing Authorisation should be kept under exceptional circumstances and agreed on a revised list of Specific Obligations.
IB/0007	IB_38_c_Change in test procedure of finished product - other changes	29/11/2004	n/a		
IB/0006	IB_30_b_Change in supplier of packaging components - replacement/addition	17/11/2004	n/a		
N/0004	The Marketing Authorisation Holder (MAH) applied for the inclusion of additional local representatives of the MAH for all new Member States. The MAH also took the opportunity to introduce minor linguistic changes in the Greek, Finnish and Swedish package leaflet. Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/05/2004	13/07/2004	PL	
II/0003	Change(s) to the manufacturing process for the active substance	24/03/2004	31/03/2004		
I/0002	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	28/11/2003	n/a	SmPC	
I/0001	15_Minor changes in manufacture of the medicinal product	22/10/2003	30/10/2003		