LUTATHERA

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
N/0045	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/09/2023		PL	
IB/0044/G	This was an application for a group of variations. B.I.a.3.z - Change in batch size (including batch size	19/09/2023	n/a		

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

	ranges) of AS or intermediate - Other variation B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS				
PSUSA/10643 /202212	Periodic Safety Update EU Single assessment - lutetium (177Lu) oxodotreotide	06/07/2023	n/a		PRAC Recommendation - maintenance
IB/0043	B.I.c.1.c - Change in immediate packaging of the AS - Liquid ASs (non sterile)	16/05/2023	n/a		
II/0038	Update of sections 2, 4.1, 4.2, 4.4, 4.5, 4.6, 4.8, 4.9, 5.1, 5.2, 5.3, 6.2, 6.4, 6.5, 6.6, 11 and 12 of the SmPC to align the Lutathera product information to the latest Core Data Sheet (CDS) version 2.0 (changes to the CDS based on data from the Lutathera existing dossier, current medical practice and new literature). Annex IIIA and the package leaflet are updated accordingly. In addition, additional corrections and changes are made throughout the product information (PI) to comply with the latest QRD template and to improve the language. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/04/2023		SmPC and PL	SmPC new text • Most of the changes were made to the posology and method of administration and instructions for preparation of radiopharmaceuticals: clarification that there is a 1 week flexibility in the interval between each administration; changes to the recommendation regarding hydration and urination during treatment to reduce toxicity risk; clarification that permanent discontinuation is needed in case of adverse reactions requiring dosing interval beyond 16 weeks; new text to allow physicians to perform infusion of the amino acid solution in the same arm as Lutathera, while infusion in different arms remain the preferred method; a footnote in the dose modification table clarifying that lymphopenia is not a dose modifying toxicity; introduction and description of the syringe pump method when delivering a reduced dose of Lutathera • Recommendation on the duration of contraception

					after the last dose of Lutathera was revised: -from 6 moths to 7 months for female patients -from 6 months to 4 months for male patients • Information regarding the time of occurrence on platelet nadir and recovery was introduced to the adverse reaction section. • Recommendation that Lutathera should not be frozen was added.
IAIN/0041	A.1 - Administrative change - Change in the name and/or address of the MAH	10/02/2023		SmPC, Labelling and PL	
IB/0040	B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation	19/01/2023	n/a		
PSUSA/10643 /202112	Periodic Safety Update EU Single assessment - lutetium (177Lu) oxodotreotide	21/07/2022	26/09/2022	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10643/202112.
R/0032	Renewal of the marketing authorisation.	19/05/2022	08/07/2022	SmPC, Annex II and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of LUTATHERA in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
IB/0037/G	This was an application for a group of variations. B.II.z - Quality change - Finished product - Other variation B.II.b.3.z - Change in the manufacturing process of the finished or intermediate product - Other variation B.II.b.3.a - Change in the manufacturing process of	27/06/2022	n/a		

	the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation				
IB/0034	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	21/04/2022	n/a		
IB/0035/G	This was an application for a group of variations. B.I.b.2.c - Change in test procedure for AS or starting material/reagent/intermediate - Other changes to a test procedure for a reagent, which does not have a significant effect on the overall quality of the AS B.I.z - Quality change - Active substance - Other variation B.I.b.1.d - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Deletion of a non-significant specification parameter (e.g. deletion of an obsolete parameter) B.I.a.2.e - Changes in the manufacturing process of the AS - Minor change to the restricted part of an ASMF 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.b - Change in the specification parameters and/or limits of an AS, starting	12/04/2022	n/a		

	material/intermediate/reagent - Tightening of specification limits B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.c.2.b - Change in the specification parameters and/or limits of the immediate packaging of the AS - Addition of a new specification parameter to the specification with its corresponding test method B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size				
II/0030	Update of the SmPC sections 4.4, 4.8, 5.1 based on the pivotal Phase III study, NETTER-1. Additionally, updates are proposed in the PI to correct some information based on currently approved data. The MAH also took the opportunity to add some minor editorial changes in the PI. The PL is updated accordingly. The MAH took also the opportunity to update the details of all local representatives in the PL. The RMP v. 2.0 has been submitted. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	24/03/2022	08/07/2022	SmPC, Labelling and PL	This variation implements updated long term efficacy and safety clinical information following the completion of study Netter-1 the pivotal study object of the initial approval. For more information, please refer to the Summary of Product Characteristics.
IA/0033/G	This was an application for a group of variations.	09/02/2022	08/07/2022	Annex II and	

	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS A.7 - Administrative change - Deletion of manufacturing sites			PL	
IA/0031	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	04/10/2021	n/a		
IB/0029	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	16/07/2021	n/a		
PSUSA/10643 /202012	Periodic Safety Update EU Single assessment - lutetium (177Lu) oxodotreotide	08/07/2021	n/a		PRAC Recommendation - maintenance
IA/0028	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	31/03/2021	n/a		
II/0022	Update of sections 4.2, 4.4, 4.5, 4.6, 4.8 and 5.1 of the SmPC in order to introduce structural changes in the dosing and administration and warnings and precautions section, include clarifications in the pregnancy and overdose sections, update instructions for use based on end user feedback and	10/12/2020	21/01/2021	SmPC, Annex II and PL	Management of severe or intolerable adverse drug reactions may require temporary dose interruption, extending dosing interval from 8 weeks up to 16 weeks, dose reduction, or discontinuation of treatment with Lutathera. Treatment with Lutathera in patients with creatinine

	update of amino acid solution information based on review and approval of LysaKare; the Package Leaflet is updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet and to include correction of typographical errors and editorial changes in the PI in line with the latest QRD template version 10.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				clearance < 40 mL/min at baseline (using Cockcroft Gault) is not recommended. No dose adjustment is recommended for renally impaired patients with creatinine clearance ≥ 40 mL/min. However, as this medicinal product is known to be substantially excreted by the kidneys, renal function should be more frequently monitored during the treatment as these patients may be at a greater risk of toxicity. The pharmacokinetic profile of lutetium (177Lu) oxodotreotide in patients with severe hepatic impairment has not been studied (total bilirubin > 3 times upper limit of normal and any ASAT), therefore those patients should only be treated with Lutathera after careful benefit-risk assessment. The recommended infusion method for administration of Lutathera is the gravity method. Addition of specific warnings and precautions in SmPC section 4.4 regarding the co-administered renal protective amino acid solution. For more information, please refer to the Summary of Product Characteristics.
PSUSA/10643 /202006	Periodic Safety Update EU Single assessment - lutetium (177Lu) oxodotreotide	14/01/2021	n/a		PRAC Recommendation - maintenance
IA/0026	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	04/12/2020	n/a		
IA/0025/G	This was an application for a group of variations. B.II.e.7.a - Change in supplier of packaging components or devices (when mentioned in the	04/12/2020	n/a		

	dossier) - Deletion of a supplier 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.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				
IB/0024/G	This was an application for a group of variations. B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.5.z - Change to in-process tests or limits applied during the manufacture of the finished product - Other variation	13/10/2020	n/a		
II/0021/G	This was an application for a group of variations. B.I.a.2.b - Changes in the manufacturing process of the AS - Substantial change to the manufacturing process of the AS which may have a significant impact on the quality, safety or efficacy of the medicinal product B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size	03/09/2020	n/a		

	B.II.b.3.b - Change in the manufacturing process of the finished or intermediate product - Substantial changes to a manufacturing process that may have a significant impact on the quality, safety and efficacy of the medicinal product B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size				
PSUSA/10643 /201912	Periodic Safety Update EU Single assessment - lutetium (177Lu) oxodotreotide	09/07/2020	n/a		PRAC Recommendation - maintenance
PSUSA/10643 /201906	Periodic Safety Update EU Single assessment - lutetium (177Lu) oxodotreotide	30/01/2020	01/04/2020	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10643/201906.
IA/0020	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	23/03/2020	n/a		
IB/0018/G	This was an application for a group of variations. B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process	12/02/2020	n/a		
IB/0017/G	This was an application for a group of variations.	24/12/2019	n/a		

	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.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size				
IB/0015/G	This was an application for a group of variations. B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the originally approved batch size B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation B.II.b.4.a - Change in the batch size (including batch size ranges) of the finished product - Up to 10-fold compared to the originally approved batch size	14/08/2019	n/a		
PSUSA/10643 /201812	Periodic Safety Update EU Single assessment - lutetium (177Lu) oxodotreotide	11/07/2019	n/a		PRAC Recommendation - maintenance

IB/0014	B.I.a.1.z - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Other variation	19/06/2019	n/a		
IB/0013	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	07/06/2019	n/a		
IA/0012	B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS	15/04/2019	n/a		
II/0005	Update of the SmPC section 5.1 to include information on the quality of life based on relevant analyses of NETTER-I study data. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	31/01/2019	25/03/2019	SmPC	Health Related Quality of Life (HRQOL) was assessed using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30) (generic instrument) and its neuroendocrine tumour module (EORTC QLQ-GI.NET-21). The results indicate an improvement in the overall global health-related quality of life up to week 84, for patients on Lutathera treatment as compared to patients on Octreotide LAR arm.
PSUSA/10643 /201806	Periodic Safety Update EU Single assessment - lutetium (177Lu) oxodotreotide	17/01/2019	n/a		PRAC Recommendation - maintenance
N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/12/2018	25/03/2019	PL	
IB/0007	B.I.b.1.z - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Other variation	05/12/2018	n/a		

PSUSA/10643 /201712	Periodic Safety Update EU Single assessment - lutetium (177Lu) oxodotreotide	12/07/2018	n/a		PRAC Recommendation - maintenance
IAIN/0004	B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer	18/05/2018	n/a		
IAIN/0003	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	21/03/2018	25/03/2019	Annex II, Labelling and PL	
IB/0001	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	21/02/2018	n/a		