Lysodren

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/0031	A.1 - Administrative change - Change in the name and/or address of the MAH	10/01/2025		SmPC, Labelling and PL	
II/0029/G	This was an application for a group of variations. Update of sections 4.2, 4.4, 4.5, 4.6, 4.8 and 4.9 of	25/07/2024		SmPC and PL	The product information of Lysodren has been updated to align the special warnings on 'adrenal insufficiency', 'triglycerides monitoring', 'mitotane tissue accumulation',

[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).

	the SmPC in order to update special warnings and pregnancy information in line with the CCSI. The terms "Corticosteroid binding globulin increased" and "Thyroxin binding globulin increased" have been added to the to the list of ADRs with frequency 'Not Known'; based on clinical practice guidance and post-marketing data. The Package Leaflet has been updated accordingly. In addition, the MAH took the opportunity to bring the PI in line with the latest QRD template version 10.3, and to implement editorial changes to the SmPC. 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				'bleeding time', 'women of childbearing potential' and 'premenopausal women' with the Company Core Safety Information. The list of adverse drug reactions has been updated to include 'Corticosteroid binding globulin increased' and 'Thyroxin binding globulin increased', based on clinical practice and post-marketing data. For more information, please refer to the Summary of Product Characteristics.
II/0030	Update of sections 4.4 and 4.8 of the SmPC in order to amend existing warnings on hepatic impairment based on a cumulative review of cases with increase of transaminases >5 ULN and the outcome of these elevations after mitotane discontinuation, following the request by PRAC in the PSUSA/00002075/202304. The Package Leaflet is updated in accordance. 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	16/05/2024		SmPC	Based on a cumulative review of cases with increase of transaminases > 5 ULN and the outcome of these elevations after mitotane discontinuation, the warnings in sections 4.4 and 4.8 of the SmPC regarding hepatotoxicity have been updated as follows: Section 4.4 'Special warnings and precautions for use' - Hepatotoxicity has been observed in patients treated with mitotane. Cases of liver damage (hepatocellular, cholestatic and mixed) and autoimmune hepatitis were observed. Liver function tests (alanine transaminase [ALT], aspartate transaminase [AST], bilirubin, and alkaline phosphatase [ALP] levels) should be periodically monitored, especially during the first months of treatment or when it is necessary

	new additional data submitted by the MAH				to increase the dose. If AST and/or ALT are increased > 5 ULN, or ALP or bilirubin > 2 ULN, there is risk of liver injury/failure. In this case, Lysodren treatment should be interrupted. Treatment can be resumed at physician's discretion depending on the severity of the event as well as the patient's clinical condition. Section 4.8 'Undesirable effects' - The activity of liver enzymes (gamma-GT, aminotransferase, alkaline phosphatase) is commonly increased. Liver enzymes levels usually normalize when the mitotane dose is decreased or temporarily interrupted or discontinued. However, autoimmune hepatitis has been reported in 7 % of patients with no other information on mechanism. Very rare serious cases of liver injury (acute hepatic failure and hepatic encephalopathy) have been observed.
IA/0028	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)	31/01/2024		Annex II and PL	
PSUSA/2075/ 202304	Periodic Safety Update EU Single assessment - mitotane	30/11/2023	n/a		PRAC Recommendation - maintenance
II/0026	Update of section 4.8 of the SmPC new safety information regarding hypersensitivity reactions and oestrogenic-like effects based on post-marketing safety report and literature. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to	01/12/2022	13/06/2023	SmPC and PL	SmPC new text Oestrogenic-like effects (such as gynaecomastia in male patients and breast development and/or vaginal bleeding in female patients) have been observed. For more information, please refer to the Summary of Product Characteristics.

	new quality, preclinical, clinical or pharmacovigilance data				
IA/0025	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)	25/05/2022	13/06/2023	Annex II and PL	
II/0024	B.I.z - Quality change - Active substance - Other variation	24/02/2022	n/a		
PSUSA/2075/202004	Periodic Safety Update EU Single assessment - mitotane	28/01/2021	22/03/2021	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/2075/202004.
IB/0022	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	02/03/2020	22/03/2021	SmPC, Annex II, Labelling and PL	
T/0021	Transfer of Marketing Authorisation	06/08/2019	19/09/2019	SmPC, Labelling and PL	
IAIN/0020	A.1 - Administrative change - Change in the name and/or address of the MAH	20/12/2018	19/09/2019	SmPC, Labelling and PL	
PSUSA/2075/201704	Periodic Safety Update EU Single assessment - mitotane	30/11/2017	n/a		PRAC Recommendation - maintenance
IAIN/0018	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	25/04/2016	16/05/2017	SmPC, Labelling and PL	

PSUV/0016	Periodic Safety Update	18/12/2014	26/02/2015	SmPC and PL	Please refer to Lysodren PSUV-16 EPAR: Scientific conclusions and grounds recommending the variation to the terms of the marketing authorisation
IAIN/0017	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	02/12/2014	n/a		
N/0015	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/12/2013	03/06/2014	PL	
II/0014	Update of sections 4.2, 4.8 and 5.1 of the SmPC based on the results of the FIRM-ACT study. The PL has been updated accordingly. In addition, the MAH took the opportunity to update the list of local representatives with Croatia in the Package Leaflet. Furthermore, the PI is being brought in line with the latest QRD template version 9. Finally the MAH made some editorial changes to the SmPC. C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	30/05/2013	03/06/2014	SmPC, Annex II, Labelling and PL	The MAH applied to remove the restriction of indication "The effect of Lysodren on non-functional adrenal cortical carcinoma is not established'' thus for the use of mitotane in non-functional adrenal cortical carcinomas. This application was supported the FIRM-ACT (First International Randomized trial in locally advanced and Metastatic Adrenocortical Carcinoma Treatment) study. Further to the assessment of the CHMP and their conclusions as detailed in this report that this extension of the indication was not considered approvable, the MAH decided not to pursue with the proposed change to the indication. However, the CHMP agreed to the proposal from the MAH to update the sections 4.2, 4.8 and 5.1 of the SmPC based on the results of the FIRM-ACT study. Please refer to Scientific Discussion Lysodren-H-521-II-14-AR.
N/0013	Changes in the local representative contact details for Ireland and United Kingdom in the package leaflet.	09/03/2012	23/08/2012	PL	

	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)				
IB/0012	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	13/01/2012	23/08/2012	SmPC	
IB/0011/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.II.d.1.a - Change in the specification parameters and/or limits of the finished product - Tightening of specification limits	28/04/2011	n/a		
N/0010	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/04/2011	n/a	PL	
IA/0009/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 responsible for batch release B.II.b.2.b.1 - Change to batch release arrangements and quality control testing of the FP - Not including batch control/testing	15/03/2011	n/a	Annex II and PL	

N/0008	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	18/12/2009	n/a	PL	
IB/0006	IB_37_b_Change in the specification of the finished product - add. of new test parameter IB_38_c_Change in test procedure of finished product - other changes	26/05/2009	n/a		
IA/0007	IA_12_a_Change in spec. of active subst./agent used in manuf. of active subst. - tightening of spec.	05/05/2009	n/a		
R/0005	Renewal of the marketing authorisation.	22/01/2009	25/03/2009	SmPC and PL	
II/0004	Update of Summary of Product Characteristics, Labelling and Package Leaflet	22/03/2007	26/04/2007	SmPC, Labelling and PL	The MAH applied for a type II variation, upon request by CHMP following the assessment of the 4th PSUR, to update sections 4.2, 4.4 and 4.9 of the SPC regarding the need of monitoring of mitotane plasma levels and section 4.4 of the SPC with further information regarding patients with impaired liver or renal function and information on storage of mitotane in fat tissues. Further, the ADR "liver damage (hepatocellular/cholestatic/mixed)" has been added to section 4.8 of the SPC. In addition, the MAH took the opportunity to update the annexes in line with the latest QRD templates (version 7.2).
IA/0003	IA_06_a_Change in ATC code: Medicinal products for human use	01/08/2005	n/a	SmPC	
IA/0002	IA_01_Change in the name and/or address of the marketing authorisation holder	01/08/2005	n/a	SmPC, Labelling and PL	

IA/0001	IA_07_a_Replacement/add. of manufacturing site: Secondary packaging site	19/05/2004	n/a		