Xermelo

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/0035/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging	12/12/2022		Annex II and PL	

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

	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 B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site				
T/0034	Transfer of Marketing Authorisation	22/07/2022	05/08/2022	SmPC, Labelling and PL	
R/0032	Renewal of the marketing authorisation.	22/04/2022	14/06/2022	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 Xermelo in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
PSUSA/10639 /202102	Periodic Safety Update EU Single assessment - telotristat	30/09/2021	n/a		PRAC Recommendation - maintenance
IA/0031/G	This was an application for a group of variations. 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.z - Changes in the manufacturing process of the AS - Other variation	02/06/2021	n/a		

IB/0029	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	10/05/2021	12/11/2021	SmPC and PL	
IB/0028/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.II.b.2.z - Change to importer, batch release arrangements and quality control testing of the FP - Other variation	07/04/2021	n/a		
PSUSA/10639 /202008	Periodic Safety Update EU Single assessment - telotristat	11/03/2021	n/a		PRAC Recommendation - maintenance
IB/0026	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	09/11/2020	12/11/2021	SmPC	
PSUSA/10639 /202002	Periodic Safety Update EU Single assessment - telotristat	01/10/2020	n/a		PRAC Recommendation - maintenance
II/0021	Submission of updated RMP version 5.1 in order to update to the GVP module V (rev 2). The commitment to revise the RMP was done during variation procedure EMEA/H/C/003937/II/0015. C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated	11/06/2020	n/a		

	by new additional data to be submitted by the MAH where significant assessment is required				
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)	29/05/2020	n/a		
II/0014	To update sections 4.2 and 5.2 of the SmPC following final results from study LX1606-111; this is a Phase 1, open-label, parallel-group study to evaluate the single-dose pharmacokinetics of Telotristat Ethyl in Male and Female Subjects with Severe Hepatic Impairment and Matched Subjects with Normal Function; the Package Leaflet is updated accordingly. Additionally, the MAH took the opportunity to include minor editorial updates to the PL. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	07/05/2020	24/09/2020	SmPC and PL	A study was conducted in subjects with severe hepatic impairment and in healthy subjects. At a single dose of 250 mg, exposure to the parent compound was increased 317.0% and 529.5% for AUCt and Cmax, respectively, and to the active metabolite (AUCt, AUCinf, and Cmax) 497%, 500%, and 217%, respectively, for subjects with severe hepatic impairment compared to subjects with normal hepatic function. In addition, the half-life of the active metabolite was increased, i.e. the mean half life was 16.0 hours in subjects with severe hepatic impairment compared to 5.47 hours in healthy subjects. Based on these findings, the use of telotristat etiprate is not recommended in patients with severe hepatic impairment (Child Pugh score C).
II/0020/G	This was an application for a group of variations. To update sections 4.5 and 5.2 of the SmPC to update the information on the interaction with Carboxylesterases 2 inhibitors based on final results from the non-clinical study IPS000610; the Package Leaflet is updated accordingly. Furthermore, update of section 5.2 to reflect the results of in vitro study	19/03/2020	24/09/2020	SmPC, Annex II, Labelling and PL	The IC50 of the inhibition of loperamide on the metabolism of telotristat ethyl by Carboxylesterase 2 inhibitors was 5.2 µM. Concomitant use of Xermelo may change the exposure of medicinal products that are Carboxylesterase 2 substrates (e.g. prasugrel, irinotecan, capecitabine and flutamide). If co-administration is unavoidable, treatment should be monitored for suboptimal efficacy and safety events.

	XT175092. Additionally, the final study reports are submitted from studies XT173065, and XT174037, with no subsequent changes to the PI. The MAH took the opportunity to update the PI to the latest QRD template v10.1. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				In vitro telotristat ethyl engages in an allosteric interaction with CYP3A4 resulting at the same time in a reduced conversion of midazolam to 1'-OH-MDZ, and increased conversion to 4-OH-MDZ. The IC50 of the inhibition of loperamide on the metabolism of telotristat ethyl by Carboxylesterase 2 was 5.2 µM. In vitro, telotristat ethyl inhibited Carboxylesterase 2 with an IC50 approximately of 0.56 µM.
N/0023	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	17/03/2020	24/09/2020	PL	
PSUSA/10639 /201908	Periodic Safety Update EU Single assessment - telotristat	12/03/2020	n/a		PRAC Recommendation - maintenance
IB/0022	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	20/02/2020	n/a		
PSUSA/10639 /201902	Periodic Safety Update EU Single assessment - telotristat	19/09/2019	19/11/2019	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10639/201902.

IA/0018	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	23/10/2019	n/a		
II/0015	To update section 5.1 of the SmPC based on final results from study LX1606.1-302.CS (TELEPATH) listed as a category 3 study in the RMP; this is a multicentre, phase III, long-term extension study to further evaluate the safety and tolerability of telotristat etiprate in patients with carcinoid syndrome (CS). The updated RMP version 4.0 has also been submitted, also updating to GVP Module V (Rev 2). C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	03/10/2019	24/09/2020	SmPC	The long-term safety and tolerability of telotristat was evaluated in a nonpivotal (nonrandomized), phase 3, multicentre, open-label, long-term extension study. Patients having participated in any Xermelo phase 2 or phase 3 carcinoid syndrome study were eligible to enter the study at the same dose level and regimen as identified in their original study, for at least 84 weeks of treatment. No new significant safety signals were identified. The secondary objective of this study was to evaluate changes in patients' quality of life (QOL) through Week 84. QOL was generally stable over the course of the study.
N/0017	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	01/08/2019	19/11/2019	PL	
II/0009	Update of sections 4.2 and 5.2 of the SmPC in order to amend posology recommendations and add PK information in relation to renal impairment based on study D-FR-01017-002 (A Phase I, open-label study to compare the pharmacokinetics of telotristat ethyl and its metabolite in subjects with impaired renal function to healthy subjects with normal renal function after a single dose of telotristat etiprate, MEA005). The Package Leaflet is updated	26/04/2019	27/05/2019	SmPC and PL	No change in dosage is required in patients with mild, moderate or severe renal impairment who are not requiring dialysis. As a precautionary measure, it is recommended that patients with severe renal impairment will be monitored for signs of reduced tolerability. The use of Xermelo is not recommended in patients with end-stage renal disease requiring dialysis (eGFR < 15 mL/min requiring dialysis) because efficacy and safety of Xermelo in these patients has not been established.

	accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				For more information please refer to the Summary of Product Characteristics.
IA/0013	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	21/03/2019	n/a		
II/0005	Update of section 5.2 of the SmPC in order to add information from an in vivo drug interaction study (study identifier: LX1606.1-110-NRM) to evaluate the effect of multiple doses of concomitant gastric acid reducers such as PPIs on the PK of telotristat ethyl, LP-778902. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/03/2019	27/05/2019	SmPC	Concomitant use of telotristat etiprate (Xermelo, the hippurate salt of telotristat ethyl) with acid-reducers (omeprazole and famotidine) showed that the AUC of telotristat ethyl was increased 2-3 fold, while the AUC of the active metabolite (telotristat) was not changed. Since telotristat ethyl is rapidly converted to its active metabolite, which is > 25× more active than telotristat ethyl, no dose adjustments are required when using Xermelo with acid reducers.
II/0010	Update of section 5.3 of the SmPC in order to add information on carcinogenicity based on final results from study 8273113 (104-Week Oral Gavage Carcinogenicity and Toxicokinetic Study with LX1606 in Rats). The MAH took also the occasion to introduce some editorial changes in section 5.3 of the SmPC in alignment with the QRD wording. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance	14/03/2019	27/05/2019	SmPC	The carcinogenic potential of telotristat etiprate was studied in transgenic mice (26 weeks) and rats (104 weeks). These studies confirmed that telotristat did not increase the incidence of tumors in both species and sexes, at doses corresponding to an exposure of approximately 10- to 15-fold and 2- to 4.5-fold the human exposure to the active metabolite at the MRHD in mice and rats, respectively.

	data				
PSUSA/10639 /201808	Periodic Safety Update EU Single assessment - telotristat	14/03/2019	n/a		PRAC Recommendation - maintenance
IA/0012	A.6 - Administrative change - Change in ATC Code/ATC Vet Code	13/03/2019	27/05/2019	SmPC	
IB/0011	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	08/03/2019	n/a		
IB/0008	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	04/01/2019	27/05/2019	SmPC	
IA/0006/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 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	20/11/2018	n/a		

	manufacturer of a novel excipient				
PSUSA/10639 /201802	Periodic Safety Update EU Single assessment - telotristat	06/09/2018	n/a		PRAC Recommendation - maintenance
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	19/04/2018	07/12/2018	PL	
II/0002/G	This was an application for a group of variations. Submission of the final report from studies LX301 (pivotal phase III study) and LX303 (supportive phase III study) two randomised, multicentre, double-blind, placebo-controlled studies listed as category 3 studies in the RMP. The objective of study LX301 is to evaluate the efficacy and safety of telotristat etriprate in patients with carcinoid syndrome not adequately controlled by Somatostatin Analog (SSA) therapy; while the objective of study LX303 is to evaluate the safety and efficacy of telotristat etiprate in patients with carcinoid syndrome. In addition, the Marketing Authorisation Holder (MAH) took the opportunity to provide updated safety data from the long-term extension study LX302; a phase 3, multicentre, open-label study to further evaluate the safety and tolerability of telotristat. The RMP (version 3.0) was updated to reflect those safety data. The requested group of variations proposed amendments to the Risk Management Plan (RMP).	08/02/2018	n/a		With regards to the efficacy, the updated results from the open-label extensions of studies LX301 and LX303 are in line with the findings in the interim analyses provided during the marketing authorisation application and no changes to the previous efficacy assessments are required. With regards to the safety, the final analysis of the open-label uncontrolled extensions of studies LX301 and LX303 as well as the updated data from the ongoing uncontrolled study LX302 do not reveal new or unexpected safety findings. Overall, these results do not warrant any change to the Product Information of Xermelo.

	C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority C.I.13 - Other variations not specifically covered elsewhere in this Annex which involve the submission of studies to the competent authority				
IB/0001	B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data)	16/01/2018	07/12/2018	SmPC, Labelling and PL	