Lokelma

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
II/0033	Update of section 4.8 of the SmPC to include information on constipation to the summary of safety profile and to add constipation to the list of adverse drug reactions (ADRs) with frequency Common based on literature review and MAH safety database. The Package Leaflet is updated accordingly. In	14/12/2023		SmPC and PL	The MAH submitted with this variation an updated Summary of Product Characteristics (SmPC) based on completed Lokelma studies with a study design including maintenance treatment of hyperkalaemia. Results obtained from this literature review and from the MAH safety database showed increased risk of constipation.

[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).

	addition, the MAH took this opportunity to introduce editorial changes to the PI. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				Consequently, the adverse reaction 'constipation' was added to section 4.8 of the SmPC, with the frequency of 'common'.
II/0032	B.II.g.2 - Introduction of a post approval change management protocol related to the finished product	12/10/2023	n/a		
IB/0031	B.I.c.2.z - Change in the specification parameters and/or limits of the immediate packaging of the AS - Other variation	31/07/2023	n/a		
IAIN/0030/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.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)	26/04/2023		Annex II and PL	
R/0027	Renewal of the marketing authorisation.	15/12/2022	15/02/2023	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 Lokelma in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity. The product information was updated in accordance with the latest QRD template. Furthermore, changes were made in the Product

					Information and Annex A to reflect the presentations that are not renewed.
PSUSA/10675 /202203	Periodic Safety Update EU Single assessment - sodium zirconium cyclosilicate	10/11/2022	10/01/2023	SmPC and PL	Refer to Scientific conclusions and grounds recommending the variation to terms of the Marketing Authorisation(s)' for PSUSA/10675/202203.
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)	27/07/2022	n/a		
II/0025	Update of section 4.5 of the SmPC in order to add drug-drug interaction information based on final report for interventional study D9480C00012, "A Two-Cohort, Randomised Sequence, Crossover, Open-label Study to Assess the Effect of a Single Dose of Sodium Zirconium Cyclosilicate (SZC) on the Pharmacokinetics of Tacrolimus and Cyclosporin in Healthy Subjects". The Package Leaflet is updated accordingly. In addition, MAH is also taking this opportunity to update the contact details of the local representatives in the Package Leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/07/2022	10/01/2023	SmPC and PL	The MAH submitted with this variation an update of the Summary of Product Characteristics (SmPC) based on the final results of study D9480C00012. As a result, section 4.5. Interaction with other medicinal products and other forms of interaction has been reviewed to indicate that in another drug-drug interaction study in healthy volunteers, co-administration of Lokelma 15 g with tacrolimus 5 mg resulted in a decreased tacrolimus AUC and Cmax by 37% and 29% respectively. Therefore, tacrolimus should be taken at least 2 hours before or after Lokelma. In the same study, co-administration of Lokelma and cyclosporin did not show a clinically meaningful interaction.
PSUSA/10675 /202103	Periodic Safety Update EU Single assessment - sodium zirconium cyclosilicate	28/10/2021	n/a		PRAC Recommendation - maintenance
IA/0024	B.I.b.2.a - Change in test procedure for AS or	11/06/2021	n/a		

	starting material/reagent/intermediate - Minor changes to an approved test procedure				
PSUSA/10675 /202009	Periodic Safety Update EU Single assessment - sodium zirconium cyclosilicate	09/04/2021	n/a		PRAC Recommendation - maintenance
II/0021/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.b.1.f - Change in the specification parameters and/or limits of an AS, starting material/intermediate/reagent - Change outside the approved specifications limits range for the AS B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside the approved specifications limits range	21/01/2021	24/01/2022	SmPC, Labelling and PL	
PSUSA/10675 /202003	Periodic Safety Update EU Single assessment - sodium zirconium cyclosilicate	29/10/2020	n/a		PRAC Recommendation - maintenance
II/0013	Update of sections 4.2, 4.4 and 5.1 of the SmPC in order to update the clinical information based final results from study DIALIZE. This was a Phase 3b, multicentre, prospective, randomised, double-blind,	26/03/2020	28/04/2020	SmPC, Labelling and PL	In this study, 196 patients (mean age 58 years, range 20 to 86 years) with end stage renal disease on stable dialysis for at least 3 months and persistent pre dialysis hyperkalaemia were randomised to receive Lokelma 5 g or

	placebo-controlled study to determine the safety and efficacy of sodium zirconium cyclosilicate in patients with hyperkalaemia and on chronic haemodialysis. The Package Leaflet are updated accordingly. The RMP version 2.2 has been updated accordingly. In addition, the Marketing authorisation Holder (MAH) took the opportunity to implement the new excipient statement for sodium in section 4.4 of the SmPC, section 2 of Labelling and section 2 of the Package Leaflet. Furthermore, minor editorial changes were introduced in section 2 of the Package leaflet. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				placebo once daily on non dialysis days. The proportion of responders, defined as those subjects who maintained a pre dialysis serum potassium between 4.0 and 5.0 mmol/L on at least 3 out of 4 dialysis treatments after Long interdialytic interval (3-day interval [Friday/Saturday to Monday/Tuesday] in thrice weekly dialysis scheme) and who did not receive rescue therapy during the evaluation period, was 41% in the Lokelma group, and 1% in the placebo group ($p < 0.001$). The shorth term safety data from the study did not raise any new safety concerns. Based on those data, the SmPC section 4.2 (dosing recommendations) have been updated as follows: • Lokelma should only be dosed on non dialysis days. • The recommended starting dose is 5 g once daily. To establish normokalaemia (4.0-5.0 mmol/L), the dose may be titrated up or down weekly based on the pre dialysis serum potassium value after the long inter dialytic interval (LIDI). • The dose could be adjusted at intervals of one week in increments of 5 g up to 15 g once daily on non-dialysis days. • It is recommended to monitor serum potassium weekly while the dose is adjusted; once normokalaemia is established, potassium should be monitored regularly (e.g. monthly, or more frequently based on clinical judgement including changes in dietary potassium or medication affecting serum potassium). In addition, the MAH took the opportunity to introduce information on sodium content in the SmPC to inform prescribers that Lokelma is considered high in sodium and this should be particularly considered for those on a low salt diet.

					The Labelling and the PL have been updated accordingly.
PSUSA/10675 /201909	Periodic Safety Update EU Single assessment - sodium zirconium cyclosilicate	17/04/2020	n/a		PRAC Recommendation - maintenance
IB/0019	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	15/04/2020	n/a		
IA/0018/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 A.7 - Administrative change - Deletion of manufacturing sites 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.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.f.1.e - Stability of FP - Change to an approved stability protocol	27/03/2020	n/a		
IA/0017/G	This was an application for a group of variations. A.4 - Administrative change - Change in the name	16/01/2020	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.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.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.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure				
IB/0015/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.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	22/11/2019	n/a		

PSUSA/10675 /201903	Periodic Safety Update EU Single assessment - sodium zirconium cyclosilicate	03/10/2019	n/a		PRAC Recommendation - maintenance
IAIN/0014/G	This was an application for a group of variations. B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	30/08/2019	28/04/2020	SmPC and Labelling	
IB/0012/G	This was an application for a group of variations. B.I.b.1.d - Change in the specification parameters	29/07/2019	n/a		

	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.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.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				
IA/0010/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	29/05/2019	n/a		
PSUSA/10675 /201809	Periodic Safety Update EU Single assessment - sodium zirconium cyclosilicate	11/04/2019	n/a		PRAC Recommendation - maintenance

IB/0009/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.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.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)	14/02/2019	n/a		
IB/0008/G	This was an application for a group of variations. B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation B.I.a.2.z - Changes in the manufacturing process of the AS - Other variation 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.c.1.a - Change in immediate packaging of the AS	10/01/2019	n/a		

	- Qualitative and/or quantitative composition 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				
IA/0006	B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure	10/12/2018	n/a		
II/0003/G	This was an application for a group of variations. Please refer to the Recommendations section. 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	06/12/2018	11/04/2019	SmPC and PL	Sections 4.8 and 5.1 of the SmPC has been updated with additional information on the long-term safety and efficacy of sodium zirconium cyclosilicate treatment in subjects with hyperkalaemia, based on the results an open-label, multicentre, multi-dose, prospective maintenance study in subjects with hyperkalaemia. Section 4.5 in the SmPC has been updated to add specific guidance for the sodium zirconium cyclosilicate use with medicinal products that have the potential for drug-drug interaction based on an increase in gastric pH, based on the results of a single-dose, open-label, single-sequence crossover drug-drug interaction study in healthy subjects.
IA/0005/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 changes to an approved test procedure	23/10/2018	n/a		

IA/0004/G	This was an application for a group of variations. B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter B.II.d.1.d - Change in the specification parameters and/or limits of the finished product - Deletion of a non-significant specification parameter 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	29/06/2018	n/a		
IAIN/0001/G	This was an application for a group of variations. B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes	27/04/2018	11/04/2019	SmPC, Labelling and PL	
IA/0002	B.II.e.4.a - Change in shape or dimensions of the container or closure (immediate packaging) - Non-sterile medicinal products	25/04/2018	n/a		