Proposed packaging material		
Code	LOKELMA 5 10 g POS-PI-03.02	
Submission	☐NDA ☐Renewal ☒Variation change detail no.: RO-Change Event-0006182-0000001	
Code of previous version	LOKELMA 5 10 g POS-PI-02.01	
Changes	Intestinal Perforation EU LR PI Updates	
Reference	☐CDS version: N/A ☐CPIL version: N/A	☒SmPC country/version/date: EU ☐GRL approval: N/A
Name & Date	MNAI (23 Oktober 2023)	

LOKELMA® 5 g & 10 g
Powder for Oral Suspension
Sodium Zirconium Cyclosilicate

NAME OF THE MEDICINAL PRODUCT

Lokelma 5 g powder for oral suspension
Lokelma 10 g powder for oral suspension

QUALITATIVE AND QUANTITATIVE COMPOSITION

Lokelma 5 g powder for oral suspension
Each sachet contains 5 g sodium zirconium cyclosilicate
Each 5 g sachet contains approximately 400 mg sodium.

Lokelma 10 g powder for oral suspension
Each sachet contains 10 g sodium zirconium cyclosilicate
Each 10 g sachet contains approximately 800 mg sodium.

PHARMACEUTICAL FORM

Powder for oral suspension.
White to grey powder.

CLINICAL PARTICULARS

Therapeutic indications

Lokelma is indicated for the treatment of hyperkalaemia in adult patients.
Lokelma should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action.

Posology and method of administration

Posology

Adults, including the elderly

Correction phase

The recommended starting dose of Lokelma is 10 g, administered three times a day orally as a suspension in water. When normokalaemia is achieved, the maintenance regimen should be followed (see below).

Typically, normokalaemia is achieved within 24 to 48 hours. If patients are still hyperkalaemic after 48 hours of treatment, the same regimen can be continued for an additional 24 hours. If normokalaemia is not achieved after 72 hours of treatment, other treatment approaches should be considered.

Maintenance phase
When normokalaemia has been achieved, the minimal effective dose of Lokelma to prevent recurrence of hyperkalaemia should be established. A starting dose of 5 g once daily is recommended, with possible titration up to 10 g once daily, or down to 5 g once every other day, as needed, to maintain a normal potassium level. No more than 10 g once daily should be used for maintenance therapy.

Serum potassium levels should be monitored regularly during treatment. Monitoring frequency will depend upon a variety of factors including other medications, progression of chronic kidney disease and dietary potassium intake.

If severe hypokalaemia should occur, Lokelma should be discontinued and the patient re-evaluated.

Patients on chronic haemodialysis
For patients on dialysis 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).

Missed dose
If a patient misses a dose, they should be instructed to take the next usual dose at their normal time.

Special populations

Patients with renal/hepatic impairment
No changes from the normal doses are required for patients with renal or hepatic impairment.

Paediatric population
The safety and efficacy of Lokelma in children and adolescents (< 18 years) have not been established. No data are available.

Method of administration
For oral use.
The suspension can be taken with or without food. For instructions on preparation of the suspension, see section 6.6.

Limitations of the clinical data
Severe hyperkalaemia
There is limited experience in patients with serum potassium concentrations greater than 6.5 mmol/L.

Long-term exposure

Clinical trials with Lokelma have not included exposure longer than one year.

Contraindications

Hypersensitivity to the active substance.

Special warnings and special precautions for use

Serum potassium levels
Serum potassium should be monitored when clinically indicated, including after changes are made to medicinal products that affect the serum potassium concentration (e.g., renin-angiotensin-aldosterone system (RAAS) inhibitors or diuretics) and after the Lokelma dose is titrated.

Hypokalaemia
Hypokalaemia may be observed (see section 4.8). Dose titration as described under maintenance posology may be required in such cases to prevent moderate to severe hypokalaemia. In patients with severe hypokalaemia, Lokelma should be discontinued and the patient re-evaluated.

QT Prolongation
During correction of hyperkalaemia, a lengthening of the QT interval can be observed as the physiologic result of a decline in serum potassium concentration.

The risk of interaction with X-rays
Sodium zirconium cyclosilicate may be opaque to X-rays. If the patient is having abdominal X-rays, radiographers should keep this in mind.

Intestinal perforation
The risk for intestinal perforation with the use of Lokelma is currently unknown. Since intestinal perforation has been reported with potassium binders including Lokelma, specific attention should be paid to signs and symptoms related to intestinal perforation.

Sodium content
This medicinal product contains approximately 400 mg sodium per 5 g dose, equivalent to 20% of the WHO recommended maximum daily intake of 2 g sodium for an adult. Lokelma is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

Interactions with other medicinal products and other forms of interaction

Effect of other medicinal products on sodium zirconium cyclosilicate
As sodium zirconium cyclosilicate is not absorbed or metabolised by the body, there are no expected effects of other medicinal products on the pharmacologic action of sodium zirconium cyclosilicate.

Effect of sodium zirconium cyclosilicate on other medicinal products
As sodium zirconium cyclosilicate is not absorbed or metabolised by the body, and does not meaningfully bind other medicinal products, there are limited effects on other medicinal products. Sodium zirconium cyclosilicate can transiently increase gastric pH by absorbing hydrogen ions and can lead to changes in solubility and absorption kinetics for co-administered medicinal products with pH-dependent bioavailability. In a clinical drug-drug interaction study conducted in healthy subjects co-administration of sodium zirconium cyclosilicate with amlodipine, clopidogrel, atorvastatin, furosemide, glipizide, warfarin, losartan or levothyroxine did not result in clinically meaningful drug-drug interactions. Consistent with co-administration of dabigatran with other gastric acid modifiers, dabigatran C_{max} and

AUC values were approximately 40% lower when co-administered with sodium zirconium cyclosilicate. No dose adjustments or separation of time of dosing are required for any of these medicinal products. However, sodium zirconium cyclosilicate should be administered at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH dependent bioavailability.

Examples of medicinal products that should be administered 2 hours before or after sodium zirconium cyclosilicate to avoid possible raised gastric pH drug interaction are azole antifungals (ketoconazole, itraconazole and posaconazole), anti-HIV drugs (atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir and rilpivirine) and tyrosine kinase inhibitors (erlotinib, dasatinib and nilotinib).

Sodium zirconium cyclosilicate can be co-administered without spacing of dosing times with oral medications that do not exhibit pH-dependent bioavailability.

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.

Fertility, pregnancy and lactation

Pregnancy
There are no data from the use of sodium zirconium cyclosilicate in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of Lokelma during pregnancy.

Breast-feeding
In a postnatal study in rats, maternal exposure to sodium zirconium cyclosilicate had no effect on postnatal development. Due to its physicochemical properties, sodium zirconium cyclosilicate is not systemically absorbed and is not expected to be excreted in breast milk. No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to sodium zirconium cyclosilicate is negligible. Lokelma can be used during breast-feeding.

Fertility
There were no adverse effects on embryo-foetal development in treated rats or in rabbits.

Effect on ability to drive and use machines

Lokelma has no or negligible influence on the ability to drive and use machines.

Undesirable effects

Summary of the safety profile
The most commonly reported adverse reactions were hypokalaemia (4.1%) and oedema related events (5.7%).

Tabulated list of adverse reactions
The safety profile of Lokelma was evaluated in clinical trials involving 1760 patients with 507 patients exposed for one year.

The adverse reactions identified from controlled trials are shown in Table 1. The following convention was used for frequency of adverse reactions: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000), not known (Cannot be estimated from the available data).

Table 1. List of Adverse Reaction in Clinical Studies

System Organ Class	Common
Metabolism and nutrition disorders	Hypokalaemia
General disorders and administration site conditions	Oedema related events

Description of selected adverse reactions

Hypokalaemia
In clinical trials, 4.1% of Lokelma patients developed hypokalaemia with a serum potassium value less than 3.5 mmol/L, which was resolved with dose adjustment or discontinuation of Lokelma.

Oedema related events
Oedema related events, including fluid overload, fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, oedema peripheral and peripheral swelling, were reported by 5.7% of Lokelma patients. The events were observed in the maintenance phase only and were more commonly seen in patients treated with 15 g. Up to 53% were managed by initiating a diuretic or adjusting a diuretic dose; the remainder did not require treatment.

Long term exposure
In 2 clinical studies with open label exposure of Lokelma up to 1 year in 874 subjects, the following events were reported as related by investigators: gastrointestinal events [constipation (2.9%), diarrhea (0.9%), abdominal pain/distension (0.5%), nausea (1.6%) and vomiting (0.5%)]; and hypersensitivity reactions [rash (0.3%) and pruritus (0.1%)]. These events were mild to moderate in nature, none were reported as serious and were generally resolved while the patient continued treatment. Due to the open label study design, a causal relationship between these events and Lokelma cannot be definitively established.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions:

Pusat Farmakovigilans : Direktorat Pengawasan Keamanan, Mutu dan Ekspor Impor Obat Narkotika, Psikotropika, Prekursor, dan Zat Adiktif Badan Pengawas Obat dan Makanan Republik Indonesia
Address : Jl. Percetakan Negara No. 23, Jakarta Pusat, 10560
Email : pv-center@pom.go.id
Phone : +62-21-4244691 Ext. 1079
Website : http://e-meso.pom.go.id/

Overdose

Overdose with sodium zirconium cyclosilicate could lead to hypokalaemia. Serum potassium should be checked and potassium supplemented as needed.

PHARMACOLOGICAL PROPERTIES

Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for treatment of hyperkalaemia and hyperphosphatemia, ATC code: V03AE10

Mechanism of action

Sodium zirconium cyclosilicate is a non-absorbed, non-polymer inorganic powder with a uniform micropore structure that preferentially captures potassium in exchange for hydrogen and sodium cations. Sodium zirconium cyclosilicate is highly selective for potassium ions, even in the presence of other cations, such as calcium and magnesium, *in vitro.* Sodium zirconium cyclosilicate captures potassium throughout the entire gastrointestinal (GI) tract and reduces the concentration of free potassium in the GI lumen, thereby lowering serum potassium levels and increasing faecal potassium excretion to resolve hyperkalaemia.

Pharmacodynamic effects

Sodium zirconium cyclosilicate starts reducing serum potassium concentrations as soon as 1 hour after ingestion and normokalaemia can be achieved typically within 24 to 48 hours. Sodium zirconium cyclosilicate does not affect serum calcium or magnesium concentrations, or urinary sodium excretion. There is a close correlation between starting serum potassium levels and effect size; patients with higher starting serum potassium levels have greater reductions in serum potassium. There is a reduction in urinary potassium excretion which is a consequence of a reduction in serum potassium concentration. In a study of healthy subjects given Lokelma 5 g or 10 g once daily for four days, dose dependent reduction in serum potassium concentration and total urinary potassium excretion were accompanied by mean increases in faecal potassium excretion. No statistically significant changes in urinary sodium excretion were observed.

There were no studies conducted to investigate the pharmacodynamics when sodium zirconium cyclosilicate is administered with or without food.

Sodium zirconium cyclosilicate has also been shown to bind ammonium *in vitro* and *in vivo*, thereby removing ammonium and increasing serum bicarbonate levels. Lokelma-treated patients experienced an increase of 1.1 mmol/L at 5 g once daily, 2.3 mmol/L at 10 g once daily and 2.6 mmol/L at 15 g once daily in bicarbonate compared with a mean increase of 0.6 mmol/L for those receiving placebo.

In an environment where other factors affecting renin and aldosterone were not controlled, Lokelma demonstrated a dose-independent change in mean serum aldosterone levels (range: -30% to -31%) compared with the placebo group (+14%). No consistent effect on systolic and diastolic blood pressure has been observed.

In addition, mean reductions in blood urea nitrogen (BUN) were observed in the 5 g (1.1 mg/dL) and 10 g (2.0 mg/dL) three times daily groups compared with small mean increases in the placebo (0.8 mg/dL) and low dose sodium zirconium cyclosilicate (0.3 mg/dL) groups.

Clinical efficacy and safety

The potassium-lowering effects of Lokelma have been demonstrated in three randomised, double-blind, placebo-controlled trials in patients with hyperkalaemia. All three studies tested the initial effect of Lokelma to correct hyperkalaemia during a 48-hour period and two studies also tested maintenance of normokalaemia effect obtained. The maintenance studies included patients with chronic kidney disease (58%), heart failure (10%), diabetes mellitus (62%) and RAAS inhibitor therapy (68%). In addition, two open-label maintenance studies tested long-term safety of Lokelma. These five studies included 1760 patients given doses of Lokelma; 507 exposed for at least 360 days.

In addition, the efficacy and safety of Lokelma was studied in a double-blind, placebo-controlled trial of 196 chronic haemodialysis patients with hyperkalaemia, who received doses of Lokelma for 8 weeks. In the studies, Lokelma reduced serum potassium and maintained normal serum potassium levels regardless of the underlying cause of hyperkalaemia, age, sex, race, comorbid disease or concomitant use of RAAS inhibitors. No dietary restrictions were imposed; patients were instructed to continue their usual diet without any specified alterations.

Study 1
A two-phase, placebo-controlled correction and maintenance use study
A two-part, double-blind, randomised, placebo-controlled clinical trial of 753 patients (mean age of 66 years, range 22 to 93 years) with hyperkalaemia (5 to ≤ 6.5 mmol/L, baseline potassium average 5.3 mmol/L), and included patients with chronic kidney disease, heart failure, diabetes mellitus and those on RAAS inhibitor therapy.

During the correction phase, patients were randomised to receive Lokelma (1.25 g, 2.5 g, 5 g or 10 g) or placebo, administered three times daily for the initial 48 hours (Table 2).

Table 2. Correction phase (Study 1): Percentage of normokalaemic subjects after 48 hours of Lokelma

		Lokelma dose (three times daily)			
	Placebo	**1.25 g**	**2.5 g**	**5 g**	**10 g**
N	158	154	141	157	143
Baseline serum potassium, mmol/L	5.3	5.4	5.4	5.3	5.3
Normokalaemic at 48 hours, %	48	51	68	78	86
p-value vs. placebo		NS	< 0.001	< 0.001	< 0.001

NS: not significant

Lokelma 10 g administered three times daily lowered serum potassium by 0.7 mmol/L at 48 hours ($p < 0.001$ vs. placebo); statistically significant 14% potassium reduction was observed 1 hour after the first dose. Patients with higher starting potassium levels had a greater response to Lokelma. Patients with pre-treatment potassium levels in excess of 5.5 mmol/L (average baseline 5.8 mmol/L) saw an average decrease of 1.1 mmol/L at 48 hours while those with starting potassium levels at or below 5.3 mmol/L had an average decrease of 0.6 mmol/L at the highest dose.

Patients who became normokalaemic after receiving Lokelma during the correction phase were re-randomised to receive once daily placebo or once daily Lokelma at the same dose level as they had received three times daily during the correction phase (Table 3).

Table 3. Maintenance phase (12 days, Study 1): Mean number of normokalaemic days

	Maintenance phase treatment (once daily)

Correction phase Lokelma dose	Placebo N	Placebo Days	Lokelma n	Lokelma Days	P-value vs placebo
1.25 g three times daily	41	7.6	49	7.2	NS
2.5 g three times daily	46	6.2	54	8.6	0.008
5 g three times daily	68	6.0	64	9.0	0.001
10 g three times daily	61	8.2	63	10.2	0.005

NS: not significant

Study 2

A multi-phase, placebo-controlled maintenance study with an additional open-label phase

In the correction phase of the study, 258 patients with hyperkalaemia (baseline average 5.6, range 4.1 - 7.2 mmol/L) received 10 g of Lokelma administered three times daily for 48 hours. Reductions in potassium were observed 1 hour after the first 10 g dose of Lokelma. Median time to normokalaemia was 2.2 hours with 66% of patients achieving normokalaemia at 24 hours and 88% at 48 hours. Responses were larger in patients with more severe hyperkalaemia; serum potassium fell 0.8, 1.2 and 1.5 mmol/L in patients with baseline serum potassium < 5.5, 5.5-5.9 and ≥ 6 mmol/L, respectively.

Patients who achieved normokalaemia (potassium levels between 3.5 and 5 mmol/L) were randomised in a double-blind fashion to one of three doses of Lokelma [5 g (n=45), 10 g (n=51), or 15 g (n=56)] or placebo (n=85) administered once daily for 28 days (the double-blind randomised withdrawal phase).

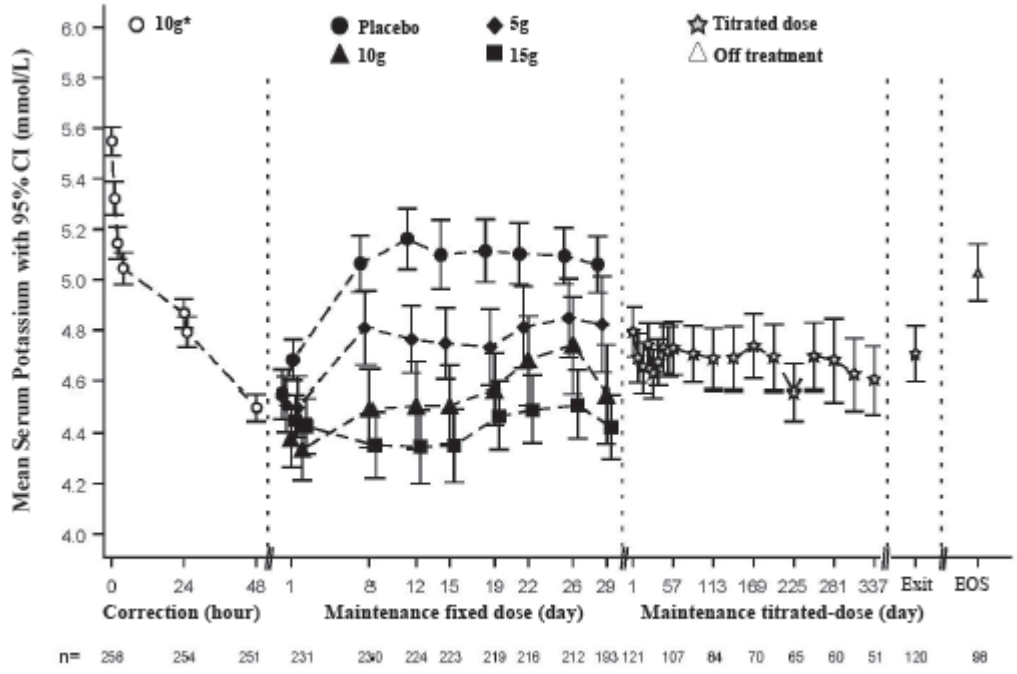
The proportion of subjects with average serum potassium < 5.1 mmol/L from Study Day 8 to 29 (three-week period) was greater at the 5 g, 10 g and 15 g once daily doses of Lokelma (80%, 90% and 94%, respectively), compared with placebo (46%). There was a mean decrease in serum potassium of 0.77 mmol/L, 1.10 mmol/L, 1.19 mmol/L and 0.44 mmol/L, respectively, and the proportion of subjects who remained normokalaemic was 71%, 76%, 85% and 48% in the 5 g, 10 g, 15 g once daily doses of Lokelma and placebo groups, respectively.

Maintenance phase with Lokelma titration (open-label) results: 123 patients entered the 11-month open-label phase. The proportion of subjects with average serum potassium < 5.1 mmol/L was 88%, the average serum potassium level was 4.66 mmol/L and the proportion of serum potassium measurements below 3.5 mmol/L was less than 1%; between 3.5 and 5.1 mmol/L was 77%; or between 3.5 and 5.5 mmol/L was 93%, irrespective of other factors that might influence the serum potassium. Treatment was discontinued on study exit (Day 365).

Kaplan-Meier estimates of time to relapse for maintenance phase showed dose dependence in time to relapse with median time for 5 g dose ranging from 4 to 21 days depending on the baseline serum potassium values. Serum potassium should be monitored periodically and the Lokelma dose titrated as described in section 4.2 Posology and Method of Administration.

Figure 1 illustrates the mean serum potassium over the correction and maintenance phases of the study.

Figure 1. Correction and maintenance phases (Study 2): mean serum potassium over time with 95% CI



Exit=Last Visit within 1 day of Last Dose, EOS=End of Study (7 days +/- 1 day after Last Dose)
*Given three times daily

Study 3
A study in chronic kidney disease patients with hyperkalaemia
This study was a double-blind placebo-controlled dose-escalating study in 90 patients (60 Lokelma patients; 30 controls) with baseline eGFR between 30-60 ml/min/1.73m^2 and hyperkalaemia (baseline serum potassium 5.2 mmol/L, range 4.6-6 mmol/L). Patients were randomised to receive escalating doses of Lokelma (0.3 g, 3 g and 10 g) or placebo, administered three times a day with meals for two to four days. The primary endpoint was the rate of change in serum potassium from baseline throughout the initial 2 days of treatment. The trial met the primary efficacy endpoint at the 3 g and 10 g doses of Lokelma compared to placebo. Lokelma at the 10 g dose and the 3 g dose resulted in mean maximal reductions of 0.92 mmol/L and 0.43 mmol/L, respectively. Twenty-four hour urine collections showed that Lokelma decreased urinary potassium excretion from baseline by 15.8 mmol/24 h compared to placebo increase by 8.9 mmol/24 h ($p < 0.001$). Sodium excretion was unchanged relative to placebo (10 g, increase by 25.4 mmol/24 h compared to placebo increase by 36.9 mmol/24 h (NS)).

Study 4
A two-phase, multicenter, multi-dose, open-label safety and efficacy study
The long term (up to 12 months) effects of Lokelma were assessed in this study in 751 subjects with hyperkalaemia (baseline average 5.59 mmol/L; range 4.3-7.6 mmol/L). Comorbid conditions included chronic kidney disease (65%), diabetes mellitus (64%), heart failure (15%) and hypertension (83%). Use of diuretics and RAAS inhibitors was reported by 51 and 70% of subjects, respectively. During the correction phase, 10 g of Lokelma was administered three times daily for at least 24 hours and up to 72 hours. Subjects who achieved normokalaemia (3.5-5.0 mmol/L, inclusive) within 72 hours entered the maintenance phase of the study. All subjects in the maintenance phase received Lokelma at a starting dose of 5 g once daily which could be increased in increments of 5 g once daily (to a maximum of 15 g once daily) or decreased (to a minimum of 5 g once every other day) based upon the titration regimen.

Normokalaemia was achieved in 494/748 (66%), 563/748 (75%) and 583/748 (78%) of subjects after 24, 48 and 72 hours of correction phase dosing with an average reduction in serum potassium of 0.81 mmol/L, 1.02 mmol/L and 1.10 mmol/L at 24 (n=748), 48 (n=104) and 72 (n=28) hours, respectively. Normokalaemia was dependent on baseline potassium concentration, with subjects with the highest baseline serum potassium concentrations having the most prominent decrease after starting the study drug but with the lowest proportion of subjects achieving normokalaemia. One hundred and twenty-six patients had a baseline serum potassium ≥ 6.0 mmol/L (mean baseline potassium 6.28 mmol/L). These subjects had a mean reduction of 1.37 mmol/L at the end of the correction phase.

Table 4. Correction phase (Study 4): proportion of subjects with serum potassium concentrations between 3.5 and 5.0 mmol/L, inclusive, or between 3.5 and 5.5 mmol/L, inclusive, by correction phase study day - ITT population

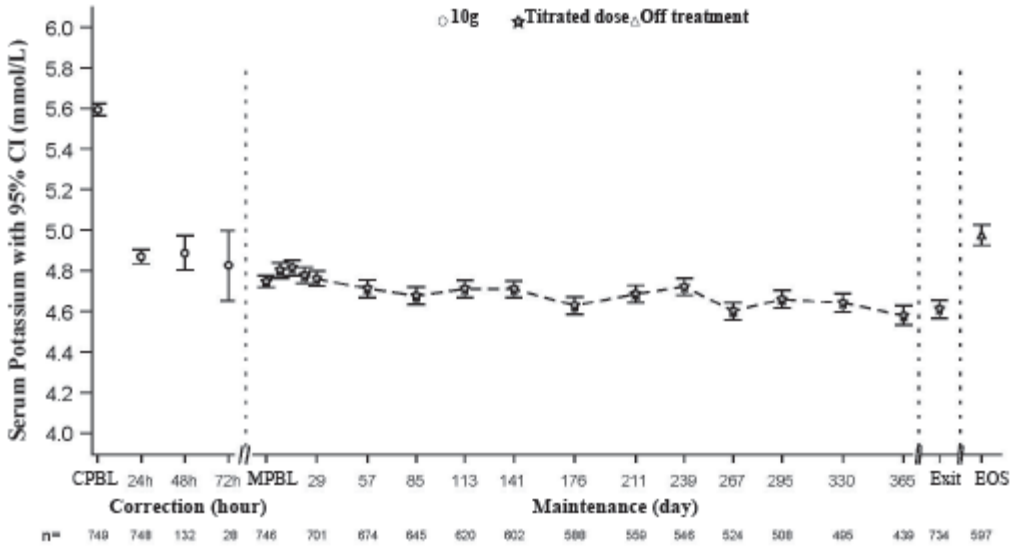
	Lokelma 10 g three times daily (N=749)					
Correction Phase (CP)	**Serum potassium 3.5 to 5.0 mmol/L, inclusive**			**Serum potassium 3.5 to 5.5 mmol/L, inclusive**		
	n/N	**Proportion**	**95% CI**	**n/N**	**Proportion**	**95% CI**
CP at 24 hours	494/748	0.660	0.625, 0.694	692/748	0.925	0.904, 0.943
CP at 48 hours	563/748	0.753	0.720, 0.783	732/748	0.979	0.965, 0.988
CP at 72 hours/CP Last	583/748	0.779	0.748, 0.809	738/748	0.987	0.976, 0.994

Note: One subject had a post-done value that was more than 1 day after last done. Therefore, the subject was eligible for the Correction Phase ITT Population; however, the time point was excluded from the analysis.

Normokalaemia was maintained while patients remained on drug and the mean serum potassium increased following discontinuation. Among those patients using RAAS inhibitors at baseline, 89% did not discontinue RAAS inhibitor therapy, 74% were able to maintain the same dose during the maintenance phase and among those not on RAAS inhibitors at baseline, 14% were able to initiate this therapy. During maintenance phase, 75.6% of subjects maintained normokalaemia, despite use of RAAS inhibitors.

Figure 2 illustrates the mean serum potassium over the correction and maintenance phases of the study.

Figure 2: Correction and maintenance phases in 12-month open-label study (Study 4) – mean serum potassium over time with 95% CI



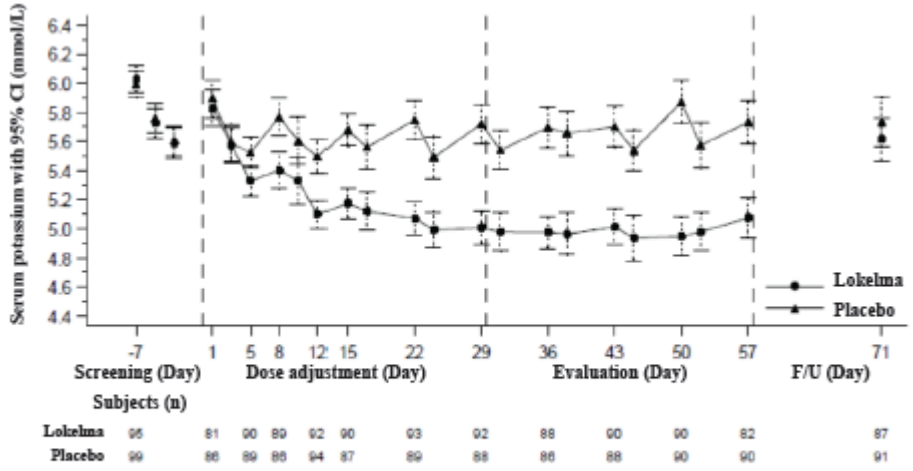
CPBL=Correction Phase Baseline, MPBL=Maintenance Phase Baseline
Exit=Last Visit within 1 day of Last Dose, EOS=End of Study (7 days +/- 1 day after Last Dose)

Study 5
A randomised, double-blind, placebo-controlled study in patients on chronic haemodialysis
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 once daily on non-dialysis days. At randomization, mean serum potassium levels were 5.8 mmol/L (range 4.2-7.3 mmol/L) in the Lokelma group and 5.9 mmol/L (range 4.2–7.3 mmol/L) in the placebo group. To achieve pre-dialysis serum potassium level between 4.0-5.0 mmol/L during the dose adjustment period (initial 4 weeks), the dose could be adjusted weekly in 5 g increments up to 15 g once daily based on pre-dialysis serum potassium measurement after the LIDI. The dose reached at the end of the dose-adjustment period was maintained throughout the subsequent 4-week evaluation period. At the end of the dose adjustment period, 37%, 43%, and 19% of patients were on Lokelma 5 g, 10 g and 15 g. 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 LIDI and who did not receive rescue therapy during the evaluation period, was 41% in the Lokelma group, and 1% in the placebo group ($p < 0.001$) (see Figure 3).

In post-hoc analyses the number of times patients had serum potassium between 4.0 and 5.0 mmol/L after the LIDI during the evaluation period was higher in the Lokelma group. 24% of patients were within this range at all 4 visits in the Lokelma group and none in the placebo group. The post-hoc analysis showed the proportion of patients who maintained serum potassium level between 3.5 and 5.5 mmol/L on at least 3 out of 4 dialysis treatments after LIDI during the evaluation period was 70% in the Lokelma group and 21% in the placebo group.

At the end of treatment, the mean post-dialysis serum potassium level was 3.6 mmol/L (range 2.6-5.7 mmol/L) in Lokelma group and 3.9 mmol/L (range 2.2-7.3 mmol/L) in the placebo group. There were no differences between Lokelma and placebo groups in interdialytic weight gain (IDWG). IDWG was defined as pre-dialysis weight minus post-dialysis weight on the previous dialysis session and was measured after the LIDI.

Figure 3: Mean pre-dialysis serum potassium levels over time in patients on chronic Dialysis



F/U- follow-up period
The displayed error bars correspond to 95% confidence intervals.
n = Number of patients with non-missing potassium measurements at a particular visit.

Paediatric population
The European Medicines Agency has deferred the obligation to submit the results of studies with Lokelma in one or more subsets of the paediatric population in male and female children from birth to less than 18 years of age, with hyperkalaemia (see section Posology and method of administration).

Pharmacokinetic properties

Absorption
Sodium zirconium cyclosilicate is an inorganic, insoluble compound that is not subject to enzymatic metabolism. In addition, clinical studies have shown it not to be systemically absorbed. An *in vivo* mass balance study in rats showed that sodium zirconium cyclosilicate was recovered in the faeces with no evidence of systemic absorption. Due to these factors and its insolubility, no *in vivo* or *in vitro* studies have been performed to examine its effect on cytochrome P450 (CYP450) enzymes or transporter activity.

Elimination
Sodium zirconium cyclosilicate is eliminated via the faeces.

Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential, toxicity to reproduction and development.

PHARMACEUTICAL PARTICULARS

List of excipients

None

Incompatibilities

Not applicable.

Shelf life

3 years.

Special precautions for storage

Do not store above 30°C.

Pack Size

Lokelma 5 g, Box, 30 Sachets: Reg. No: DKI2327900623A1
Lokelma 5 g, Box, 3 Sachets: Reg. No: DKI2327900623A1
Lokelma 10 g, Box, 30 Sachets: Reg. No: DKI2327900623B1

HARUS DENGAN RESEP DOKTER

Special precautions for disposal

Preparation of oral suspension
The entire contents of the sachet should be emptied in a drinking glass containing approximately 45 ml of water and stirred well. The tasteless liquid should be drunk while still cloudy. The powder will not dissolve. If the powder settles, the liquid should be stirred again and taken. If needed, rinse the glass with more water to ensure that all of the content is taken.

No special requirement for disposal.

Manufactured and packed by

AndersonBrecon Incorporated
4545 Assembly Drive
Rockford, IL 61109
United States

Released by

AstraZeneca Pharmaceuticals
LP508 Wrangler Drive
Coppell, TX 75019
United States

Imported by

PT AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

Date of revision of text

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Informasi untuk Pasien
LOKELMA® 5 & 10 g
Serbuk Untuk Suspensi Oral
Sodium Zirconium Cyclosilicate

Bacalah seluruh isi leaflet ini dengan seksama sebelum Anda mulai menggunakan obat ini karena leaflet ini berisi informasi penting bagi Anda.

- Simpan leaflet ini, Anda mungkin memerlukannya di kemudian hari.
- Apabila Anda memiliki pertanyaan lebih lanjut, hubungi dokter, apoteker, atau perawat Anda.
- Obat ini hanya diresepkan untuk Anda. Dilarang memberikan obat ini untuk orang lain. Hal ini dapat membahayakan orang lain, bahkan jika tanda penyakit yang mereka derita sama dengan penyakit Anda.
- Apabila Anda mengalami efek samping, komunikasikan dengan dokter, apoteker atau perawat Anda. Hal ini termasuk efek samping yang mungkin timbul yang tidak terdaftar dalam leaflet ini.

Informasi yang terkandung dalam leaflet ini:

1. Lokelma dan kegunaannya

Lokelma mengandung zat aktif natrium zirkonium siklosilikat.

Lokelma digunakan untuk mengobati hiperkalemia pada orang dewasa. Hiperkalemia merupakan adanya kadar kalium yang tinggi dalam darah. Lokelma tidak boleh digunakan sebagai pengobatan darurat untuk hiperkalemia yang mengancam jiwa karena efek dari obat tersebut timbul secara bertahap.

Lokelma menurunkan kadar kalium yang tinggi dalam tubuh Anda dan membantu menjaganya pada tingkat normal. Saat Lokelma melewati perut dan usus Anda, ia akan menempel pada kalium dan keduanya dibawa bersama keluar dari tubuh melalui feses Anda, dimana dapat menurunkan jumlah kalium dalam tubuh.

2. Hal yang perlu Anda ketahui sebelum mengkonsumsi Lokelma

Jangan gunakan Lokelma :
- Jika Anda alergi terhadap zat aktif Lokelma.

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Peringatan dan pencegahan

Pemantauan

Dokter atau perawat Anda akan memeriksa kadar kalium darah Anda saat Anda mulai minum obat ini:

- Ini untuk memastikan Anda mendapatkan dosis yang benar. Dosis dapat dinaikkan atau diturunkan berdasarkan kadar kalium darah Anda.
- Pengobatan dapat dihentikan jika kadar kalium darah Anda menjadi terlalu rendah.

Saat Anda menggunakan Lokelma, beri tahu dokter atau perawat Anda jika:

- Anda perlu melakukan rontgen, karena Lokelma dapat mempengaruhi interpretasi hasil.
- Anda mengalami sakit perut yang tiba-tiba atau parah karena ini mungkin merupakan tanda dari masalah yang diamati dengan obat lain yang bekerja di saluran pencernaan.

Bicaralah dengan apoteker atau dokter Anda jika Anda membutuhkan Lokelma 5 g atau lebih setiap hari untuk waktu yang lama, terutama jika Anda telah disarankan untuk mengikuti diet rendah garam (natrium).

Anak-anak dan remaja

Jangan berikan obat ini kepada anak-anak dan remaja di bawah usia 18 tahun. Ini karena efek Lokelma pada anak-anak dan remaja belum diketahui.

Lokelma dan obat-obatan lain

Beri tahu Dokter atau Perawat Anda jika Anda sedang mengonsumsi, baru saja mengonsumsi atau mungkin sedang mengonsumsi obat lain.

Secara khusus, beri tahu mereka tentang obat apa pun yang dapat mengubah kadar kalium darah Anda karena dosis Lokelma Anda mungkin perlu diubah. Obat-obatan Ini termasuk:

- diuretik (obat yang meningkatkan produksi urin)
- penghambat enzim pengubah angiotensin (ACE) seperti enalapril, dan penghambat reseptor angiotensin yang namanya diakhiri dengan sartan (obat untuk tekanan darah tinggi dan untuk masalah jantung)
- inhibitor renin seperti aliskiren (untuk tekanan darah tinggi)

Juga, beri tahu dokter atau perawat Anda jika Anda menggunakan salah satu dari yang berikut ini:

- tacrolimus (digunakan untuk menekan sistem kekebalan tubuh untuk mencegah penolakan pada transplantasi organ)
- ketoconazole, itraconazole, dan posaconazole (digunakan untuk mengobati infeksi jamur)
- atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, dan rilpivirine (digunakan untuk mengobati infeksi HIV)
- inhibitor tirosin kinase seperti erlotinib, dasatinib dan nilotinib (digunakan untuk mengobati kanker)

Kehamilan dan menyusui

Kehamilan

Jangan gunakan obat ini selama kehamilan karena tidak ada informasi tentang penggunaannya pada kehamilan. Laporkan pada dokter apabila Anda sedang hamil atau berencana akan hamil.

Menyusui

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Tidak ada efek pada bayi baru lahir/bayi yang sedang mendapatkan ASI. Lokelma dapat digunakan selama menyusui.

Mengemudi dan penggunaan mesin
Obat ini tidak memiliki pengaruh atau dapat diabaikan jika Anda sedang mengemudi atau menggunakan mesin.

3. Cara menggunakan Lokelma

Selalu gunakan obat ini persis seperti yang diinstruksikan dokter Anda. Apabila Anda tidak yakin, periksa ulang dengan dokter, apoteker, atau perawat Anda.

Berapa banyak yang harus digunakan
Dosis awal - untuk menurunkan kadar kalium tinggi Anda menjadi normal:
- Dosis yang dianjurkan adalah 10 g diminum tiga kali sehari.
- Obat ini membutuhkan waktu satu sampai dua hari untuk bekerja.
- Jangan gunakan dosis awal ini selama lebih dari tiga hari.

Dosis pemeliharaan - untuk menjaga kadar kalium Anda dalam kisaran normal setelah diturunkan:
- Dosis yang dianjurkan adalah 5 g diminum sekali sehari.
- Dokter Anda mungkin memutuskan bahwa Anda membutuhkan lebih banyak (10 g sekali sehari) atau kurang dari ini (5 g setiap hari).
- Jangan gunakan dosis pemeliharaan lebih dari 10 g sekali sehari.

Jika Anda sedang menjalani terapi hemodialisis:
- Gunakan Lokelma hanya pada hari pasien tidak sedang menjalani dialisis
- Dosis awal yang dianjurkan adalah 5 g diminum sekali sehari.
- Dokter Anda mungkin memutuskan bahwa Anda membutuhkan lebih banyak (sampai 15 g sekali sehari).
- Jangan mengonsumsi lebih dari 15 g sekali sehari.

Minum obat ini
- Usahakan untuk mengonsumsi Lokelma pada waktu yang sama setiap hari.
- Anda dapat meminum obat ini dengan atau tanpa makan.

Cara menggunakan Lokelma
- Buka sachet dan tuangkan serbuk ke dalam gelas minum dengan kira-kira 45 ml air (tidak berkarbonasi).
- Aduk rata dan langsung minum cairan yang tidak berasa.
- Serbuk tidak larut dan cairan akan tampak keruh. Serbuk akan mengendap di gelas dengan cepat. Jika ini terjadi, aduk kembali cairan dan minum obat yang tersisa dengan segera
- Apabila serbuk masih tersisa di dalam gelas, tambahkan air sebanyak 45 ml, lalu aduk kembali, dan minum keseluruhan obat hingga habis.

Apabila Anda menggunakan Lokelma dalam jumlah lebih dari yang seharusnya
Jika Anda meminum obat ini lebih dari yang seharusnya, segera bicarakan dengan dokter. Jangan minum lagi sampai Anda berbicara dengan dokter.

Apabila Anda lupa menggunakan Lokelma
- Jika Anda lupa meminum satu dosis obat ini, lewati dosis yang tertinggal.
- Kemudian minum dosis berikutnya seperti biasa pada waktu normal Anda.

- Jangan gunakan dosis ganda untuk mengganti dosis yang terlupakan.

Apabila Anda berhenti menggunakan Lokelma
Jangan mengurangi dosis obat ini atau berhenti meminumnya tanpa berkonsultasi atau berkomunikasi dengan dokter yang meresepkannya. Ini dikarenakan Anda mungkin akan mendapatkan kadar kalium yang tinggi dalam darah Anda lagi.

Apabila Anda memiliki pertanyaan lebih lanjut mengenai penggunaan obat ini, tanyakan pada dokter atau apoteker Anda.

4. Efek samping yang mungkin terjadi

Seperti semua obat-obatan, obat ini dapat mengakibatkan efek samping, yang tidak dialami oleh setiap orang.

Beri tahu dokter atau apoteker Anda jika Anda mengalami salah satu dari berikut ini:
Efek samping yang umum (dapat mempengaruhi hingga 1 dari 10 orang).
- Anda mulai merasa lelah, atau mengalami kelemahan otot atau kram, ini mungkin merupakan tanda bahwa kalium darah Anda menjadi terlalu rendah. Bicaralah dengan dokter Anda segera jika gejala ini menjadi parah.
- Anda mulai mengalami penumpukan cairan di jaringan, yang menyebabkan pembengkakan di bagian tubuh mana pun (biasanya di kaki dan pergelangan kaki).

Tidak diketahui (frekuensi tidak dapat diperkirakan dari data yang tersedia).
- Anda mulai mengalami sakit perut atau ketidaknyamanan, mual, muntah, diare atau sembelit.
- Anda mulai merasakan gatal-gatal pada kulit atau kemerahan atau pada kulit Anda.

Pelaporan efek samping
Apabila Anda mengalami efek samping, hubungi dokter, apoteker, atau perawat Anda. Hal ini termasuk efek samping yang mungkin terjadi yang tidak disebutkan dalam leaflet ini.

5. Cara penyimpanan Lokelma

Jauhkan obat ini dari penglihatan dan jangkauan anak-anak.

Jangan gunakan obat ini setelah lewat tanggal kadaluwarsa yang dapat dilihat pada blister atau karton setelah tanda ‘EXP’. Tanggal kadaluwarsa disini mengacu pada tanggal terakhir bulan yang tercantum.

Jangan disimpan pada suhu di atas 30°C

Jangan membuang obat-obatan melalui air limbah atau limbah rumah tangga. Tanyakan Apoteker Anda bagaimana membuang obat-obatan yang tidak lagi Anda gunakan. Langkah-langkah ini akan membantu melindungi lingkungan.

6. Isi kemasan obat dan informasi lainnya

Zat aktif obat ini adalah natrium zirkonium siklosilikat.

<u>Lokelma 5 g serbuk untuk suspensi oral</u>
Setiap sachet mengandung 5 g natrium zirkonium siklosilikat.

<u>Lokelma 10 g serbuk untuk suspensi oral</u>

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Setiap sachet mengandung 10 g natrium zirkonium siklosilikat.

Tidak ada bahan tambahan dalam obat ini.

Seperti apa bentuk Lokelma dan isi bungkusnya
Serbuk untuk suspensi oral adalah bubuk putih sampai abu-abu. Dikemas dalam dus berisi 30 sachet.

HARUS DENGAN RESEP DOKTER

Pemegang Hak Pemasaran dan Produsen
Diproduksi dan dikemas oleh:

AndersonBrecon Incorporated
4545 Assembly Drive
Rockford, IL 61109
United States

Dirilis oleh:

AstraZeneca Pharmaceuticals LP
508 Wrangler Drive
Coppell, TX 75019
United States

Diimpor oleh:
PT AstraZeneca Indonesia
Cikarang, Bekasi – Indonesia

Nomor Izin Edar:
Lokelma Serbuk Untuk Suspensi Oral 5 g, Dus, 30 sachet: DKI2327900623A1
Lokelma Serbuk Untuk Suspensi Oral 5 g, Dus, 3 sachet: DKI2327900623A1
Lokelma Serbuk Untuk Suspensi Oral 10 g, Dus, 30 sachet: DKI2327900623B1

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