

ANNEX I
SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

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

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Lokelma 5 g powder for oral suspension
Each sachet contains 5 g sodium zirconium cyclosilicate

Lokelma 10 g powder for oral suspension
Each sachet contains 10 g sodium zirconium cyclosilicate

3. PHARMACEUTICAL FORM

Powder for oral suspension.

White, free flowing powder essentially free of debris and particulates.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Lokelma is indicated for the treatment of hyperkalaemia in adult patients (see section 4.4 and 5.1).

4.2 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 entire contents of the sachet should be emptied in a drinking glass containing approximately 45 ml of water and stirred well. The powder will not dissolve. The tasteless liquid should be drunk while still cloudy. If the powder settles, the water should be stirred again. It should be ensured that all of the content is taken.

The suspension can be taken with or without food.

4.3 Contraindications

Hypersensitivity to the active substance.

4.4 Special warnings and 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. No events of intestinal perforation have been reported with Lokelma. Since intestinal perforation has been reported with polymers that act in the gastrointestinal tract, 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 for sodium.

Lokelma is considered high in sodium. This should be particularly taken into account for those on a low salt diet.

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.

4.5 Interaction 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.

4.6 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.

4.7 Effects on ability to drive and use machines

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

4.8 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 ($\geq 1/10$); Common ($\geq 1/100$ to $< 1/10$); Uncommon ($\geq 1/1,000$ to $< 1/100$); Rare ($\geq 1/10,000$ to $< 1/1,000$); Very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Table 1. List of adverse reactions 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 via the national reporting system listed in Appendix V.

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

5.1 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 \leq 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)				
	Placebo	Lokelma		P-value vs. placebo	
Correction phase Lokelma dose	N	Days	n	Days	
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

At the end of the maintenance period, when Lokelma was no longer administered, average potassium levels increased to near baseline levels.

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).

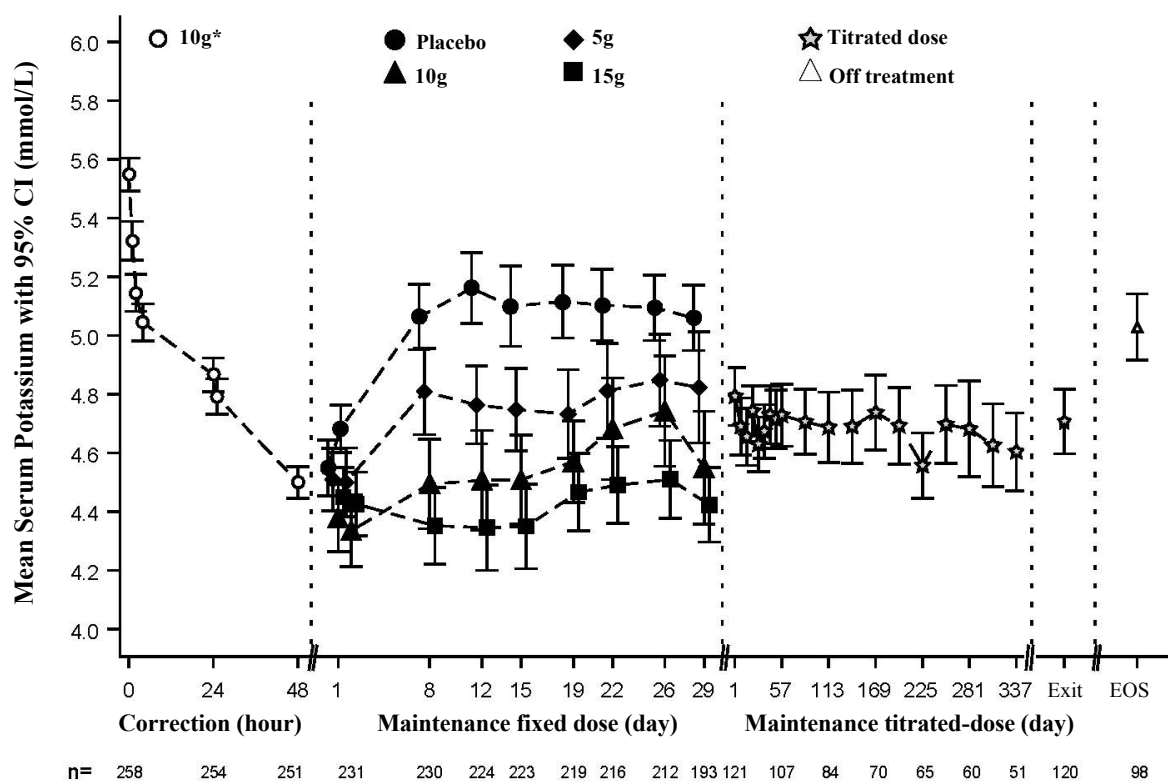
The proportion of subjects with average serum potassium < 5.1 mmol/L from Study Day 8 to 29 (three-week period) was greater at the 5 g, 10 g and 15 g once daily doses of Lokelma (80%, 90% and 94%, respectively), compared with placebo (46%). There was a mean decrease in serum potassium of 0.77 mmol/L, 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/1.73m² 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

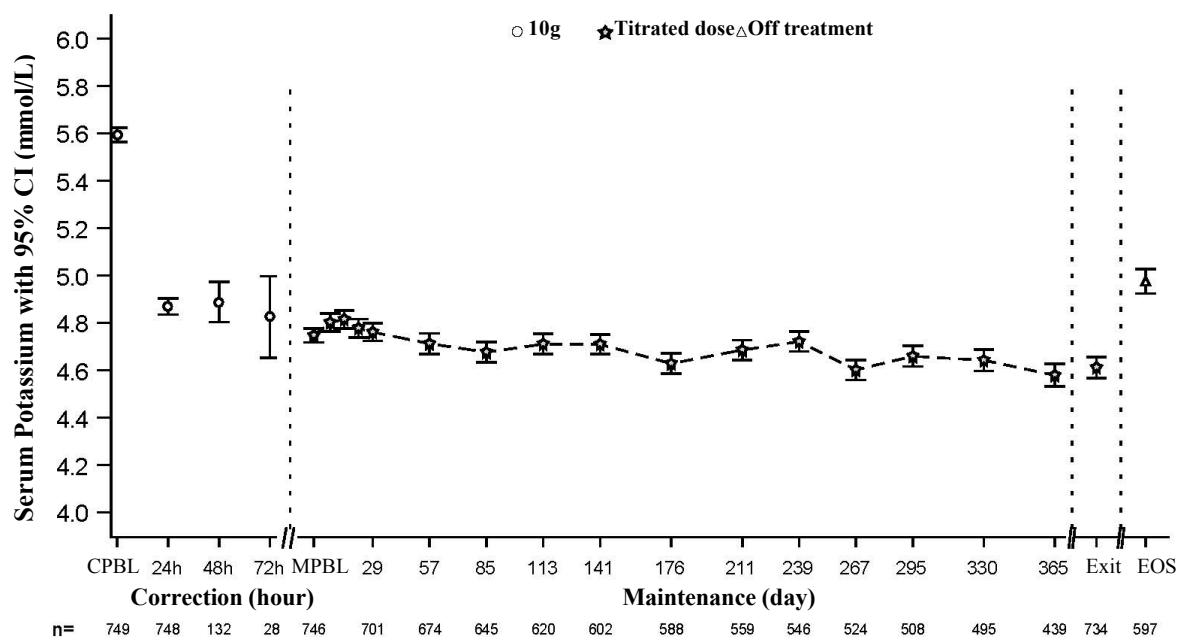
Correction Phase (CP)	Lokelma 10 g three times daily (N=749)					
	Serum potassium 3.5 to 5.0 mmol/L, inclusive			Serum potassium 3.5 to 5.5 mmol/L, inclusive		
	n/N	Proportion	95% CI	n/N	Proportion	95% CI
CP at 24 hours	494/748	0.660	0.625, 0.694	692/748	0.925	0.904, 0.943
CP at 48 hours	563/748	0.753	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-dose value that was more than 1 day after last dose. 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

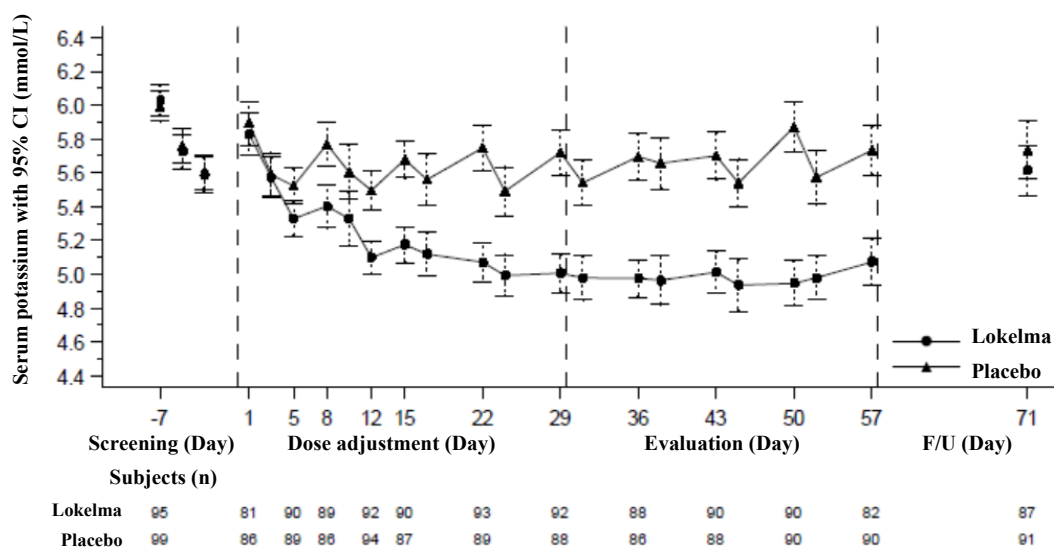
A randomised, double-blind, placebo-controlled study in patients on chronic haemodialysis

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 4.2 for information on paediatric use).

5.2 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.

5.3 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.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

5 or 10 g of powder in sachets made of a PET/alu/LLDPE or PET/LDPE/alu/EAA/LLDPE laminate

Pack sizes: 3, 28 or 30 sachets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1173/001
EU/1/17/1173/002
EU/1/17/1173/003
EU/1/17/1173/004
EU/1/17/1173/005
EU/1/17/1173/006
EU/1/17/1173/007
EU/1/17/1173/008
EU/1/17/1173/009
EU/1/17/1173/010
EU/1/17/1173/011
EU/1/17/1173/012

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22 March 2018

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency <http://www.ema.europa.eu>

ANNEX II

- A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE**
- B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**
- C. OTHER CONDITIONS AND REQUIREMENTS OF THE
MARKETING AUTHORISATION**
- D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE
AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer responsible for batch release

AstraZeneca AB
Gärtunavägen
SE-151 85 Södertälje
Sweden

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III
LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lokelma 5 g powder for oral suspension
sodium zirconium cyclosilicate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 5 g of sodium zirconium cyclosilicate.
High in sodium – see leaflet for further information.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension.

3 sachets

28 sachets

30 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1173/001 3 sachets
EU/1/17/1173/005 28 sachets
EU/1/17/1173/002 30 sachets
EU/1/17/1173/007 3 sachets
EU/1/17/1173/008 28 sachets
EU/1/17/1173/009 30 sachets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

lokelma 5 g

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Lokelma 10 g powder for oral suspension
sodium zirconium cyclosilicate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each sachet contains 10 g of sodium zirconium cyclosilicate.
High in sodium – see leaflet for further information.

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for oral suspension.

3 sachets

28 sachets

30 sachets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

AstraZeneca AB
SE-151 85 Södertälje
Sweden

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1173/003 3 sachets
EU/1/17/1173/006 28 sachets
EU/1/17/1173/004 30 sachets
EU/1/17/1173/010 3 sachets
EU/1/17/1173/011 28 sachets
EU/1/17/1173/012 30 sachets

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

lokelmä 10 g

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lokelma 5 g powder for oral suspension
sodium zirconium cyclosilicate
Oral use

2. METHOD OF ADMINISTRATION

To open, cut across top.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each sachet contains 5 g.

6. OTHER

AstraZeneca

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SACHET

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Lokelma 10 g powder for oral suspension
sodium zirconium cyclosilicate
Oral use

2. METHOD OF ADMINISTRATION

To open, cut across top.
Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

Each sachet contains 10 g.

6. OTHER

AstraZeneca

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

Lokelma 5 g powder for oral suspension Lokelma 10 g powder for oral suspension sodium zirconium cyclosilicate

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Lokelma is and what it is used for
2. What you need to know before you take Lokelma
3. How to take Lokelma
4. Possible side effects
5. How to store Lokelma
6. Contents of the pack and other information

1. What Lokelma is and what it is used for

Lokelma contains the active substance sodium zirconium cyclosilicate.

Lokelma is used to treat hyperkalaemia in adults. Hyperkalaemia means that there is a high level of potassium in the blood.

Lokelma lowers the high levels of potassium in your body and helps to keep it at a normal level. As Lokelma passes through your stomach and gut it attaches to potassium and the two are carried together out of the body in your stools, lowering the amount of potassium in the body.

2. What you need to know before you take Lokelma

Do not take Lokelma

- If you are allergic to the active substance.

Warnings and precautions

Monitoring

Your doctor or nurse will check your blood potassium level when you start taking this medicine:

- This is to make sure you are getting the correct dose. The dose may be raised or lowered based on your blood potassium level.
- Treatment may be stopped if your blood potassium level becomes too low.

While you are taking Lokelma, tell your doctor or nurse if

- you need to have an X-ray, as Lokelma may affect the interpretation of the results.

- you have sudden or severe pain in your abdomen as this may be a sign of a problem that is observed with other medications that work in the gastrointestinal tract.

Talk to your pharmacist or doctor if you need Lokelma 5 g or more daily for a prolonged period, especially if you have been advised to follow a low salt (sodium) diet.

Children and adolescents

Do not give this medicine to children and adolescents under 18 years of age. This is because the effects of Lokelma in children and adolescents are not known.

Other medicines and Lokelma

Tell your doctor or nurse if you are taking, have recently taken or might take any other medicines.

In particular, tell them about any medicines which can change your blood potassium levels because your dose of Lokelma may need to be changed. These include:

- diuretics (medicines that increase urine production)
- angiotensin converting enzyme (ACE) inhibitors such as enalapril, and angiotensin receptor blockers which name ends with sartan (medicines for high blood pressure and for heart problems)
- renin inhibitors such as aliskiren (for high blood pressure)

Also, tell your doctor or nurse if you are taking any of the following:

- ketoconazole, itraconazole and posaconazole (used to treat fungal infections)
- atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir and rilpivirine (used to treat HIV infection)
- tyrosin kinase inhibitors such as erlotinib, dasatinib and nilotinib (used to treat cancer)

If any of the above apply to you (or you are not sure), tell your doctor, pharmacist or nurse before taking this medicine.

Pregnancy and breast feeding

Pregnancy

Do not use this medicine during pregnancy because there is no information on its use in pregnancy.

Breast-feeding

No effects on the breastfed newborn/infant are anticipated since the systemic exposure of the breast-feeding woman to Lokelma is negligible. Lokelma can be used during breast-feeding.

Driving and using machines

This medicine has no or negligible influence on your ability to drive or to use machines.

3. How to take Lokelma

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

How much to take

Starting dose - to lower your high potassium level to normal:

- The recommended dose is 10 g taken three times a day.
- The medicine takes one to two days to work.
- Do not take this starting dose for more than three days.

Maintenance dose - to keep your potassium level within the normal range after it has been lowered:

- The recommended dose is 5 g taken once a day.

- Your doctor may decide that you need more (10 g once a day) or less than this (5 g every other day).
- Do not take a maintenance dose of more than 10 g once a day.

If you are on haemodialysis therapy:

- Take Lokelma only on non-dialysis days.
- The recommended starting dose is 5 g taken once a day.
- Your doctor may decide that you need more (up to 15 g once a day).
- Do not take more than 15 g once a day.

Taking this medicine

- Try to take Lokelma at the same time each day.
- You can take this medicine with or without meal.

How to take

- Open the sachet and pour the powder into a drinking glass with approximately 45 ml of still (non-carbonated) water.
- Stir well and drink the tasteless liquid straight away.
- The powder does not dissolve and the liquid appears cloudy. The white powder will settle in the glass quickly. If this happens, stir the liquid again and drink it all up.
- Rinse the glass with more water and drink it all up to take all the medicine.

If you take more Lokelma than you should:

If you take more of this medicine than you should, talk to a doctor straight away. Do not take any more until you have spoken to a doctor.

If you forget to take Lokelma

- If you forget to take a dose of this medicine, skip the missed dose.
- Then take the next dose as usual at your normal time.
- Do not take a double dose to make up for a forgotten dose.

If you stop taking Lokelma

Do not reduce the dose of this medicine or stop taking it without talking to the doctor who prescribed it. This is because you may get high potassium levels in your blood again.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor or nurse if you experience any of the following:

Common side effects (may affect up to 1 in 10 people).

- you start to feel tired, or have muscle weakness or cramps, this may be a sign that your blood potassium has become too low. Talk to your doctor immediately if these symptoms become severe.
- you start to have a build up of fluid in the tissues, leading to swelling anywhere in your body (usually in the feet and ankles).

Not known (frequency cannot be estimated from the available data).

- you start to have abdominal pain or discomfort, nausea, vomiting, diarrhoea or constipation.
- you start to have itching of the skin or recognise redness or scaling of your skin.

Reporting of side effects

If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via [the national reporting system](#) listed in [Appendix V](#). By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Lokelma

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and the sachet after 'EXP'. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Lokelma contains

The active substance is sodium zirconium cyclosilicate.

Lokelma 5 g powder for oral suspension

Each sachet contains 5 g of sodium zirconium cyclosilicate.

Lokelma 10 g powder for oral suspension

Each sachet contains 10 g of sodium zirconium cyclosilicate.

There are no other ingredients in this medicine.

What Lokelma looks like and contents of the pack

The powder for oral suspension is a white, free flowing powder, essentially free of debris and particulates. It comes in a sachet.

Lokelma 5 g powder for oral suspension

Each sachet contains 5 g of powder.

Lokelma 10 g powder for oral suspension

Each sachet contains 10 g of powder.

The sachets are supplied in a carton containing 3, 28 or 30 sachets.

Marketing Authorisation Holder

AstraZeneca AB
SE-151 85 Södertälje
Sweden

Manufacturer

AstraZeneca AB
Gärtnavägen
SE-151 85 Södertälje
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Other sources of information

Detailed information on this medicine is also available on the European Medicines Agency web site:

<http://www.ema.europa.eu>