LOKELMA®
(sodium zirconium cyclosilicate)

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 grams (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.

Sodium zirconium cyclosilicate is a white to grey, crystalline, insoluble powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

LOKELMA is indicated for the treatment of hyperkalaemia in adult patients.

4.2 Posology and method of administration

Posology

Use in adults

Treatment of hyperkalaemia correction phase

For patients whose serum potassium level is >5.0 millimoles per litre (mmol/L) the recommended starting dose of LOKELMA is 10 g, administered three times a day (TID) orally as a suspension in water, to achieve normokalaemia (normal potassium levels between 3.5 and 5.0 mmol/L). Typically, normokalaemia is achieved within 24 to 48 hours. If the measured serum potassium is still above 5.0 mmol/L at the end of 48 hours, an additional day (24 hours) of 10 g three times a day dosing may be given, prior to initiation of the maintenance dose. If normokalaemia is not achieved at the end of day 3, other treatment approaches should be considered.

Treatment of hyperkalaemia maintenance phase

For continued maintenance treatment, the minimal effective dose to prevent recurrence of hyperkalaemia should be established. A 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).

Method of administration

For oral use.

Patients should be instructed to empty the entire contents of the sachet into a drinking glass containing approximately 45 ml of water. Stir well and drink while the powder, which does not dissolve, is still suspended. The suspension is tasteless and will appear as a cloudy liquid. If the powder settles the water should be stirred again. Ensure all product is taken.

LOKELMA can be taken with or without food.

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 or hepatic impairment

No dose adjustment required for patients with renal or hepatic impairment.

Elderly patients

Dose adjustment is not required in the elderly.

Pediatric patients

Safety and efficacy of LOKELMA in pediatric patients have not been established.

4.3 Contraindications

No contraindications.

4.4 Special warnings and special precautions for use

Hypokalaemia

Hypokalaemia may be observed. Dose titration as described under maintenance posology may be required in such cases to prevent moderate to severe hypokalaemia.

Serum potassium levels

In patients with serum potassium levels <3.0 mmol/L, LOKELMA should be discontinued and the patient re-evaluated. Serum potassium should be monitored when clinically indicated for example, if changes are made to medications that affect serum potassium levels (e.g. use of renin-angiotensin-aldosterone system [RAAS] inhibitors or diuretics) and the LOKELMA dose titrated if necessary.

Oedema

Each 5 g dose of LOKELMA contains approximately 400 mg of sodium. In clinical trials of LOKELMA, oedema was generally mild to moderate in severity and was more commonly seen in patients treated with 15 g once daily. Monitor for signs of oedema, particularly in patients who should restrict their sodium intake or are prone to fluid overload (e.g., heart failure or renal disease). Advise patients to adjust dietary sodium, if appropriate. Increase the dose of diuretics as needed.

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.

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 LOKELMA

As LOKELMA is not absorbed or metabolised by the body, there are no expected effects of other medicinal products on the pharmacological action of LOKELMA.

Effect of LOKELMA on other medicinal products

As LOKELMA is not absorbed or metabolised by the body and does not meaningfully bind other medicinal products, there are limited effects on other medicinal products.

LOKELMA can transiently increase gastric pH by absorbing hydrogen ions that can lead to changes in solubility and absorption kinetics for co-administrated drugs with pH-dependent bioavailability. Therefore, LOKELMA should be administered at least 2 hours before or 2 hours after oral medications with clinically meaningful gastric pH dependent bioavailability.

Examples of drugs that should be taken 2 hours before or after LOKELMA to avoid possible raised gastric pH drug interaction are listed below:

Class of Drug	**Drugs**
Azole antifungals	Ketoconazole, Itraconazole, Posaconazole
Anti-HIV drugs	Atazanavir, Nelfinavir, Indinavir, Ritonavir, Saquinavir, Raltegravir, Ledipasvir, Rilpivirine
Tyrosine kinase inhibitors	Erlotinib, Dasatinib, Nilotinib

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

In a clinical drug-drug interaction study conducted in healthy subjects, co-administration LOKELMA with amlodipine, dabigatran, 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 the time of dosing are required for these drugs.

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.

4.6 Pregnancy and lactation

No clinical study has been conducted in pregnant or lactating women.

Reproduction studies performed at human equivalent doses of 115 g/day in rabbits and 58 g/day in rats, (assuming a 60 kg body mass) do not indicate direct harmful effects with respect to pregnancy, embryonal/foetal development, parturition, or postnatal development. Because animal reproduction studies are not always predictive of a human response, LOKELMA should be used during pregnancy only if the potential benefit to the mother justifies any potential risks to the foetus.

Due to its physicochemical properties, sodium zirconium cyclosilicate is not systemically absorbed and is not expected to be excreted in breast milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

4.8 Undesirable effects

Clinical trials

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

The most commonly reported adverse reaction was oedema related events which were reported by 5.7% LOKELMA patients; 1.7, 2.7, 5.2, and 14.3% of patients randomised to placebo, LOKELMA 5 g, 10 g, or 15 g once daily up to one month, respectively. Fifty-three percent were managed with initiating a diuretic or adjusting a diuretic dose; the remainder did not require treatment. In longer-term uncontrolled trials in which most patients were maintained on doses <15 g once daily, adverse reactions of oedema (oedema, generalized oedema and peripheral oedema) were reported in 8% to 11% of patients.

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.

In 2 clinical trials 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.

Tabulated list of adverse reactions

The following convention was used for frequency of adverse drug 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 reactions in clinical studies

System Organ Class and Frequency	Common
Metabolism and nutrition disorders	Hypokalaemia
General disorders and administration site conditions	Oedema related events[a,b]

[a] Includes Fluid overload, Fluid retention, Generalised oedema, Hypervolaemia, Localised oedema, Oedema, Oedema peripheral, Peripheral swelling

[b] Adverse reaction only in the maintenance phase

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group (ATC code): V03AE10

Pharmacotherapeutic group: Drugs for treatment of hyperkalaemia and hyperphosphatemia

5.1 Pharmacodynamic properties

Mechanism of action

LOKELMA is a non-absorbed, non-polymer inorganic powder with a uniform micropore structure that preferentially captures potassium in exchange for hydrogen and sodium cations. LOKELMA is highly selective for potassium ions, even in the presence of other cations such as calcium and magnesium, *in vitro*. LOKELMA captures potassium throughout the entire 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

LOKELMA reduces serum potassium levels as soon as 1 hour after ingestion and serum potassium concentrations continue to decline over the 48-hour treatment period. Sodium zirconium cyclosilicate has no effect on serum calcium, magnesium, and sodium levels. In patients not continuing treatment, potassium levels increase. 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.

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.

LOKELMA 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. LOKELMA demonstrated a reduction in serum aldosterone levels (range: -30% to -31%) compared with the placebo group (+14%). No effect on systolic and diastolic blood pressure has been observed.

In addition, mean reductions in BUN (blood urea nitrogen) 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 LOKELMA (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. In addition, two open-label maintenance studies tested long-term safety of LOKELMA. The maintenance studies included patients with chronic kidney disease (58%), heart failure (10%), diabetes mellitus (62%), and RAAS inhibitor therapy (68%). One thousand seven hundred sixty patients have received 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.

A two-phase, randomised, double-blind placebo-controlled study

In this study, 753 patients (mean age 66 years, range 22 to 93 years) with hyperkalaemia (5.0 - ≤6.5 mmol/L, baseline potassium average 5.3 mmol/L) were randomised to receive LOKELMA 1.25 g, 2.5 g, 5 g, or 10 g or placebo three times a day for the initial 48 hours.

LOKELMA showed dose-dependent reductions in serum potassium at the 2.5 g, 5 g, and 10 g doses within hours of administration of the first dose (Table 2). Statistically significant reductions in potassium were observed 1 hour after the first 10 g dose of LOKELMA. Mean serum potassium reduction was -0.7 mmol/L and 86% of patients had normal potassium values within 48 hours at the 10 g 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. Potassium reduction was similar among patients with chronic kidney disease, heart failure, diabetes mellitus, and those taking RAAS inhibitor therapy (angiotensin receptor blockers, angiotensin converting enzyme inhibitors, aldosterone antagonists).

Table 2 Acute phase potassium change from baseline at 48 hours

Mean serum potassium change mmol/L (95% Confidence intervals) Sample size	Placebo	1.25 g TID	2.5 g TID	5 g TID	10 g TID
All Patients	-0.2 (-0.3, -0.2) n=158	-0.3 (-0.4, -0.2) n=150	-0.5* (-0.5, -0.4) n=137	-0.5* (-0.6, -0.5) n=152	-0.7* (-0.8, -0.7) n=140
Baseline serum potassium <5.3 mmol/L	-0.2 (-0.2, -0.1) n=95	-0.2 (-0.3, -0.1) n=73	-0.4* (-0.5, -0.3) n=71	-0.4* (-0.5, -0.3) n=87	-0.6* (-0.7, -0.5) n=92
Baseline serum potassium 5.4-5.5 mmol/L	-0.4 (-0.5, -0.2) n=22	-0.4 (-0.5, -0.2) n=37	-0.5 (-0.6, -0.4) n=29	-0.7* (-0.8, -0.5) n=36	-1.0* (-1.1, -0.8) n=26
Baseline serum potassium >5.5 mmol/L	-0.4 (-0.6, -0.3) n=40	-0.3 (-0.5, -0.2) n=40	-0.6 (-0.7, -0.4) n=37	-0.9* (-1.0, -0.7) n=29	-1.1* (-1.3, -0.9) n=22

*= p-value <0.05

Patients achieving normokalaemia (potassium levels between 3.5 and 5.0 mmol/L) were then re-randomised to active drug at the same dose level or placebo administered once daily for 12 days (Table 3). This phase of the study met the predefined efficacy endpoints at the 2.5 g, 5 g, and 10 g doses when compared with their respective placebo groups. Efficacy was consistent across pre-specified subgroups with heart failure, chronic kidney disease, and diabetes mellitus, or in patients on RAAS inhibitors. At the end of the treatment period, when LOKELMA was no longer administered, potassium increased to near baseline levels.

Table 3 Maintenance phase (12 days): 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

A multi-phase, placebo-controlled maintenance study with extension

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

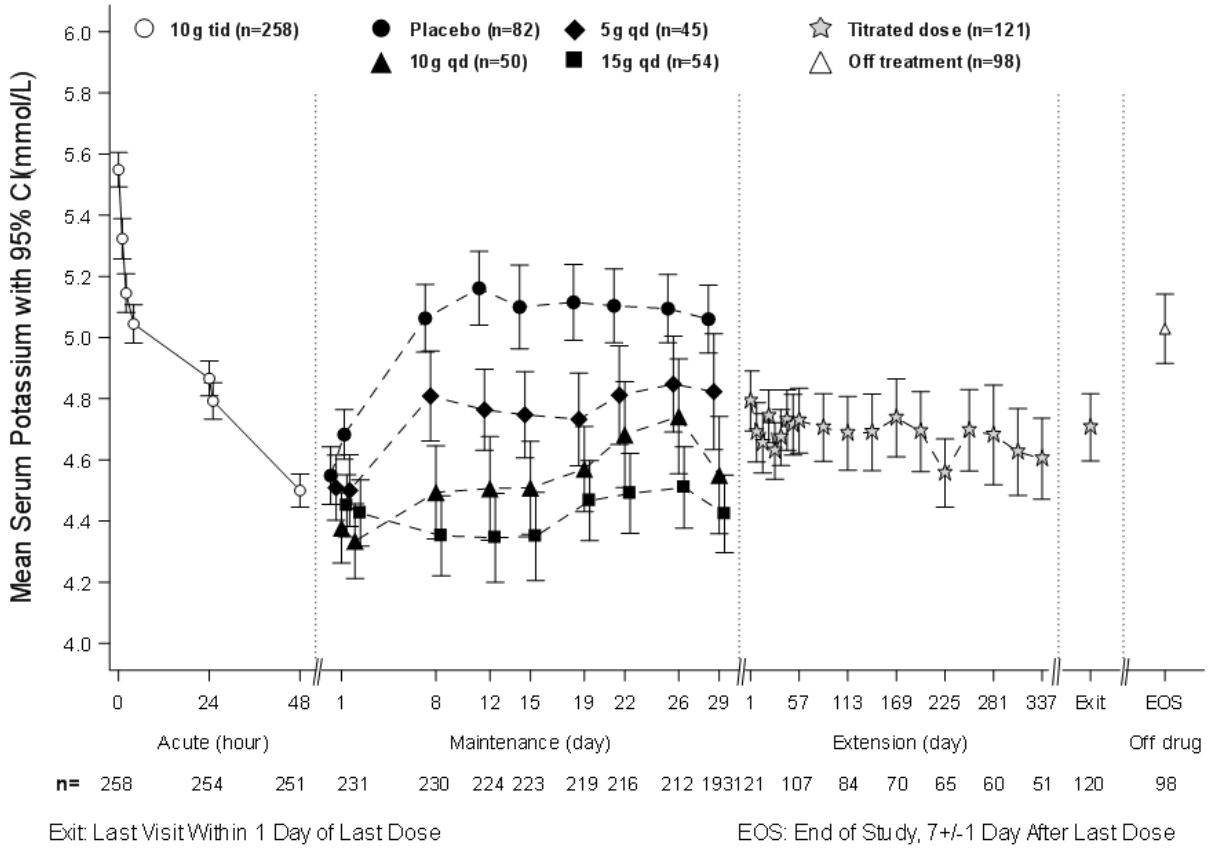
48 hours. Reductions in potassium were observed 1 hour after the first 10 g dose of LOKELMA. Median time to normokalaemia was 2.2 hours with 84% of patients achieving normokalaemia within 24 hours and 98% within 48 hours. Responses were larger in patients with more severe hyperkalaemia; serum potassium fell 0.8, 1.2, and 1.5 mmol/L in patients with baseline serum potassium <5.5, 5.5-5.9, and ≥6.0 mmol/L, respectively.

Patients who achieved normokalaemia (potassium levels between 3.5 and 5.0 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 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 in the 5 g, 10 g, 15 g once daily doses of LOKELMA and placebo groups, 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.

Extended maintenance phase (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. Average serum potassium levels were 4.66 mmol/L throughout the extension. Treatment was discontinued on study exit (Day 365). Figure 1 illustrates the mean serum potassium levels over the correction and maintenance phase of the study.

Figure 1 Correction and maintenance phase: Mean serum potassium levels



Intent-to-Treat population includes subjects with at least one valid Serum Potassium (SK) measurement on or after Day 8

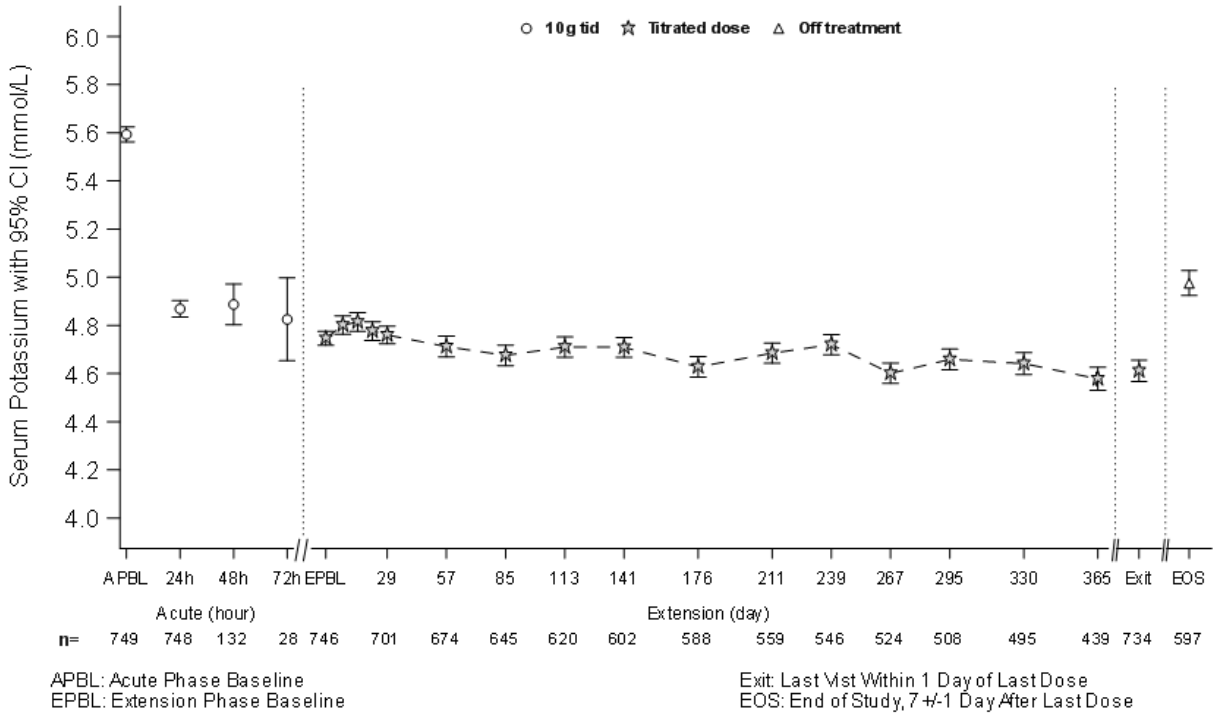
A two-phase, multi-center, multi-dose, open-label safety and efficacy study

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 CKD (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, LOKELMA was administered 10 g TID for at least 24 hours and up to 72 hours. Subjects who achieved normokalaemia (3.5-5.0 mmol/L, inclusive) within 72 hours (n=746; 99%) entered the maintenance phase of the study. All subjects in the maintenance phase received LOKELMA at a starting dose of 5 g QD which could be increased in increments of 5 g QD (to a maximum of 15 g QD) or decreased (to a minimum of 5 g QOD) 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 was -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. One hundred and twenty six patients had a baseline S-K ≥ 6.0 mmol/L (mean baseline potassium 6.28 mmol/L) and these patients had a mean reduction of -1.37 mmol/L at the end of the acute phase.

The proportion of subjects with a mean serum potassium ≤ 5.1 mmol/L across the Maintenance Phase Days 85-365 was 88% (95% CI 0.857, 0.908) and ≤ 5.5 mmol/L across the Maintenance Phase Days 85-365 was 99% (95% CI 0.976, 0.995). 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 RAASi 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.

Figure 2 12-Month Open-Label Study with Correction and Maintenance Phases - Mean Serum Potassium



Intent-to-Treat population includes subjects with at least one valid Serum Potassium (SK) measurement on or after Day 8

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 4.6-6.0 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; -15.8 mmol/24 hours compared to placebo +8.9 mmol/24 hours ($p < 0.001$). Sodium excretion was unchanged relative to placebo (10 g TID, +25.4 mmol/24 hours compared to placebo +36.9 mmol/24 hours (NS)).

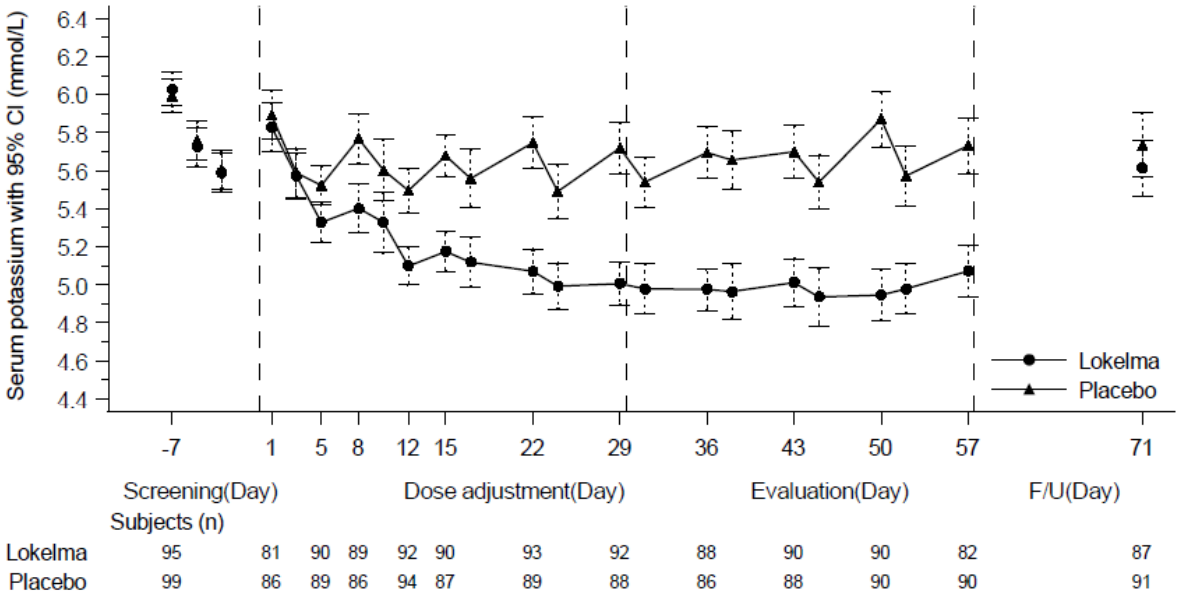
A randomised, double-blind, placebo-controlled study in patients on chronic haemodialysis

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.

5.2 Pharmacokinetic properties

Absorption

LOKELMA 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

LOKELMA is eliminated via the faeces.

5.3 Preclinical safety data

Preclinical data reveal no hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, toxicity to reproduction, and development. Carcinogenicity studies have not been conducted.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

Refer to the outer carton and/or inner product label for expiration date.

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

5 or 10g of powder packaged in high barrier aluminium sachets made of a 3-layer or 5-layer material laminate.

Pack size: 30 sachets

6.6 Instructions for use, handling and disposal

No special requirements.

Product Owner

AstraZeneca AB
SE-151 85, Södertälje, Sweden

Date of revision of text

April 2022

04/BB/SG/Doc ID-004025194 V7.0