

PRODUCT MONOGRAPH
INCLUDING PATIENT MEDICATION INFORMATION

Pr **LOKELMA®**

sodium zirconium cyclosilicate powder for oral suspension

5 g and 10 g

Potassium Binder (ATC Code V03AE10)

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PART I: HEALTH PROFESSIONAL INFORMATION

1 INDICATIONS

LOKELMA (sodium zirconium cyclosilicate) is indicated for:

- the treatment of hyperkalemia in adult patients.

1.1 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

1.2 Geriatrics

Geriatrics (> 65 years of age): Evidence from clinical studies and experience suggests that use in the geriatric population is not associated with differences in safety or effectiveness.

2 CONTRAINDICATIONS

- LOKELMA is contraindicated in patients who are hypersensitive to this drug or to any component of the container. For a complete listing, see Dosage Forms, Strengths, Composition and Packaging.

3 DOSAGE AND ADMINISTRATION

3.1 Recommended Dose and Dosage Adjustment

Treatment of hyperkalemia in adults

LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action. LOKELMA starts to reduce serum potassium 1 hour after administration in patients with hyperkalemia (see Pharmacodynamics and CLINICAL TRIALS).

Correction phase

For patients whose serum potassium level is >5.0 mmol/L the recommended starting dose of LOKELMA is 10 g, administered three times a day (TID) for up to 48 hours. When normokalemia (between 3.5 and 5.0 mmol/L) is achieved, the maintenance regimen should be followed (see below).

If normokalemia is not achieved at the start of day 3, other treatment approaches should be considered.

Maintenance phase

For continued maintenance treatment, the minimal effective dose of LOKELMA to prevent recurrence of hyperkalemia should be established. Monitor serum potassium as standard of clinical practice and adjust the dose of LOKELMA based on the serum potassium level and desired target range (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests).

The recommended dose is 5 g once daily, with possible titration (in increments of 5 g once daily) 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.

Treatment of patients on chronic hemodialysis

For patients on dialysis, LOKELMA should only be dosed on non-dialysis days. The recommended starting dose is 5 g once daily on every non-dialysis day; no correction phase is necessary. To establish normokalemia (4.0-5.0 mmol/L), the dose may be titrated up or down once per week based on the pre-dialysis serum potassium value after the long inter-dialytic interval (LIDI). The dose can be adjusted weekly in increments of 5 g up to 15 g once daily on non-dialysis days, or down to zero (dose interruption) for a few days to reach normokalemia. To maintain normokalemia, it is recommended to monitor pre-dialysis post-LIDI serum potassium regularly (e.g. every four or more weeks).

Health Canada has not authorized an indication for pediatric use.

3.2 Administration

LOKELMA is for oral use and can be taken with or without food. Administer LOKELMA orally as a suspension in water.

3.3 Reconstitution

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. Use additional water to ensure the entire dose is taken. See STORAGE, STABILITY AND DISPOSAL.

3.4 Missed Dose

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

4 OVERDOSAGE

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

For management of a suspected drug overdose, contact your regional poison control centre.

5 DOSAGE FORMS, STRENGTHS, COMPOSITION AND PACKAGING

Table 1 - Dosage Forms, Strengths, Composition and Packaging

Route of Administration	Dosage Form / Strength/Composition	Non-medicinal Ingredients
oral	powder for oral suspension, sachets of 5 g, 10 g	None

LOKELMA is a white to grey, insoluble, powder that is reconstituted in water for oral use.

Each sachet contains 5 g or 10 g sodium zirconium cyclosilicate. Each 5 g of sodium zirconium cyclosilicate contains approximately 400 mg of sodium.

LOKELMA 5 g is available in cartons of 30 sachets.

LOKELMA 10 g is available in cartons of 3 or 30 sachets.

6 WARNINGS AND PRECAUTIONS

Cardiovascular

During correction of hyperkalemia, QT prolongation can be observed as the physiologic result of a decline in serum potassium concentration.

Driving and Operating Machinery

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

Edema

Each 5 g of LOKELMA contains approximately 400 mg of sodium. LOKELMA preferentially captures potassium in exchange for hydrogen and sodium cations, therefore increases the risk of edema and fluid retention. Monitor for signs of edema, particularly in patients who should restrict their sodium intake or are prone to fluid overload associated with comorbidities (e.g., heart failure or renal disease). Advise patients to reduce dietary sodium, if appropriate.

Gastrointestinal

LOKELMA has not been studied in patients with severe gastrointestinal disorders or history of major gastrointestinal surgery. Avoid use of LOKELMA in patients with severe constipation, bowel obstruction or impaction, including abnormal postoperative bowel motility disorders.

LOKELMA can transiently increase gastric pH, resulting in changes in solubility and absorption kinetics of co-administered drugs with pH-dependent bioavailability (see DRUG INTERACTIONS).

Hepatic/Biliary/Pancreatic:

No data in patients with hepatic impairment are available.

Monitoring and Laboratory Tests

Serum potassium should be monitored when clinically indicated, including after changes are made to medications that affect serum potassium levels (e.g., use of renin-angiotensin-

aldosterone system [RAAS] inhibitors or diuretics) and after the LOKELMA dose is titrated.

Hypokalemia may be observed. Dose titration may be required in such cases to prevent moderate to severe hypokalemia (see DOSAGE AND ADMINISTRATION, Maintenance phase). In patients with serum potassium levels <3.0 mmol/L, LOKELMA should be discontinued and the patient should be re-evaluated.

Reduced serum aldosterone levels and increased serum bicarbonate levels may be observed in patients treated with LOKELMA (see CLINICAL TRIALS).

Renal

LOKELMA has not been studied in patients receiving peritoneal dialysis treatment.

Sexual Health

Fertility

There are no data of LOKELMA on fertility in humans. There were no significant adverse effects on male or female fertility in rats (see NON-CLINICAL TOXICOLOGY).

6.1 Special Populations

6.1.1 Pregnant Women

No clinical study has been conducted in pregnant women.

Reproduction studies were performed in rabbits and rats with sodium zirconium cyclosilicate administered at doses up to 6 g/kg/day (human equivalent doses of 116 g/day and 58 g/day, respectively, assuming a 60 kg body mass). These studies did not indicate direct harmful effects with respect to pregnancy, embryonal/fetal development, parturition, or postnatal development (see NON-CLINICAL TOXICOLOGY). 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 fetus.

6.1.2 Breast-feeding

No clinical study has been conducted in lactating women.

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

6.1.3 Pediatrics

Pediatrics (< 18 years): No data are available to Health Canada; therefore, Health Canada has not authorized an indication for pediatric use.

7 ADVERSE REACTIONS

7.1 Adverse Reaction Overview

The safety of LOKELMA was evaluated in clinical trials for the treatment of hyperkalemia involving 1760 patients with 507 patients exposed for at least one year.

The most commonly reported adverse reaction was edema related events which were reported in 5.7% of patients treated with LOKELMA; 1.7, 1.8, 5.3 and 14.3% of patients randomized 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 clinical trials 4.1% of patients treated with LOKELMA developed hypokalemia with a serum potassium value less than 3.5 mmol/L, which was resolved with dose adjustment or discontinuation of LOKELMA.

In addition, the safety of LOKELMA was evaluated in a double-blind, placebo-controlled trial in chronic hemodialysis patients with hyperkalemia who received doses of LOKELMA (n=96) or placebo (n=99) for 8 weeks. The most common adverse events observed in the trial were constipation (LOKELMA: 4%; placebo: 3%) and diarrhea (LOKELMA: 4%; placebo: 6%). Hypokalemia (serum potassium less than 3.5 mmol/L) occurred in 5.2% of participants receiving LOKELMA and 6.1% of participants receiving placebo. Hypokalemia was resolved with dose interruption of LOKELMA, with no change in dialysis parameters. There were no edema-related adverse events in hemodialysis participants treated with LOKELMA.

7.2 Clinical Trial Adverse Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Table 2 provides a summary of the most common adverse reactions (occurring in $\geq 1\%$ of patients), assessed as being related to study treatment, in the maintenance phase of the placebo-controlled studies ZS-003 and ZS-004.

Table 2 – Adverse Drug Reactions* Occurred in ≥ 1% of Patients, Studies ZS-003 (maintenance phase up to 12 days) and ZS-004 (maintenance phase up to 28 days)

System Organ Class Preferred Term	ZS <5 g QD ^a (N=199)	ZS 5 g QD (N=110)	ZS 10 g QD (N=114)	ZS 15 g QD ^b (N=56)	Placebo (N=301)
	Number (%) ^c of patients				
Metabolism and nutrition disorders					
Hypokalemia (S-K < 3.5 mmol/L)	1 (0.5)	0 (0.0)	7 (6.1)	11 (19.6)	2 (0.7)
General disorders and administration site conditions					
Edema related events ^d	2 (1.0)	2 (1.8)	6 (5.3)	8 (14.3)	5 (1.7)
Fluid overload	0 (0.0)	1 (0.9)	0 (0.0)	0 (0.0)	0 (0.0)
Fluid retention	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.8)	0 (0.0)
Generalised edema	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.6)	0 (0.0)
Edema	0 (0.0)	1 (0.9)	1 (0.9)	1 (1.8)	0 (0.0)
Edema peripheral	2 (1.0)	0 (0.0)	5 (4.4)	6 (10.7)	5 (1.7)

* As determined by the sponsor based on aggregate data.

^a Includes patients who were dosed with 1.25 g or 2.5 g.

^b 15 g was only administered in Study ZS-004.

^c Percentages are based on the total number of subjects in the treatment group (N).

^d One patient had more than one edema-related event.

N=Number of subjects in treatment group; QD=once daily; S-K=serum potassium.

Table 3 and Table 4 provide a summary of the most common adverse reactions (occurring in ≥ 1% of patients), assessed as being related to study treatment, in the open-label long-term studies ZS-004E and ZS-005, respectively.

Table 3 – Adverse Reactions* Occurred in ≥ 1% of Patients in Study ZS-004E (LOKELMA QD maintenance for up to 11 months)

System Organ Class Preferred Term	Study 004E (N=123)
	Number (%)^a of patients
General Disorders and Administration Site Conditions Edema peripheral	2 (1.6)
Investigations Electrocardiogram QT prolonged	2 (1.6)
Metabolism and Nutrition Disorders Hypomagnesemia	2 (1.6)
Musculoskeletal and Connective Tissue Disorders Muscle spasms	3 (2.4)

* As determined by the investigator based on individual case data.

^a Percentages are based on the total number of subjects in the treatment group (N).
N=Number of subjects in treatment group; QD=once daily.

Table 4 – Adverse Reactions* Occurred in ≥ 1% of Patients in Study ZS-005 (LOKELMA QD maintenance for up to 12 months)

System Organ Class Preferred Term	Study 005 (N=746)
	Number (%)^a of patients
Gastrointestinal Disorders Constipation	23 (3.1)
Nausea	13 (1.7)
General Disorders and Administration Site Conditions Edema peripheral	13 (1.7)

* As determined by the investigator based on individual case data.

^a Percentages are based on the total number of subjects in the treatment group (N).
N=Number of subjects in treatment group; QD=once daily.

Table 5 provides a summary of the most common adverse reactions (occurring in ≥ 1% of patients), assessed as being related to study treatment in the study of patients on chronic hemodialysis.

Table 5 – Adverse Reactions* Occurred in ≥1% of Patients on Chronic Hemodialysis (Study D9480C00006)

System Organ Class Preferred Term	LOKELMA (N=96)	Placebo (N=99)
	Number (%)^a of patients	
Gastrointestinal Disorders		
Constipation	2 (2.1)	1 (1.0)
Diarrhea	1 (1.0)	3 (3.0)

* As determined by the investigator based on individual case data

^a Percentages are based on the total number of patients in the treatment group (N).

N=Number of patients in treatment group.

Includes adverse reactions that occurred in ≥ 1% of the study population during the treatment period or follow-up period.

7.3 Less Common Clinical Trial Adverse Reactions (<1%)

The following is a list of less common treatment-related adverse events as assessed by the investigator, reported in <1% of patients (and in more than 2 patients) in the open-label long-term studies ZS-004E and ZS-005 and which are not represented in Table 3 and Table 4.

Cardiac disorders: Cardiac failure congestive

Gastrointestinal disorders: Diarrhea, vomiting

Infections and infestations: Gastroenteritis

Investigations: Calcium ionized decrease

Metabolism and nutrition disorders: Hypocalcemia, hypokalemia

7.4 Abnormal Laboratory Findings: Hematologic, Clinical Chemistry and Other Quantitative Data

Table 6 – Abnormal Laboratory Findings: Clinical Chemistry in Non-dialysis Patients

		Patients treated with LOKELMA
Serum Potassium	Values <3.5 mmol/L	4.1%*
	Values <2.5 mmol/L	0.0%

* Resolved with dose adjustment or discontinuation of LOKELMA

Table 7 – Abnormal Laboratory Findings: Clinical Chemistry in Patients on Chronic Hemodialysis

		LOKELMA (N=96)	Placebo (N=99)
		Number (%)^a of patients	
Serum Potassium ^b	Values <3.5 mmol/L	5 (5.2)	6 (6.1)
	Values <3.0 mmol/L	3 (3.1)	1 (1.0)
	Values <2.5 mmol/L	2 (2.1)	1 (1.0)

^a Percentages are based on the total number of patients in the treatment group (N).

^b Includes pre-dialysis serum potassium values.

N=Number of patients in treatment group.

8 DRUG INTERACTIONS

8.1 Overview

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

LOKELMA can transiently increase gastric pH, resulting in changes in solubility and absorption kinetics of co-administered drugs with pH-dependent bioavailability. Therefore, oral medications with gastric pH-dependent bioavailability should be administered at least 2 hours before or 2 hours after LOKELMA.

8.2 Drug-Drug Interactions

The drugs listed in Table 8 are based on either drug interaction case reports or studies, or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated). Co-administration of LOKELMA with amlodipine, dabigatran, clopidogrel, atorvastatin, furosemide, glipizide, warfarin, losartan, or levothyroxine were examined in a drug-drug interaction study conducted in healthy subjects. Amlodipine, glipizide, losartan, and levothyroxine did not show changes in exposure when co-administered with LOKELMA. Co-administration of LOKELMA with clopidogrel, furosemide and warfarin resulted in changes in the concentration of these drugs. However the changes in exposure of these drugs are not considered clinically meaningful, and no dose adjustment is required. Co-administration of LOKELMA with atorvastatin and dabigatran resulted in clinically significant changes in exposure and these drugs should be administered at least 2 hours before or 2 hours after LOKELMA.

Table 8 - Established or Potential Drug-Drug Interactions

Common Name	Source of Evidence	Effect	Clinical Comment
Atorvastatin	CT	Co-administration of 10 g LOKELMA with 10 mg atorvastatin resulted in increase of C _{max} of atorvastatin and o-OH atorvastatin by 69% and 37%, respectively, 16% increase in systemic exposure to o-OH atorvastatin compared to atorvastatin administered alone.	Atorvastatin should be administered at least 2 hours before or 2 hours after LOKELMA.
Azole antifungals (e.g., ketoconazole, itraconazole, posaconazole)	T	LOKELMA transiently increases gastric pH, resulting in change of the absorption of co-administered drugs with pH-dependent solubility.	Azole antifungals should be administered at least 2 hours before or 2 hours after LOKELMA.
Dabigatran	CT	Co-administration of 10 g LOKELMA with 75 mg dabigatran resulted in a 40% decrease in systemic exposure to dabigatran compared to dabigatran administered alone.	Dabigatran should be administered at least 2 hours before or 2 hours after LOKELMA.
Protease inhibitors (PIs) (e.g., atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir, ledipasvir, rilpivirine)	T	LOKELMA transiently increases gastric pH, resulting in change of the absorption of co-administered drugs with pH-dependent solubility.	PIs should be administered at least 2 hours before or 2 hours after LOKELMA.
Tyrosine kinase inhibitors (TKIs) (e.g., erlotinib, dasatinib, nilotinib)	T	LOKELMA transiently increases gastric pH, resulting in change of the absorption of co-administered drugs with pH-dependent solubility.	TKIs should be administered at least 2 hours before or 2 hours after LOKELMA.

Legend: CT = Clinical Trial; T = Theoretical

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

8.3 Drug-Food Interactions

Interactions with food have not been established.

8.4 Drug-Herb Interactions

Interactions with herbal products have not been established.

8.5 Drug-Laboratory Test Interactions

Interactions with laboratory tests have not been established.

9 ACTION AND CLINICAL PHARMACOLOGY

9.1 Mechanism of Action

LOKELMA (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. *In vitro*, sodium zirconium cyclosilicate is highly selective for potassium ions, even in the presence of other cations such as calcium and magnesium. Sodium zirconium cyclosilicate increases fecal potassium excretion through binding of potassium throughout the lumen of the gastrointestinal (GI) tract. Binding of potassium reduces the concentration of free potassium in the GI lumen, reduces potassium absorption, thereby lowering serum potassium levels.

9.2 Pharmacodynamics

Sodium zirconium cyclosilicate starts reducing serum potassium 1 hour after administration in patients with hyperkalemia. Normokalemia can be achieved typically within 24 to 48 hours of treatment at dosage of 10 g TID. Sodium zirconium cyclosilicate has no net effect on serum calcium or magnesium levels. Normokalemia is sustained in patients taking sodium zirconium cyclosilicate continuously. In patients not continuing treatment, potassium levels increase again. There is a close correlation between starting serum potassium levels and potassium lowering effect; patients with higher starting serum potassium levels have greater reductions in serum potassium.

There were no studies conducted to investigate the effect of food on the pharmacodynamics of sodium zirconium cyclosilicate.

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 fecal potassium excretion. No statistically significant changes in urinary sodium excretion were observed in this study.

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 serum bicarbonate concentrations 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.

9.3 Pharmacokinetics

Sodium zirconium cyclosilicate (ZS) is an inorganic, insoluble compound that is not subject to

enzymatic metabolism. No *in vivo* or *in vitro* studies have been performed to examine its effect on cytochrome P450 (CYP450) enzymes or transporter activity. In patients with hyperkalemia (Study ZS-004), whole blood and urine samples were assayed for zirconium concentrations after once daily administration of ZS 5 g to 15 g for 14 or 28 days, zirconium concentrations were below the lower limit of quantification. An *in vivo* mass balance study in rats showed that $\geq 97\%$ sodium zirconium cyclosilicate was recovered in the feces within 3 days with no evidence of systemic absorption.

10 STORAGE, STABILITY AND DISPOSAL

Store at 15 to 30°C. LOKELMA should be taken immediately after reconstitution.

Keep out of the reach and sight of children.

Any unused product or waste material should be disposed of in accordance with local requirements.

11 SPECIAL HANDLING INSTRUCTIONS

No special requirements.

PART II: SCIENTIFIC INFORMATION

12 PHARMACEUTICAL INFORMATION

Drug Substance

Common name: sodium zirconium cyclosilicate

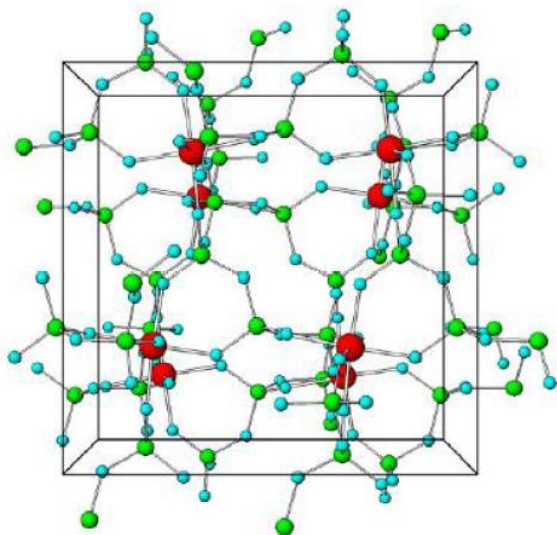
Chemical name: sodium zirconium silicate hydrate

Molecular formula and molecular mass:

$\text{Na}_{-1.5}\text{H}_{-0.5}\text{ZrSi}_3\text{O}_9 \cdot 2-3\text{H}_2\text{O}$

390.5–408.5 Daltons

Structural formula:



Unit cell structural representation (stick-and-ball) of main framework of microporous sodium zirconium cyclosilicate. Red= Zirconium, Green= Silicon, Blue= Oxygen atoms. Cations are not pictured.

Physicochemical properties: White to grey powder, completely insoluble and highly selective for potassium over divalent cations.

13 CLINICAL TRIALS

13.1 Trial Design and Study Demographics

Table 9 - Summary of patient demographics for clinical trials in hyperkalemia

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n) Treated / Completed	Mean age (Range)	Sex n (%)
ZS-002	Randomized, double-blind, placebo-controlled, dose escalating	ZS 0.3 g ZS 3 g ZS 10 g Placebo TID orally with meals for 48-96 hours	90 treated 12 / 12 24 / 24 24 / 24 30 / 30	71.1 years (42 – 96)	M: 52 (58%) F: 38 (42%)
ZS-003	Two phase Correction phase: randomized, double-blind, placebo-controlled	Correction phase			
		ZS 1.25 g ZS 2.5 g ZS 5 g ZS 10 g Placebo TID for 48 hours orally, with meals	753 treated 154 / 150 141 / 137 157 / 152 143 / 140 158 / 157	65.7 years (22 – 93)	M: 448 (59.5%) F: 305 (40.5%)
		Maintenance phase			

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n) Treated / Completed	Mean age (Range)	Sex n (%)
	Maintenance phase: randomized withdrawal for subjects who received ZS during correction phase	from Correction phase ZS subjects: ZS 1.25 g placebo ZS 2.5 g placebo ZS 5 g placebo ZS 10 g Placebo QD for 12 days from Correction phase placebo subjects: ZS 1.25 g ZS 2.5 g	447 ZS treated 49 / 48 41 / 38 54 / 52 46 / 43 65 / 59 68 / 66 63 / 61 61 / 58 96 ZS treated 46 / 44 50 / 49	65.5 years (22 – 93) 66.8 years (27 – 88)	M: 261 (58%) F: 186 (42%) M: 56 (58%) F: 40 (42%)
ZS-004	Correction phase: single ZS treatment group, open-label	Correction phase			
		ZS 10 g TID for 48 hours	258 / 251	64.0 years (22 – 89)	M: 149 (58%) F: 109 (42%)
	Maintenance phase: randomized, double-blind, placebo-controlled	Maintenance phase			
		ZS 5 g ZS 10 g ZS 15 g Placebo QD for 28 days Subjects with S-K 3.0-3.4 mmol/L to reduce dosing to QOD	237 treated 45 / 40 51 / 44 56 / 49 85 / 75	63.6 years (22 – 89)	M: 138 (58%) F: 99 (42%)

Study #	Trial design	Dosage, route of administration and duration	Study subjects (n) Treated / Completed	Mean age (Range)	Sex n (%)
ZS-004E	Extension of ZS-004, open-label, uncontrolled	Maintenance phase: starting dose: ZS 10 g QD, for up to 11 months Dose adjusted in 5 g increments to maximum 15 g QD or minimum 5 g QOD based on potassium level	123 / 79	64.0 years (22 – 85)	M: 71 (58%) F: 52 (42%)
ZS-005	Open-label, uncontrolled	Correction phase: ZS 10 g TID for 24, 48 or 72 hours Maintenance phase: starting dose ZS 5 g QD for up to 12 months. Dose adjusted in 5 g increments to maximum 15 g QD or minimum 5 g QOD based on potassium level	751 / 746 746 / 466	63.6 years (21 – 93)	M: 448 (60%) F: 303 (40%)
D9480C 00006	Randomized, double-blind, placebo-controlled 4-week dose adjustment period followed by 4-week evaluation period	Starting dose: ZS 5 g or Placebo QD on non-dialysis days After at least 1 LIDI, dose could be adjusted up or down in 5 g increments to a maximum of 15 g per non-dialysis day to maintain pre-dialysis S-K 4.0-5.0 mmol/L	ZS – 96/92 Placebo – 99/96	58.1 years (20 – 86)	M: 115 (59%) F: 81 (41%)

F: Female, M: Male; LIDI: long inter-dialytic interval; QD: once daily; QOD: every other day; S-K: serum potassium; TID: 3 times daily; ZS: sodium zirconium cyclosilicate

The potassium-lowering effects of LOKELMA have been demonstrated in two randomized, double-blind, placebo-controlled trials (ZS-003, ZS-004) in patients with hyperkalemia. The two studies tested the initial effect of LOKELMA to correct hyperkalemia during a 48-hour period and then the effect on maintenance of normokalemia (serum potassium levels between 3.5 and 5.0 mmol/L). The studies included patients (84% White, 12% Black) with chronic kidney disease (58%), heart failure (10%), diabetes mellitus (62%) and renin angiotensin aldosterone (RAAS) inhibitor therapy (68%). In addition, two open-label studies (ZS-004E, ZS-005) tested long-term safety of LOKELMA. The patients were instructed to continue their usual diet without any specified alterations or dietary restrictions. There is limited clinical trial experience of LOKELMA in patients with serum potassium concentrations greater than 6.5 mmol/L.

In addition, the efficacy and safety of LOKELMA were shown in a double-blind placebo-controlled trial of 196 chronic hemodialysis patients with hyperkalemia, who received doses of LOKELMA for 8 weeks. The study included participants (52% White, 34% Asian, 10% Black) who had been on dialysis for 7.9 years on average, primarily accessed through arteriovenous fistula (89%).

13.2 Study Results

In the studies, LOKELMA reduced serum potassium and maintained normal serum potassium levels regardless of age, sex, race, comorbid disease (chronic kidney disease (CKD), heart failure, diabetes mellitus) or concomitant use of RAAS inhibitors. Significant reduction in serum aldosterone levels and increased serum bicarbonate levels were observed in patients treated with LOKELMA compared to placebo.

ZS-003: Two-phase, randomized, double-blind, placebo-controlled study

During the correction phase, 753 patients with hyperkalemia (baseline potassium average 5.3 mmol/L, range from 5.0 to 6.5 mmol/L) were randomized 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 greater reductions in serum potassium at the 2.5 g, 5 g and 10 g doses compared to placebo (Table 10). 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 TID.

Table 10 - Correction phase: Percentage of normokalemic subjects after 48 hours of LOKELMA

	Placebo	LOKELMA dose (three times daily)		
		2.5 g	5 g	10 g
N	158	141	157	143
Baseline serum potassium (mmol/L)	5.3	5.4	5.3	5.3
Normokalemic at 48 hours (%)	48	68	78	86
p-value vs. placebo		< 0.001	< 0.001	< 0.001

Patients with higher starting potassium levels had a greater response to LOKELMA (Table 11). 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 CKD, heart failure, diabetes mellitus and those taking RAAS inhibitor therapy (angiotensin receptor blockers, angiotensin converting enzyme inhibitors, aldosterone antagonists).

Table 11 - Correction phase: Serum potassium change from baseline to 48 hours after start of dosing

Mean serum potassium change mmol/L (95% Confidence intervals) Sample size	Placebo	2.5 g TID	5 g TID	10 g TID
All Patients	-0.2 (-0.3, -0.2) n=158	-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	-0.4* (-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	-0.5 (-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	-0.6 (-0.7, -0.4) n=37	-0.9* (-1.0, -0.7) n=29	-1.1* (-1.3, -0.9) n=22

*= p-value <0.05Z

Patients achieving normokalemia at end of the correction phase were then re-randomized to receive once daily administration of either LOKELMA at the same dose level as for correction or placebo for 12 days. 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 (Table 12). Efficacy was consistent across pre-specified subgroups with heart failure, CKD, and diabetes mellitus, or in patients on RAAS inhibitors. At the end of the treatment period, when LOKELMA was no longer administered, serum potassium increased to near baseline levels.

Table 12 - Maintenance phase (12 days): Mean number of normokalemic days

Correction phase LOKELMA dose	Maintenance phase treatment (once daily)				
	Placebo		LOKELMA		P-value vs. placebo
	n	Days	n	Days	
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

ZS-004: Open-label, 48-hour correction phase, and randomized, double-blind, placebo-controlled 28-day maintenance study

In the correction phase of the study, 258 patients with hyperkalemia (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 normokalemia was 2.2 hours and 66% of patients were normokalemic at 24 hours and 88% at 48 hours. Responses were larger in patients with more severe hyperkalemia; 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 \geq 6.0 mmol/L, respectively.

Of the 258 patients, 237 patients (92%) who achieved normokalemia at end of the correction phase were randomized 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.

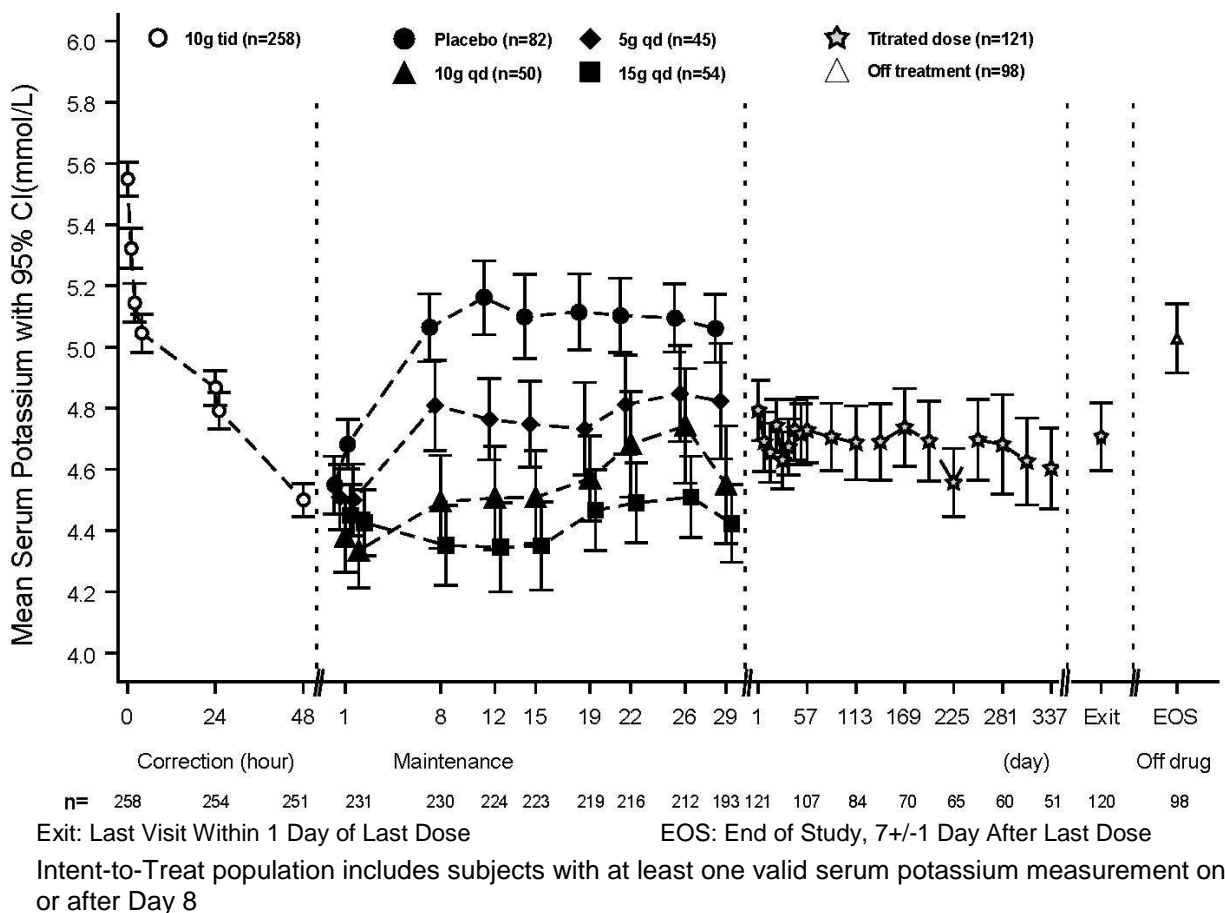
The mean serum potassium values from study days 8 to 29 of once daily treatment as the primary endpoint for the Maintenance Phase was 4.8, 4.5, and 4.4 mmol/L for the 5, 10, and 15 g LOKELMA groups, respectively, vs. 5.1 mmol/L in the placebo group, $p \leq 0.0001$ for all doses (Figure 1). The proportion of subjects with average serum potassium <5.1 mmol/L from Study Day 8 to 29 was statistically significantly higher at the 5 g, 10 g and 15 g once daily doses of LOKELMA (80%, 90%, and 94%, respectively), compared with placebo (46%). A greater proportion of patients remained normokalemic (71%, 76%, 85% at the 5 g, 10 g, 15 g once daily doses, respectively) in LOKELMA groups than the placebo group (48%).

ZS-004E: Open-label, uncontrolled, long-term (up to 11 months) extension study to ZS-004

One hundred and twenty-three patients who completed the ZS-004 28-day maintenance phase entered the 11-month open-label extension phase. During the study days 8 to 337, the proportion of subjects with mean serum potassium \leq 5.1 mmol/L was 88%. The mean serum potassium level was 4.66 mmol/L. The proportion of patients with mean serum potassium measurements between 3.5 and 5.0 mmol/L was 80% (range from 70.3% to 84.3%); below 3.5 mmol/L was less than 1%.

Figure 1 illustrates the mean serum potassium levels over the correction, maintenance phases of ZS-004, and extension phase of the study (ZS-004E).

Figure 1 – Mean serum potassium levels – ZS-004 and ZS-004E



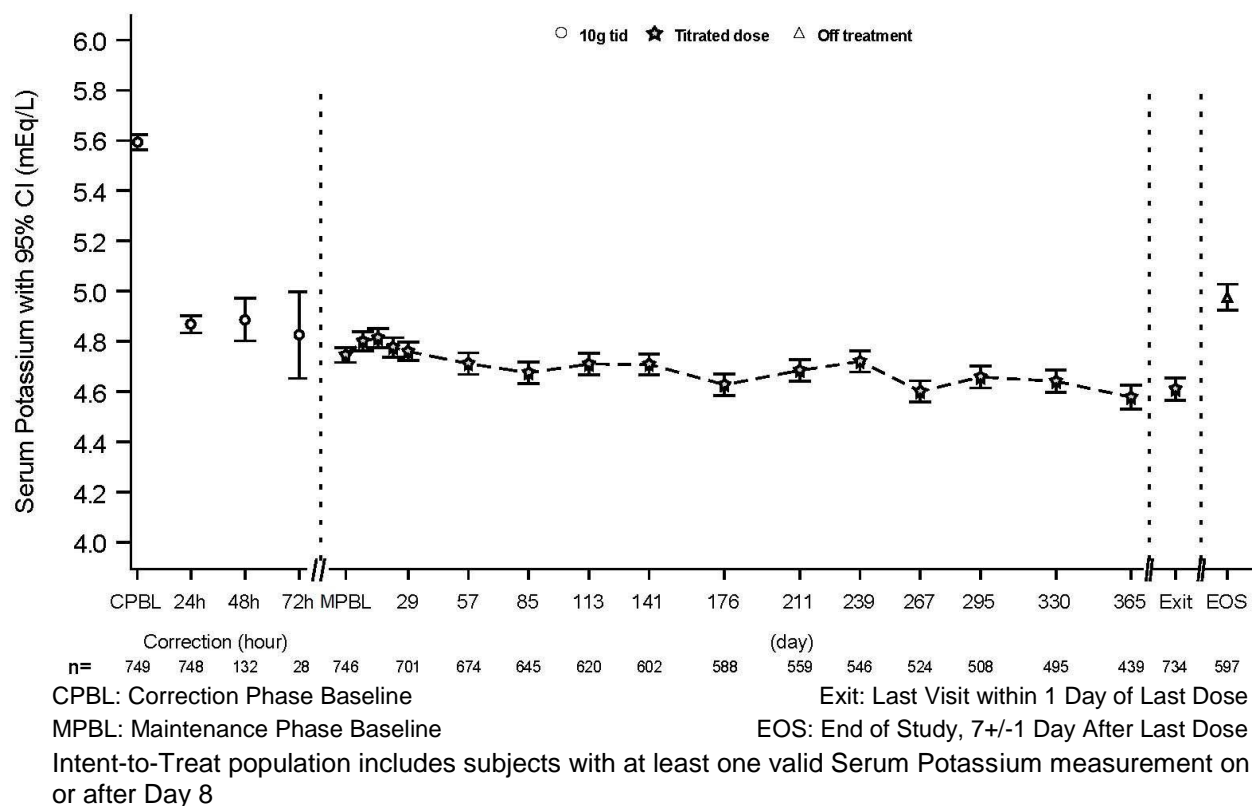
ZS-005: Open-label, uncontrolled, two-phase, long-term (up to 12 months) study

The effects of LOKELMA were assessed in this study in 751 subjects (83% White, 12% Black) with hyperkalemia (baseline average 5.6 mmol/L; range 4.3 to 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 normokalemia 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.

In the correction phase, normokalemia was achieved in 66%, 75% and 78% of patients at 24, 48 and 72 hours after the first dosing of LOKELMA 10 g TID, respectively. Responses were larger in patients with more severe hyperkalemia with mean 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 (Figure 2). One hundred and twenty six patients had a baseline serum potassium ≥ 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 correction phase.

During the maintenance phase (Days 8 to 365), 75.6% of patients maintained normokalemia. 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). Normokalemia was maintained while patients remained on drug and the mean serum potassium increased following discontinuation (Figure 2). Among those patients using RAAS inhibitors at baseline, 89.4% did not discontinue RAAS inhibitor therapy, 74.1% were able to maintain the same dose during the maintenance phase and among those not on RAAS inhibitors at baseline, 14% initiated RAAS inhibitor therapy.

Figure 2 - Mean serum potassium – 12-month open-label study with correction and maintenance phases



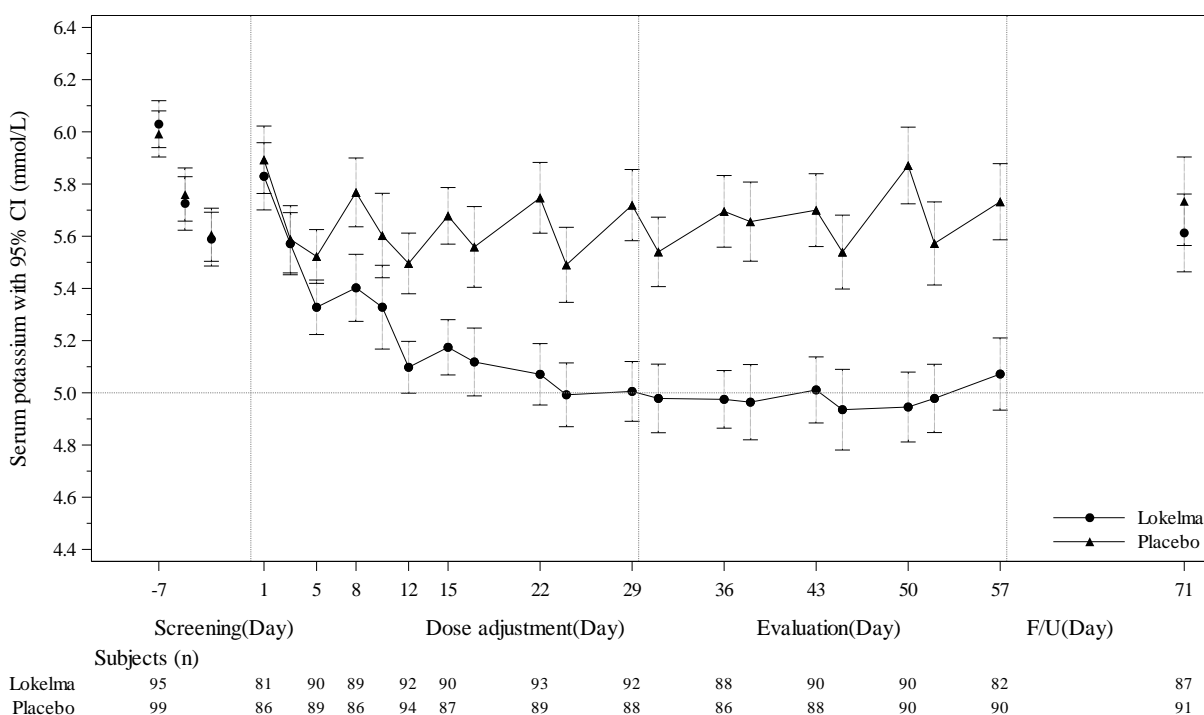
D9480C00006: Randomized, double-blind, placebo-controlled study in patients on chronic hemodialysis

In this study, 196 patients with end stage renal disease on stable dialysis for at least 3 months and persistent pre-dialysis hyperkalemia were randomized to receive LOKELMA 5 g or placebo once daily on non-dialysis days. At randomization, mean pre-dialysis 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. 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 post-LIDI measurements and who did not receive rescue therapy during the evaluation period, was 41% in the LOKELMA group, and 1% in the placebo group ($p < 0.001$). Mean pre-dialysis serum potassium levels during the study are presented in Figure 3.

At the end of treatment, the mean post-LIDI pre-dialysis serum potassium level was 5.1 mmol/L (range 3.6 – 7.3 mmol/L) in the LOKELMA group and 5.7 mmol/L (range 3.3 – 7.3 mmol/L) in the placebo group. There were no significant differences between the LOKELMA and placebo groups in interdialytic weight gain (IDWG), a marker of the sodium and fluid retention. 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.

14 NON-CLINICAL TOXICOLOGY

General Toxicology (single and repeat-dose studies):

Both rats and dogs tolerated chronic oral administration of sodium zirconium cyclosilicate at very high dose levels that resulted in excretion of light-colored feces due to the presence of excreted sodium zirconium cyclosilicate. Rats tolerated sodium zirconium cyclosilicate at up to the maximum feasible dose level of 2 g/kg/tid (6 g/kg/day) for up to 26 weeks, and dogs tolerated sodium zirconium cyclosilicate at 1 g/kg/day for up to 39 weeks. These dose levels are equivalent to human dose levels of approximately 58 g/day (rats) and 33 g/day (dogs) based on a 60 kg body weight, yielding margins of ~5- and 3-fold respectively.

There was no mortality associated with sodium zirconium cyclosilicate treatment. The only effects of sodium zirconium cyclosilicate administration in either species were related to its intended pharmacodynamic activity, which is to reduce potassium absorption from the GI tract. Renal tubular inflammation, lipid vacuolization, and reduced levels of aldosterone were observed when animals experienced treatment-related hypokalemia.

Carcinogenicity studies:

Carcinogenicity studies have not been conducted.

Genotoxicity:

No genotoxic potential was exhibited in the Ames assay and in a chromosomal aberration assay. Sodium zirconium cyclosilicate did not induce bone marrow micronuclei in Sprague Dawley rats following an oral dosing regime up to 6 g/kg/day (2 g/kg/tid) and produced no hyperplastic or pre-neoplastic findings in chronic toxicity studies. Together with the absence of genotoxic potential and the lack of systemic absorption, sodium zirconium cyclosilicate is considered unlikely to present a carcinogenic hazard to humans.

Reproductive and Developmental Toxicology:

Sodium zirconium cyclosilicate did not affect reproductive function in rats of either sex nor in female rabbits at doses up to 6 g/kg/day, which is equivalent to a human dose level of approximately 58 g/day (rats) or 116 g/day (rabbits) and provide safety margins of ~6- and 11-fold respectively. Sodium zirconium cyclosilicate also did not significantly affect maintenance of pregnancy or fetal development in either species. However, in rats dosed during the fertility and embryofetal development phases retarded or impaired fetal ossification was observed. There was evidence of reduced body weight gain in pups in the pre and postnatal study.

READ THIS FOR SAFE AND EFFECTIVE USE OF YOUR MEDICINE
PATIENT MEDICATION INFORMATION

LOKELMA
sodium zirconium cyclosilicate powder for oral suspension

Read this carefully before you start taking LOKELMA and each time you get a refill. This leaflet is a summary and will not tell you everything about this drug. Talk to your healthcare professional about your medical condition and treatment and ask if there is any new information about LOKELMA.

What is LOKELMA used for?

- To treat hyperkalemia in adults. Hyperkalemia means that there is a high level of potassium in the blood.

How does LOKELMA work?

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 binds to potassium. The two are then carried together out of the body in your stools. This lowers the amount of potassium in the body.

LOKELMA starts to lower your potassium within one hour of taking it. The amount of decrease depends on your starting potassium level. Most patients have normal levels within 24 to 48 hours of treatment.

What are the ingredients in LOKELMA?

Medicinal ingredient: sodium zirconium cyclosilicate

Non-medicinal ingredients: None

LOKELMA comes in the following dosage forms:

Powder for oral suspension in sachets of 5 g and 10 g

Each 5 g of sodium zirconium cyclosilicate contains about 400 mg of sodium.

Do not use LOKELMA if:

- you are hypersensitive or allergic to the ingredient sodium zirconium cyclosilicate.

To help avoid side effects and ensure proper use, talk to your healthcare professional before you take LOKELMA. Talk about any health conditions or problems you may have, including if you:

- are pregnant or planning to become pregnant.
- have any existing heart rhythm problems.
- are reducing how much salt (sodium) you eat. LOKELMA contains about 400 mg of sodium per 5 g.
- sometimes have excess water in your body because you have heart failure or kidney disease.
- have severe constipation, a bowel obstruction or a bowel motility disorder.

Other warnings you should know about:

- Do not give this medicine to children under 18 years of age. This is because the effects of LOKELMA in children are not known.
- Your doctor may monitor your potassium levels when required. Your doctor may also order other blood tests during your treatment with LOKELMA.

Tell your healthcare professional about all the medicines you take, including any drugs, vitamins, minerals, natural supplements or alternative medicines.

If you take any of the following medicines, you may need to take LOKELMA at least 2 hours before or 2 hours after taking any of them:

- atorvastatin (drug to lower cholesterol)
- ketoconazole, itraconazole, posaconazole (drugs to treat fungal infections)
- atazanavir, nelfinavir, indinavir, ritonavir, saquinavir, raltegravir (drugs to prevent and treat HIV/AIDS)
- erlotinib, dasatinib, nilotinib (drugs to treat certain types of cancer)
- dabigatran (drug to thin the blood)

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.
- Try to take LOKELMA at the same time each day.
- You can take this medicine with or without food.
- Before opening the sachets, hold the top corner of the sachet and shake it to move the powder to the bottom.
- Open the sachet and pour the powder into a glass with approximately 45 mL (3 tablespoons) of water.
- Stir well and drink the tasteless liquid right away before the powder settles.
- The powder does not dissolve and the liquid will appear cloudy.
- Add a little more water to the glass. Swirl and drink it to take all the medicine.

Monitoring

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

- 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 becomes too low.

Usual dose:Correction 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.

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 (5 g every other day). Do not take a maintenance dose of more than 10 g once a day.

Dosing **only** for patients on hemodialysis 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) or that you need to stop for a few days.
- If your doctor recommends a 15 g dose, you will need to use a 5 g sachet and a 10 g sachet to make a 15 g dose. If you are taking 15 g, you still need to use approximately 45 mL (3 tablespoons) of water.
- Do not take more than 15 g once a day.

Do not reduce the dose of this medicine or stop taking it without talking to the doctor. This is because your blood potassium levels may rise again.

Overdose:

If you think you have taken too much LOKELMA, contact your healthcare professional, hospital emergency department or regional poison control centre immediately, even if there are no symptoms.

Missed Dose:

- 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.

What are possible side effects from using LOKELMA?

These are not all the possible side effects you may feel when taking LOKELMA. If you experience any side effects not listed here, contact your healthcare professional.

You may experience:

Common (more than 1% of people but less than 10% of people):

- **Hypokalemia** (low level of potassium in the blood): feel tired, or have muscle weakness or cramps.
- **Hypomagnesemia** (low level of magnesium in the blood): abnormal eye movements, fatigue, muscle spasms or cramps, muscle weakness, numbness.
- **Muscle spasms.**
- **Gastrointestinal disorders:** diarrhea, nausea

Uncommon (less than 1% of people):

- **Hypocalcemia** (low calcium levels in the blood): confusion or memory loss, muscle spasms, numbness and tingling in the hands, feet and face, muscle cramps, weak and brittle nails.
- **Gastroenteritis** (inflammation of the stomach and intestines) **or other gastrointestinal disorders:** abdominal pain, vomiting.

Serious side effects and what to do about them			
Symptom / effect	Talk to your healthcare professional		Stop taking drug and get immediate medical help
	Only if severe	In all cases	
COMMON Constipation	✓		
Edema: a build up of fluid in the tissues. Swelling anywhere in the body, usually in the ankles and feet.		✓	
UNCOMMON Prolongation of QT interval (a heart rhythm condition): irregular heartbeat, fainting, loss of consciousness, seizures.		✓	
Congestive Heart Failure (heart does not pump blood as well as it should): shortness of breath, fatigue and weakness, swelling in ankles, legs and feet, cough, fluid retention, lack of appetite, nausea, rapid or irregular heartbeat, reduced ability to exercise.		✓	

If you have a troublesome symptom or side effect that is not listed here or becomes bad enough to interfere with your daily activities, talk to your healthcare professional.

<p>Reporting Side Effects</p> <p>You can report any suspected side effects associated with the use of health products to Health Canada by:</p> <ul style="list-style-type: none"> • Visiting the Web page on Adverse Reaction Reporting (https://www.canada.ca/en/health-canada/services/drugs-health-products/medeffect-canada/adverse-reaction-reporting.html) for information on how to report online, by mail or by fax; or • Calling toll-free at 1-866-234-2345. <p><i>NOTE: Contact your health professional if you need information about how to manage your side effects. The Canada Vigilance Program does not provide medical advice.</i></p>
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Storage:

- Store LOKELMA at 15-30°C.
- Keep out of reach and sight of children.
- Do not use this medicine after the expiry date stated on the carton and the sachet after 'EXP'. The expiry date refers to the last day of that month.
- 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.

If you want more information about LOKELMA:

- Talk to your healthcare professional
- Find the full product monograph that is prepared for healthcare professionals and includes this Patient Medication Information by visiting the Health Canada website (<https://health-products.canada.ca/dpd-bdpp/index-eng.jsp>); the manufacturer's website www.astrazeneca.ca, or by calling 1-800-668-6000.
- This Patient Medication Information is current at the time of printing. The most up-to-date version can be found at www.astrazeneca.ca

This leaflet was prepared by AstraZeneca Canada Inc., Mississauga, Ontario L4Y 1M4

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