

Date: 21 May 2021

Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Lokelma

International non-proprietary name: natrii zirconii cyclosilicas

Pharmaceutical form: Powder for oral suspension

Dosage strength(s): 10 g and 5 g

Route(s) of administration: oral

Marketing Authorisation Holder: AstraZeneca AG

Marketing Authorisation No.: 67851

Decision and Decision date: approved on 16 April 2021

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
Cmax	Maximum observed plasma/serum concentration of drug
CYP	Cytochrome P450
ERA	Environmental Risk Assessment
GLP	Good Laboratory Practice
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PSP	Pediatric Study Plan (US-FDA)
RMP	Risk Management Plan
SwissPAR	Swiss Public Assessment Report
TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status

The applicant requested the status of a new active entity for the active substance sodium zirconium cyclosilicate of the medicinal product mentioned above.

2.2 Indication and Dosage

2.2.1 Requested Indication

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

2.2.2 Approved Indication

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

2.2.3 Requested Dosage

Adults, including the elderly

Correction phase

The recommended starting dose of Lokelma is 10 g for patients with a serum potassium level of > 5.0 mmol/l, administered three times a day orally as a suspension in water. When normokalaemia (normal potassium level between 3.5 and 5.0 mmol/l) is achieved, the maintenance regimen should be followed.

Typically, normokalaemia (normal potassium level between 3.5 and 5.0 mmol/l) is achieved within 24 to 48 hours. If the serum potassium level is still > 5.0 mmol/l after 48 hours of treatment, the same regimen can be continued for an additional 24 hours before the maintenance regimen is started. If normokalaemia is not achieved after 3 days of treatment, other treatment approaches should be considered.

Maintenance phase

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.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	31 January 2020
Formal control completed	11 February 2020
List of Questions (LoQ)	4 June 2020
Answers to LoQ	31 August 2020
Predecision	27 November 2020
Answers to Predecision	26 January 2021
Final Decision	16 April 2021
Decision	approval

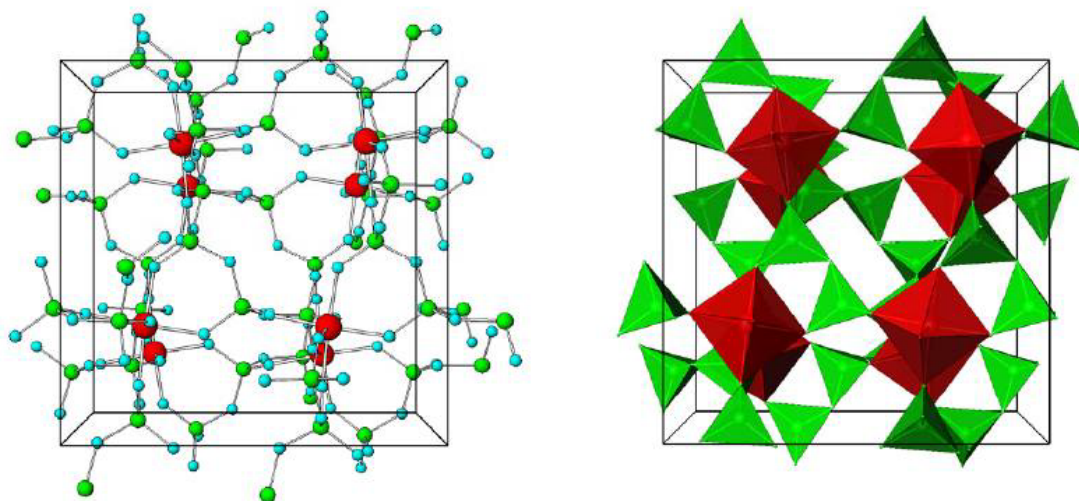
3 Medical Context

Hyperkalaemia is the presence of an abnormally high concentration of potassium in the blood. The cause is often multifactorial, but most commonly insufficient elimination of potassium is involved. Symptoms of hyperkalaemia may include malaise, muscle weakness or signs of cardiac arrhythmias, with the latter being of the greatest concern.

4 Quality Aspects

4.1 Drug Substance

INN: Sodium zirconium cyclosilicate
 Chemical name: Sodium zirconium silicate hydrate
 Molecular formula: $\text{Na}_{\sim 1.5}\text{H}_{\sim 0.5}\text{ZrSi}_3\text{O}_9 \cdot 2\text{--}3 \text{H}_2\text{O}$
 Molecular mass: 390.5 to 408.5
 Molecular structure:



Unit cell structural representation, stick-and-ball (left) and polyhedral (right) of main framework of microporous sodium zirconium cyclosilicate. Red: zirconium, Green: silicon, Blue: oxygen atoms. Cations are not pictured.

Physico-chemical properties:

Sodium zirconium cyclosilicate is a white to grey crystalline powder and is insoluble in water or in organic solvents. It is neither hygroscopic nor sensitive to light. The possibility that other crystalline phases are formed exists. The crystalline form of the drug substance is controlled by the parameters of the manufacturing process and release specifications. No change in the crystalline form was observed in the forced degradation studies.

Synthesis:

The drug substance is manufactured using a hydrothermal synthesis process. The manufacturing process is described in acceptable detail (materials, quantities, temperatures, pressures and typical yields).

Specification:

The drug substance specification includes tests for appearance (visual), identity (FT-IR, XRPD), potassium exchange capacity (ion chromatography), crystalline impurities (XRPD), zirconium content (WD-XRF), silicon content (WD-XRF), sodium content (WD-XRF), hafnium content (WD-XRF), pH (potentiometry), moisture content (TGA), particle size (laser diffraction) and elemental impurities (ICP-

MS or WD-XRF). The specifications are in line with the recommendations of the relevant ICH guidelines and are considered appropriate in order to ensure a consistent quality of the drug substance. The analytical methods used have been adequately described and non-compendial methods have been appropriately validated in accordance with ICH guideline Q2(R1). Batch analysis data on production scale batches are provided. The results are within the specifications and consistent from batch to batch.

Stability:

The stability studies have been conducted in accordance with the ICH guidelines for stability testing. Based on the data provided, an appropriate re-test period and storage conditions have been set. Photostability testing following the ICH guideline Q1B was performed showing that the drug substance is not photosensitive.

4.2 Drug Product

Description and composition:

The finished product is presented as a powder for oral suspension containing 5 g or 10 g of sodium zirconium cyclosilicate as active substance. The finished product contains no excipients. Powder for oral suspension was selected as the optimal dosage form based on posology requirements. The powder is readily suspended in water with stirring.

Pharmaceutical development:

No formulation development was required for the drug product, as the finished product is the neat active substance in a sachet presentation.

Manufacture:

The manufacturing process consists of two main steps: filling and sealing of the pouches containing the drug substance. Satisfactory validation of the manufacturing process was performed.

Specification:

For the control of the finished product, adequate tests and acceptance criteria for release and at shelf-life are established. The specifications include relevant physicochemical characteristics, identification of the drug substance as well as an in-vitro potassium exchange capacity test. All the analytical procedures are adequately described and non-compendial methods are validated according to the current requirements of ICH Q2(R1). Batch analysis data of several batches were provided. All batch release data comply with the drug product specifications.

Container Closure System:

Satisfactory information on the proposed container closure systems has been provided.

Stability:

Appropriate stability data have been generated in the packaging materials for commercial use and following the relevant international guidelines. Based on these studies, an appropriate shelf-life was established. The storage recommendation is "Do not store above 30°C".

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

5 Nonclinical Aspects

Regarding the marketing authorisation application of Lokelma, Swissmedic Preclinical Review conducted an abridged evaluation, which was based on the CHMP assessment report (25.01.2018; EMA/CHMP/24821/2018-Rev. 1) provided by the applicant.

Overall, the submitted non-clinical documentation is considered appropriate to support the approval of Lokelma in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. There were no particular safety issues identified in the nonclinical studies that would be of concern for human use. The safety margins are considered reasonable. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

6 Clinical and Clinical Pharmacology Aspects

The evaluation of the clinical and clinical pharmacology data of this application has been carried out in reliance on previous regulatory decisions by EMA and FDA. The available assessment reports and corresponding product information texts from these authorities were used as a basis for the clinical and clinical pharmacology evaluation.

For further details concerning clinical pharmacology, dosing recommendations, efficacy and safety, see section 8.1 of this report.

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.

The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

8 Appendix**8.1 Approved Information for Healthcare Professionals**

Please be aware that the following version of the information for healthcare professionals relating to Lokelma was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:

The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

▼ 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 new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

LOKELMA®

Composition

Active substances

Sodium zirconium cyclosilicate

Excipients

N.A.

Pharmaceutical form and active substance quantity per unit

Powder for oral suspension.

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

LOKELMA 5 g: Each sachets contains 5 g sodium zirconium cyclosilicate (contains approximately 400 mg sodium)

LOKELMA 10 g: Each sachets contains 10 g sodium zirconium cyclosilicate (contains approximately 800 mg sodium).

Indications/Uses

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

Dosage/Administration

LOKELMA should not be used as an emergency medication in life-threatening hyperkalaemia.

Initiation of treatment

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.

Maintenance therapy

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.¹

Usual dosage

Adults

Please see "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.

Special dosage instructions

Treatment of 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 interdialytic 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. To maintain normokalaemia it is recommended to monitor serum potassium regularly (e.g. monthly).

Patients with impaired hepatic function

No dose adjustment required for patients with hepatic impairment.

Patients with impaired renal function

No dose adjustment required for patients with renal impairment.

Elderly patients

Dose adjustment is not required in the elderly.

Children and adolescents

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

Delayed administration

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

Mode of administration

For oral use.

The entire contents of the sachet should be placed in a drinking glass with about 45 ml of water and should be stirred well. The powder does not dissolve. The tasteless liquid should be drunk as long as it is still turbid and the powder is in suspension. When the powder settles, stir again. Ensure that the entire contents are consumed.

LOKELMA can be taken independently of meals.

Contraindications

Known hypersensitivity to the active ingredient.

Warnings and precautions

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

This medicine contains about 400 mg (LOKELMA 5 g) or 800 mg (LOKELMA 10 g) sodium per sachet, corresponding to 20% or 40% of the maximum daily sodium intake recommended by the WHO. LOKELMA is considered to be rich in sodium. This should be considered especially in patients with a low sodium diet.

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.

Interactions

Pharmacokinetic interactions

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.

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

In vivo data

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. No dose adjustments or separation of the time of dosing are required for these drugs (see table 1).

Table 1: Interactions between LOKELMA and other medicinal products

Active Substance (dosage regimen)	Effects on drug concentration GMR% (90%CI)	Recommendation on concomitant use
Atorvastatin (10 mg single dose) LOKELMA (10 g single dose)	Atorvastatin AUC: 103.99 (95.04–113.78) C _{max} : 168.54 (144.07–197.17) (Transient increase of gastric pH)	No dose adjustment or dose separation recommended
Furosemide (20 mg single dose) LOKELMA (10 g single dose)	Furosemide AUC: 106.13 (98.36–114.51) C _{max} : 166.15 (128.28–215.19) (Transient increase of gastric pH)	No dose adjustment or dose separation recommended
Dabigatran (75 mg single dose) LOKELMA (10g single dose)	Dabigatran AUC: 59.08 (39.59–88.15) C _{max} : 57.41 (40.30–81.78) (Transient increase of gastric pH)	No dose adjustment or dose separation recommended

Pharmacodynamic interactions

N.A.

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.

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 (not licenced in Switzerland), Indinavir (not licenced in Switzerland), Ritonavir, Saquinavir, Raltegravir, Ledipasvir, Rilpivirine
Tyrosine kinase inhibitors	Erlotinib, Dasatinib, Nilotinib

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.

Pregnancy, lactation

Pregnancy

So far there is no experience with the use of sodium zirconium cyclosilicate in pregnant women. Animal studies have shown no evidence of reproductive toxicity (see "Preclinical data"). For reasons of precaution, the use of LOKELMA should be avoided during pregnancy. Lactation

Fertilität

It is not known whether sodium zirconium cyclosilicate passes into breast milk in humans or animals. Due to its physicochemical properties, sodium zirconium cyclosilicate is not systemically absorbed. Therefore no excretion into breast milk and no exposure of the breastfed newborn/infant are anticipated. In deciding whether to discontinue breastfeeding or to discontinue sodium zirconium cyclosilicate therapy, the benefit of breastfeeding for the child must be weighed against the benefit of therapy for the woman.

Effects on ability to drive and use machines

No studies on the effect on human fertility have been performed.

Undesirable effects

Summary of the safety profile

The most commonly reported adverse reactions were hypokalaemia (4.1%) and oedema related events (5.7%).

Clinical trials

The safety of LOKELMA was evaluated in clinical trials for the reduction of hyperkalaemia involving over 1,750 patients with 507 patients exposed for one year.

List of adverse effects

The adverse effects listed below are classified by frequency and system organ classes (MedDRA). The frequency information is based on the following categories: 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).

Metabolism and nutrition disorders

Common: hypokalaemia

General disorders and administration site conditions

Common: Oedema related events includes fluid overload (fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, oedema peripheral, peripheral swelling, which only occurred in the maintenance phase as adverse reaction).

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

The most commonly reported adverse reaction was oedema related events which were reported by 5.7% LOKELMA patients (1.7% of patients to placebo and 2.7%, 5.2% and 14.3% of patients randomised to LOKELMA 5 g, 10 g, or 15 g once daily up to one month, respectively). 53 % were managed with 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 suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Signs and symptoms

Overdose with LOKELMA could lead to hypokalaemia.

Treatment

Serum potassium should be checked and potassium supplemented as needed.

Properties/Effects

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. 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.

Pharmacodynamics

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, dosedependent 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

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%). 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. The study included patients with chronic kidney disease, heart failure, diabetes mellitus and those on RAAS inhibitor therapy.

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 3*). 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.

Table 3 *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 Stunden, %	48	51	68	78	86
p-value vs. placebo		NS	< 0,001	< 0,001	< 0,001

NS: not significant

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. 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. At the end of the treatment period, when LOKELMA was no longer administered, potassium increased to near baseline levels.

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 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 double-blind randomised withdrawal phase).

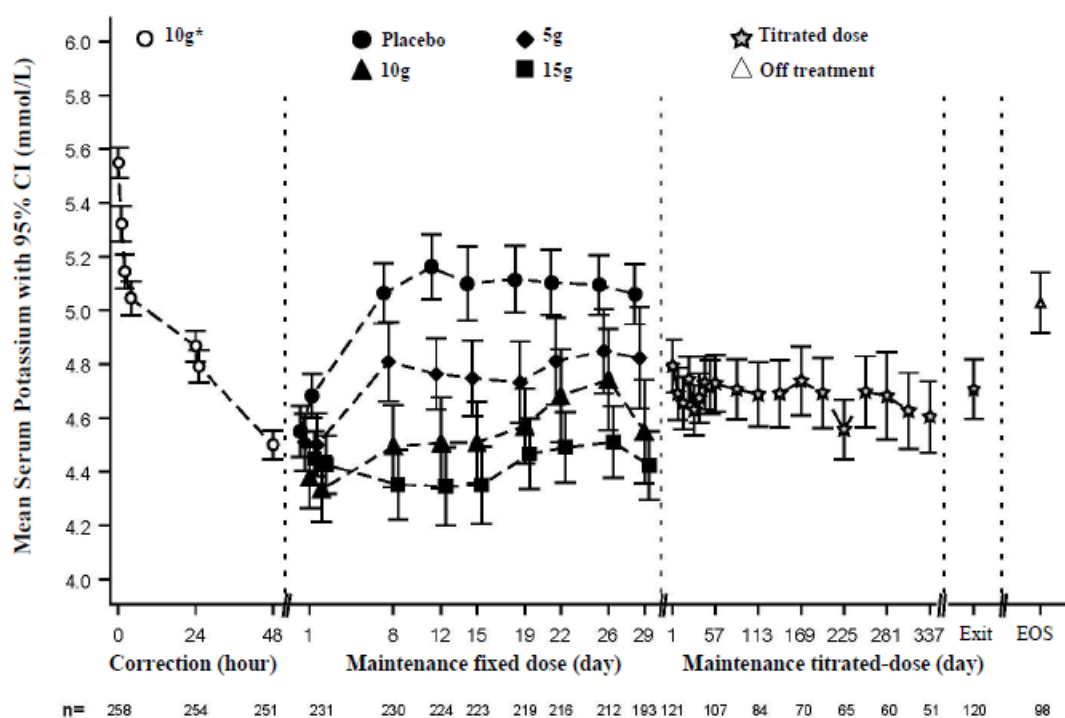
The proportion of subjects with average serum potassium < 5.1 mmol/L from Study Day 8 to 29 (three-week period) was greater at the 5 g, 10 g and 15 g once daily doses of LOKELMA (80%, 90% and 94%, respectively), compared with placebo (46%). There was a mean decrease in serum potassium of 0.77 mmol/L,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

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)).

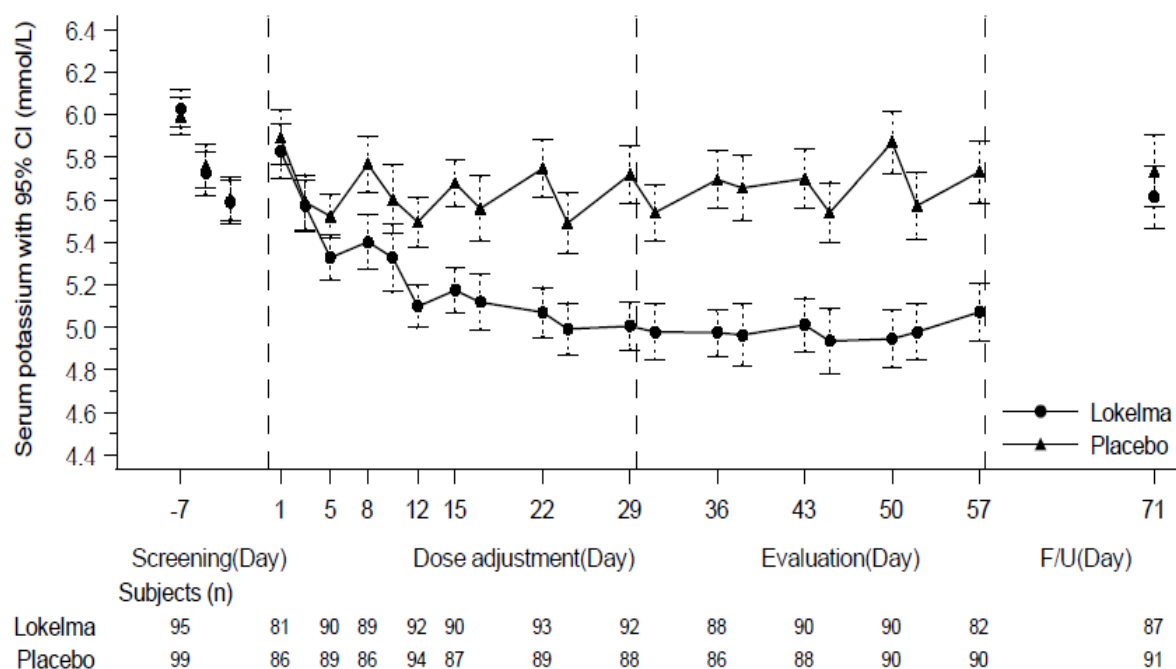
A randomised, double-blind, placebo-controlled study in patients on chronic haemodialysis

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 2).

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 2: 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.

Long-term data

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 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

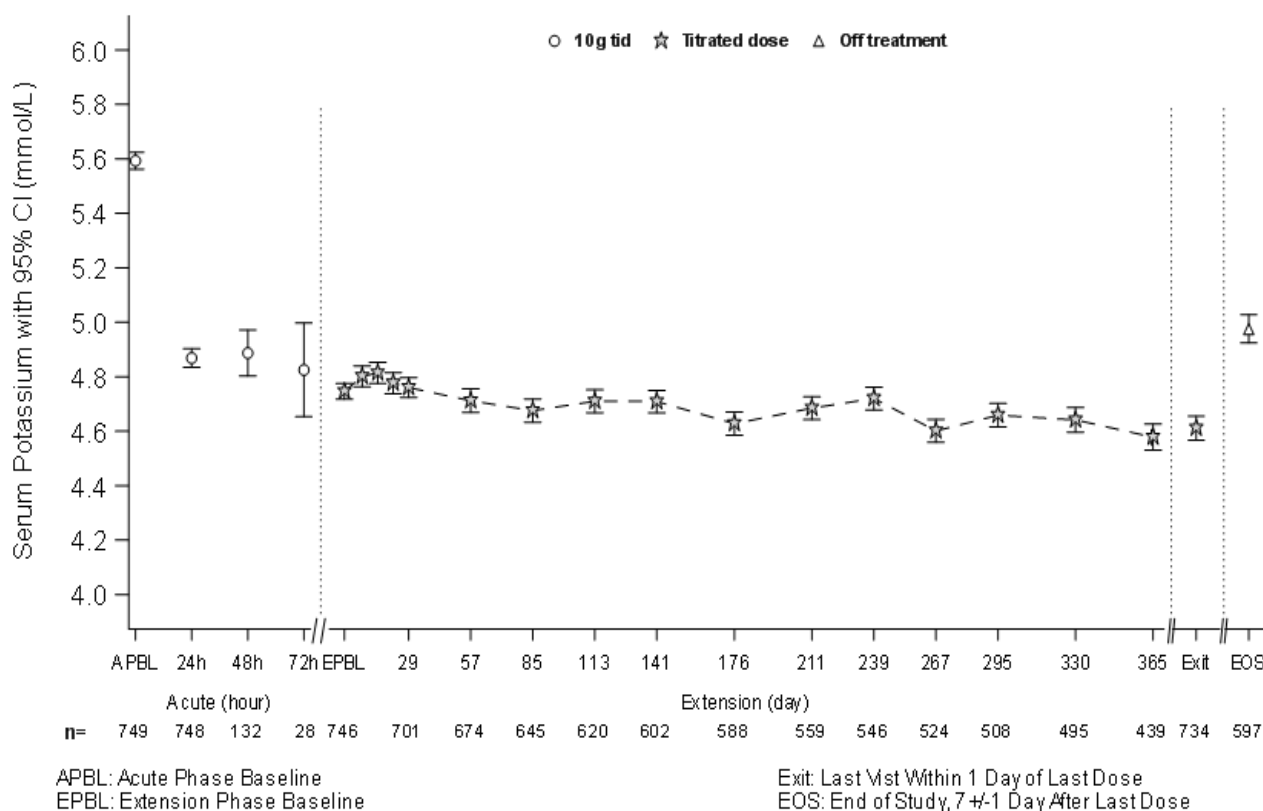
ITT-Population

<i>correction phase (CP)</i>	LOKELMA 10 g three times daily (N=749)					
	Serum potassium 3,5 bis 5,0 mmol/L, inclusive			Serum potassium 3,5 bis 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 the 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 3 illustrates the mean serum potassium over the correction and maintenance phases of the study.



Pharmacokinetics

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.

Distribution

N.A.

Metabolism

N.A.

Elimination

LOKELMA is eliminated via the faeces.

Preclinical 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

Long term carcinogenicity studies with sodium zirconium cyclosilicate have not been conducted.

Other information

Incompatibilities

N.A.

Shelf life

Do not use this medicine after the expiry date "EXP" stated on the container.

Special precautions for storage

Do not store above 30°C.

Keep out of the reach of children.

Authorisation number

67851 (Swissmedic)

Packs

LOKELMA 5 g: Packs of 30 and 90 sachets. (B)

LOKELMA 10 g: Pack of 30 and 90 sachets. (B)

Marketing authorisation holder

AstraZeneca AG, 6340 Baar

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November 2020
