Summary Report of Benefit-Risk Assessment

LOKELMA POWDER FOR ORAL SUSPENSION 5G/10G

NEW DRUG APPLICATION

Active Ingredient(s)	Sodium zirconium cyclosilicate
Product Registrant	AstraZeneca Singapore Pte Ltd
Product Registration Number	SIN15961P, SIN15962P
Application Route	Abridged evaluation
Date of Approval	22 June 2020

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A INTRODUCTION

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

The active substance, sodium zirconium cyclosilicate (SZC) is a non-absorbed, non-polymer inorganic cation-exchange crystalline compound highly selective for monovalent cations, specifically potassium and ammonium ions. It remains highly selective in the presence of other multivalent cations such as calcium and magnesium. It acts locally within the gastrointestinal tract by specifically binding potassium and exchanging it for hydrogen and sodium, thus lowering serum potassium concentrations.

Lokelma is available as powder for oral suspension containing 5 g and 10 g of SZC. No other ingredients are contained in the drug product.

B ASSESSMENT OF PRODUCT QUALITY

The drug substance, sodium zirconium cyclosilicate, is manufactured at AstraZeneca Pharmaceuticals LP, Coppell (Texas), United States. The drug products, Lokelma for Oral Suspension 5g and 10g are manufactured & packaged at Sharp Corporation, United States and AndersonBrecon Incorporated, United States.

Drug substance:
Adequate controls have been presented for the starting materials, intermediates and reagents. The in-process control tests and acceptance criteria applied during the manufacturing of the drug substance are considered appropriate.

The characterisation of the drug substance and its impurities are in accordance with ICH guidelines. Potential and actual impurities are adequately controlled.

The drug substance specifications are established in accordance with ICH Q6A and the impurity limits are considered appropriately qualified. The analytical methods used are adequately described and non-compendial methods are appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing was presented.

The stability data were adequate to support the approved storage condition and re-test period. The packaging is Low-density Polyethylene (LDPE) bag and linear low-density polyethylene (LLDPE) bag. The drug substance is approved for storage at or below 30ºC with a re-test period of 36 months.

Drug product:
The drug product is manufactured by direct filling of the neat drug substance powder into an aluminium sachet, followed by sealing of the sachet.

All manufacturing sites involved are compliant with Good Manufacturing Practice (GMP). Proper development and validation studies were conducted. It has been demonstrated that the manufacturing process is reproducible and consistent. Adequate in-process controls are in place.

The specifications are established in accordance with ICH Q6A and impurity limits are considered adequately qualified. The analytical methods used are adequately described and non-compendial methods were appropriately validated in accordance with ICH guidelines. Information on the reference standards used for identity, assay and impurities testing is presented.

The stability data submitted were adequate to support the approved shelf-life of 36 months when stored at or below 30ºC. The container closure system is a high barrier aluminium sachet made of a 3-layer or 5-layer material laminate.

C ASSESSMENT OF CLINICAL EFFICACY

The clinical efficacy of SZC for the treatment of hyperkalaemia was based primarily on data from two pivotal phase III studies (ZS-003 and ZS-004), two supportive phase III long-term studies (ZS-004E and ZS-005) and one dose ranging phase II study (ZS-002). The four Phase III studies investigated the efficacy of SZC in the treatment of hyperkalaemia in both the correction and maintenance phases.

Study ZS-002 was a phase II, multicentre, prospective, randomised, placebo-controlled, double-blind study conducted in subjects with mild hyperkalaemia having chronic kidney disease (CKD) and moderate kidney dysfunction (N=90). Subjects were randomised to receive 0.3 g, 3 g or 10 g of SZC or placebo three times daily (TID) with meals for 48 hours and the primary efficacy endpoint was the exponential rate of change in serum potassium (S-K) from baseline to 48 hours of treatment. The results showed statistically significant dose-dependent decreases in S-K from baseline to 48 hours compared to placebo at the 10 g TID dose (maximal mean reduction = 0.92 mmol/L, $p < 0.0001$) and the 3 g TID dose (maximal mean reduction = 0.43 mmol/L, $p = 0.048$), but not for the 0.3 g TID regimen (mean maximal reduction = 0.39 mmol/L, $p = 0.4198$).

Study ZS-003 was a phase III, multicentre, two-phase, multi-dose, prospective, randomised, double-blind, placebo-controlled study investigating the safety and efficacy of SZC in subjects with mild to moderate hyperkalaemia. In the Correction Phase, patients were randomised in a 1:1:1:1:1 ratio to receive one of four doses of SZC (1.25 g, 2.5 g, 5 g, and 10 g) or placebo TID for 48 hours. Subjects who completed and achieved normokalaemia (S-K: 3.5-5.0 mmol/L) at the end of the Correction Phase were entered into the 12 days Maintenance Phase. Subjects who received SZC in the Correction Phase were then randomised to either continue their Correction Phase dose or switch to placebo (randomised withdrawal) administered once daily (QD) for 12 days, whereas subjects who received placebo in the Correction Phase were randomised to either the 1.25 g QD or 2.5 QD regimen.

The statistical analysis of this study was conducted according to two approaches (US and EU). The primary efficacy endpoint in the Correction Phase was the same as that in Study ZS-002 in the US analysis, while in the EU analysis, it was the percentage of subjects achieving normokalaemia after 48 hours of therapy. For the Maintenance Phase, the primary efficacy endpoint was the exponential rate of change in S-K over 12 days in the US analysis and the number of normokalaemic days in the EU analysis. Key secondary endpoints included the number of normokalaemic days, time to normalisation in S-K values (defined as S-K values between 3.5 and 5.0 mmol/L, inclusive), time to a decrease in S-K values of 0.5 mmol/L and, mean change (absolute and percent) from baseline in S-K values and proportions of normokalaemic subjects.

A total of 754 patients were randomised to placebo and the four respective treatment arms in the Correction phase (placebo: 158; SZC 1.25 g TID: 154; SZC 2.5 g TID: 141; SZC 5 g TID: 158; SZC 10 g TID: 143). The patient demographics and baseline characteristics were well balanced between the treatment arms. The mean age was about 65 years and the majority of subjects in each of the treatment groups were male (range: 53.9% to 64.5%). The probable cause of hyperkalaemia was chronic kidney disease (CKD) (71 to 80%). Other causes of elevated S-K included use of renin-angiotensin-aldosterone system (RAAS) inhibitors (63.9 to 83.3%) and diabetes mellitus (56.6 to 60.8%).

In the Correction Phase, the primary endpoint was met and SZC treatment was effective in reducing S-K in hyperkalaemic patients after 48 hours in both the US and EU analyses. Statistically significant dose-dependent exponential decreases in S-K from baseline to 48 hours compared to placebo were observed at 10 g TID, 5 g TID and 2.5 g TID (p=0.0009). SZC at the 10 g TID, 5 g TID and 2.5 g TID dosages resulted in maximal mean reductions of -0.73 mmol/L, -0.54 mmol/L and -0.46 mmol/L, respectively, at 48 hours. Normal S-K values were achieved at 48 hours for 86.4%, 77.6%, 67.9%, 51.3% and 47.8% of subjects in the 10 g TID, 5 g TID, 2.5 g TID, 1.25 g TID and placebo groups, respectively. Only the lowest dose of 1.25 g TID did not reach statistical significance in both analyses. The primary efficacy results were consistent in various sensitivity analyses based on different subgroups, demonstrating robustness of the data.

In the 12-day Maintenance Phase, the 10 g QD and 5 g QD regimens resulted in a statistically significantly greater exponential decrease in S-K (p<0.0001 and p=0.0083, respectively) and longer normokalaemic duration compared to treatment withdrawal (10.2 days vs 8.2 days and 9.0 days vs 6.0 days, respectively). The 2.5 g QD regimen produced a significantly longer normokalaemic duration than treatment withdrawal by around 2 days but the difference in terms of exponential decrease in S-K was not statistically significant (p=0.8396). On the other hand, the 1.25 QD regimen was not significantly different to treatment withdrawal in maintaining normokalaemia (0.4 days) or in exponentially decreasing S-K (p=0.4252). When comparing the mean change in S-K between maintenance dosing and treatment withdrawal over the 12-day maintenance phase, a statistically significant difference was only seen in the 10 g dose group (0.06 mmol/L versus 0.58 mmol/L, respectively, p<0.001). The benefit of SZC over placebo was similarly demonstrated in various subgroups and secondary efficacy analyses.

Summary of Key Efficacy Results (ZS-003)

	Correction Phase Dose				
	Placebo	**1.25 g**	**2.5 g**	**5 g**	**10 g**
Correction Phase (TID dosing)					
Exponential decrease in S-K at 48 hours					
p-value vs placebo	-	0.5037	0.0009*	<0.0001*	<0.0001*
Normokalaemic subjects at 48 hours					
n/N (%)	75/157 (47.8)	77/150 (51.3)	93/137 (67.9)*	118/152 (77.6)*	121/140 (86.4)*
p-value vs placebo	-	0.0972	0.0001*	0.0001*	0.0001*
12 days Maintenance Phase (QD dosing)					
Exponential decrease in S-K relative to maintenance phase baseline					
p-value vs placebo	-	0.4252	0.8396	0.0083*	<0.0001*
Total no. of normokalaemic days over 12 days vs placebo (randomised withdrawal)					
SZC vs Placebo	2.5 g: 8.2 1.25 g: 8.5	7.2 vs 7.6	8.6 vs 6.2*	9.0 vs 6.0*	10.2 vs 8.2*
p-value vs placebo	-	0.6145	0.0096*	0.0002*	0.0338*

*statistically significant

Study ZS-004 was a phase III, multicentre, multi-phase, multi-dose, prospective, randomised, double-blind, placebo-controlled maintenance study to investigate the safety and efficacy of SZC in subjects with hyperkalaemia. In the Correction Phase, subjects were treated with SZC 10 g TID for 48 hours. Subjects who completed and achieved normokalaemia at the end of the Correction Phase were randomised into the 28 days Maintenance Phase in a double-blind manner in a 4:4:4:7 ratio to one of three doses of SZC (5 g, 10 g or 15 g) or placebo administered QD for a further 28 days.

The primary efficacy endpoint in Study ZS-004 was the model-based least squares mean of all available S-K values during the Maintenance Phase Study Days 8 to 29. The key secondary efficacy endpoints for the Correction Phase included the proportion of subjects who achieved normokalaemia at 24 and 48 hours after start of dosing and time to normalisation in S-K values (normalisation was defined as S-K values between 3.5 and 5.0 mmol/L, inclusive).

A total of 258 subjects were enrolled in the open label Correction Phase treated with SZC 10 g TID for 48 hours. Of the 251 subjects who completed the Correction Phase, 237 subjects entered the 28-day Maintenance phase (placebo: 85; SZC 5 g QD: 45; SZC 10 g QD: 51; SZC 15 g QD: 56). The mean age was 64 years and the majority were males in both study phases. The baseline S-K values were < 5.5 mmol/L for 46.1% of subjects, ≥ 5.5 to < 6.0 mmol/L for 38.8% of subjects, and ≥ 6.0 mmol/L for 15.1% of subjects. The probable causes of hyperkalaemia were use of RAAS inhibitor medication (69.8%), CKD (69.4%) and diabetes mellitus (65.9%).

Study ZS-004 demonstrated that SZC 10 g TID was effective in achieving normalised S-K levels in 84.3% of subjects at 24 hours and 97.6% of subjects at 48 hours after the first dose SZC. The median time to normalisation of S-K values during the Correction Phase was 2.17 hours after the first dose of SZC. The primary efficacy endpoint was met by demonstrating a statistically significantly (p≤0.0001) lower mean S-K compared to placebo from days 8 to 29 for all the maintenance doses (4.8 mmol/L for SZC 5 g, 4.5 mmol/L for 10 g, 4.4 mmol/L for 15 g QD versus 5.1 mmol/L for placebo). The proportion of subjects who remained normokalaemic was statistically significantly larger in the SZC 5 g QD, SZC 10 g QD, and SZC 15 g QD groups (71.1%, 76.0% and 85.2% of subjects, respectively) than in the placebo group (47.6% of subjects). The efficacy of SZC 10 g TID was consistent across different co-morbidities (CKD, diabetes and heart failure).

Summary of Key Efficacy Results (ZS-004)

	Maintenance Phase Treatment			
	Placebo	**5 g QD**	**10 g QD**	**15 g QD**
Primary efficacy endpoint				
Mean S-K value (Maintenance Phase Study Days 8-29)				
Least squares mean (mmol/L)	5.1	4.8	4.5	4.4
p-value vs placebo	-	≤0.0001	≤0.0001	≤0.0001
Notable secondary efficacy endpoints				
Number of normokalaemic days (Maintenance Phase Study Days 8-29)				
Mean	7.4	13.4	13.9	16.8
p-value vs placebo	-	0.0001	<0.0001	<0.0001
Proportion of normokalaemic subjects at study exit (Day 29)				
n/N (%)	39/82 (47.6)	32/45 (71.1)	38/50 (76.0)	46/54 (85.2)
p-value vs placebo	-	0.0148	0.0018	<0.0001

The clinical efficacy of SZC for the long-term maintenance of normokalaemia was demonstrated in the open-label studies ZS-004E and ZS-005. Study ZS-004E was the 48-week extension of Study ZS-004. Subjects entering this study with an S-K value between 3.5 and 5.5 mmol/L directly entered the long term Maintenance Phase starting with a 10 g QD dose, while those with S-K greater than 5.5 mmol/L underwent a Correction Phase (10 g TID for 24 hours or 48 hours, depending on their daily S-K measurement). Study ZS-005 was a 12-month study where patients entered the Correction Phase (10 g TID for 24 to 72 hours) until normokalaemia was restored before continuing into the Maintenance Phase to receive SZC at an initial dose of 5 g QD. In both studies, the maintenance dose could be down- or up-titrated in case of hypo- or hyperkalaemia, respectively, by decreasing or increasing the dose in steps of 5 g QD to a minimum of 5 g every other day (QOD) or a maximum of 15 g QD.

In both studies, the primary efficacy endpoint during the Maintenance Phase was the proportion of subjects with average S-K ≤ 5.1 mmol/L. Study ZS-005 included an additional primary efficacy endpoint during the Correction Phase, which was the restoration of normal S-K values. Key secondary efficacy endpoints included the proportion of subjects with average S-K ≤ 5.5 mmol/L.

A total of 123 subjects from Study ZS-004 were enrolled in the extension study ZS-004E, out of which 121 (98.4%) subjects directly entered the maintenance phase with an initial regimen of SZC 10 g QD, and 2 (1.6%) subjects required correction phase dosing (SZC 10 g TID) to achieve normokalaemia before entering the maintenance phase. In study ZS-005, 746 subjects completed Correction Phase treatment and all were eligible to enter the maintenance phase. The mean age was 63.6 years and majority were males (59.7%) in Study ZS-005. Comorbid conditions included CKD (based on eGFR < 60 mL/min, 73.5%), diabetes mellitus (62.7%), and heart failure (37.9%). Majority of the subjects had a history of hypertension (82.8%), diuretic use (51.0%) and use of RAAS inhibitor medication (70.2%).

The proportions of subjects with S-K 3.5-5.0 mmol/L in the correction phase in study ZS-005 at 24, 48 and 72 hours were 66.0%, 75.3% and 77.9% of subject, whereas 98.7% of subjects reached 3.5-5.5 mmol/L at 72 hours. These results were generally consistent with the results reported in the previous studies.

The results from both studies indicated that SZC maintained normokalaemia in most subjects. The proportion of subjects with mean S-K ≤5.1 mmol/L during the long-term maintenance phase was 88% in both studies, and nearly all subjects (99-100%) had mean S-K ≤5.5 mmol/L in each study. The efficacy of SZC was sustained throughout the long-term maintenance phase of 12 months and also consistent across different co-morbidities (CKD, diabetes and Heart Failure). In addition, in Study ZS-005, there was a greater proportion of subjects with lower baseline S-K (<5.5 mmol/L) achieving a mean S-K≤5.1 mmol/L during the Maintenance Phase, compared to subjects with higher baseline S-K (≥6.0 mmol/L), 94.8% versus 75.5%, respectively.

Summary of Key Efficacy Results (ZS-004E and ZE-005)

	Study ZS-004E	Study ZE-005
Primary Efficacy Endpoint (Long-term Maintenance Phase)		
Proportion of subjects with average S-K ≤5.1 mmol/L		
n/N (%)	106/120 (88.3)	571/646 (88.4)
95% confidence interval	81.2%, 93.5%	85.7%, 90.8%
Secondary Efficacy Endpoint (Long-term Maintenance Phase)		
Proportion of subjects with average S-K ≤5.5 mmol/L		
n/N (%)	120/120 (100)	638/646 (98.8)
95% confidence interval	97.0%, 100%	97.6%, 99.5%

About 53.1% of subjects had their dose increased from 5g QD to 10g QD in Study ZS-005 (starting maintenance dose of 5g QD). In study ZS-004E (starting maintenance dose of 10g QD), 32 (26.0%) subjects had dose adjustments, out of which 16 (13.0%) subjects had their dose increased to 15g QD, 15 (12.2%) subjects had doses decreased to 5g QD and 1 subject had a dose reduction from 10 g QD to 5 g QD. There was also a dose-dependent increase in the proportion of subjects achieving the target range of 3.5-5.0 mmol/L among subjects with higher baseline serum potassium concentrations (>5.5 mmol/L). Majority of subjects had adequate potassium control on either 5 or 10g once daily, and a relatively low proportion of subjects (10-13%) were required to be up-titrated to 15g once daily. Based on the data from the maintenance studies, the minimal effective dose of 5 g QD was chosen as the recommended starting maintenance dose with flexibility to up- or down-titrate based on S-K monitoring.

In conclusion, the studies demonstrated efficacy in achieving normokalaemia with SZC 10 g TID in the correction phase and this was consistently observed across different subgroups of patients. In the maintenance phase, a starting dose of 5 g QD with possible titration up to 10 g QD, or down to 5 g QOD, as needed, was able to maintain a normal potassium level in most subjects up to 12 months.

D ASSESSMENT OF CLINICAL SAFETY

The clinical safety of Lokelma was based on a total of 1760 subjects exposed to at least 1 dose of SZC in the clinical programme. This includes 1009 subjects in studies ZS-002, ZS-003 and ZS-004 and its extension and 751 subjects in the open-label study ZS-005.

A total of 869 subjects entered the long-term open-label maintenance phase in studies ZS-004E and ZS-005. Of these, 652 subjects were treated for at least 6 months and 507 subjects were treated for at least 12 months. In addition, 222 healthy volunteers were exposed to SZC during phase 1 single dose pharmacodynamic study ZS-006 and drug-drug study ZS-009. In the correction phase, majority of the subjects in each of the treatment groups received between 4 and 6 doses of study drug (94.7% placebo; 97.4% total SZC).

Overall summary of safety profile - correction phase

	ZS-002, ZS-003 and ZS-004*				ZS-005*
	Placebo (N=188)	SZC≤3 g TID (N=331)	SZC 5 g TID (N=157)	SZC 10 g TID (N=425)	SZC 10 g TID (N=751)
Any TEAE, n (%)	20 (10.6%)	41 (12.4%)	22 (14.0%)	44 (10.4%)	31 (4.1%)
Treatment-related TEAE	3.7%	3.3%	5.7%	2.4%	0.9%
SAE	<1.0%	0	0	1 (0.2%)	1 (0.1%)
Treatment-related SAE	0	0	0	0	0
Discontinuations due to AE	1 (0.5%)	8 (2.4%)	5 (3.2%)	10 (2.4%)	2 (0.3%)
Deaths due to AE	0	0	0	0	0

AE: adverse event; SAE: serious adverse event; TEAE: treatment emergent adverse event
*Study ZS-002 and ZS-003 were placebo controlled during correction phase. In correction phase of study ZS-004 and ZS-005, subjects were treated with open-label SZC 10 g TID for up to 72 hrs.

The overall incidence of TEAEs during the Correction Phase was similar among the treatment groups in studies ZS-002, ZS-003, and ZS-004 (10.6% subjects in the placebo group, and 12.4%, 14.0%, and 10.4% of subjects in the SZC ≤3 g TID, 5 g TID, and 10 g TID groups, respectively). The only TEAE reported by ≥2.0% of subjects in any treatment group was diarrhoea, with a similar incidence observed between placebo and all SZC dose groups (2.1% of subjects in the placebo group, and 2.4%, 1.9%, and 1.2% of subjects in the SZC ≤3 g TID, 5 g TID, and 10 g TID groups, respectively). Only one subject developed severe TEAEs (vomiting and diarrhoea) that were considered related to the study drug (study ZS-003; SZC 10 g tid group) and led to premature discontinuation of study drug. A similar TEAE profile was observed during the correction phase of open-label study ZS-005.

Long-term maintenance Study ZS-004E reported a total of 82 (66.7%) subjects with at least 1 TEAE (event rate per 100 patient years of 114.4) in the long-term maintenance phase. The most common TEAEs were hypertension (12.2%; event rate 20.9), urinary tract infection (8.9%; event rate 15.3), and peripheral oedema (8.1%; event rate 14.0). The only related TEAE reported by ≥2.0% of subjects was muscle spasms reported in 3 subjects (2.4%, event rate 4.2). Only one subject had a TEAE considered related to study drug (hypersensitivity) which led to study discontinuation. Long-term maintenance phase of Study ZS-005 reported a total of 489 (65.5%) subjects with at least 1 TEAE (event rate per 100 patient years of 83.7). The most common TEAEs were peripheral oedema (9.7%, event rate 12.3), hypertension (11.0%; event rate 14.0), and urinary tract infection (7.9%; event rate 10.1). Severe TEAEs considered related to study drug were reported in single patients and included dyspnoea, congestive cardiac failure, hypokalaemia, decreased white blood cell count, decreased neutrophil count, increased monocyte count, increased eosinophil count and peripheral oedema. No deaths were reported that were considered related to the study drug neither in the Correction nor Maintenance phases of the studies.

The identified adverse reactions included oedema and hypokalaemia. Oedema related events preferred terms included fluid overload, fluid retention, generalised oedema, hypervolaemia, localised oedema, oedema, oedema peripheral and peripheral swelling. In a placebo controlled study ZS-003, oedema-related TEAEs were observed more frequently in the SZC 10 g QD dose group compared to placebo (event rates per 100 patient years of 107.1 vs 38.4). In study ZS-004, the oedema-related event rates per 100 patient years was 200.0 for SZC 15 g QD dose group. In the long-term open label study ZS-005, there were a few subjects (4 [0.5%]) who reported treatment-emergent oedema-related SAEs (fluid overload in 3 [0.4%] subjects and generalised oedema in 1 [0.1%] subject). A dose-related increase in the incidence of hypokalaemia (S-K <3.5 mmol/L) was observed, but the incidence across all the studies was low (73/1760, 4.1%). No cases of severe hypokalaemia (<2.5 mmol/L) have been reported.

Overall, Lokelma was well tolerated and the TEAEs observed were generally similar to placebo. The reported TEAEs were manageable with no major safety concerns. The identified adverse reactions included oedema-related events and hypokalaemia. Relevant warnings and precautions have been included in the package insert.

E ASSESSMENT OF BENEFIT-RISK PROFILE

The current standard of care for hyperkalaemia includes medications that increase urinary excretion (e.g. loop or thiazide diuretics) or bind potassium, including resins such as sodium polystyrene sulfonate, calcium polystyrene sulfonate and patiromer.

The efficacy of SZC in the correction and maintenance phases was consistently demonstrated in the clinical studies presented. Study ZS-003 demonstrated statistically superior efficacy of SZC 10 g TID versus placebo in reducing S-K during the Correction Phase and of SZC 5 g and 10 g QD versus placebo in maintaining S-K during the 12 days of the Maintenance Phase across a variety of subpopulation analyses, including subjects with diabetes mellitus, congestive heart disease, CKD, and concurrent use of RAAS inhibitor medication. Study ZS-004 also demonstrated statistically significant superior efficacy of SZC versus placebo in maintaining S-K and this outcome was evident across all predefined subpopulations (diabetes mellitus, HF, CKD and concurrent use of RAAS inhibitor medication). Studies ZS-004E and ZS-005 demonstrated maintenance of normokalaemia up to 12 months with a maintenance dose of 5 or 10 g once daily.

The safety profile of Lokelma was considered acceptable and well tolerated. The overall rate of TEAEs and laboratory abnormalities were low and generally similar to those observed with placebo. The identified adverse reactions included oedema-related events and hypokalaemia, which have been adequately addressed in the package insert.

Overall, the benefit-risk profile of Lokelma for the treatment of hyperkalaemia in adult patients was considered favourable.

F CONCLUSION

Based on the review of quality, safety and efficacy data, the benefit-risk balance of Lokelma indicated for the treatment of hyperkalaemia in adult patients was deemed favourable and approval of the product registration was granted on 22 June 2020.

APPROVED PACKAGE INSERT AT REGISTRATION

1. NAME OF THE MEDICINAL PRODUCT

LOKELMA 5 g powder for oral suspension

LOKELMA 10 g powder for oral suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

LOKELMA 5 g powder for oral suspension: Each sachet contains 5 grams (g) sodium zirconium cyclosilicate.

LOKELMA 10 g powder for oral suspension: Each sachet contains 10 g sodium zirconium cyclosilicate.

3. PHARMACEUTICAL FORM

Powder for oral suspension.

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

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

4.2 Posology and method of administration

Posology

Use in adults

Treatment of hyperkalaemia correction phase

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

Treatment of hyperkalaemia maintenance phase

For continued maintenance treatment, the minimal effective dose to prevent recurrence of hyperkalaemia should be established. A dose of 5 g once daily is recommended, with possible titration up to 10 g once daily, or down to 5 g once every other day, as needed, to maintain a normal potassium level. No more than 10 g once daily should be used for maintenance therapy.

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

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

Method of administration

For oral use.

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

LOKELMA can be taken with or without food.

Missed dose

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

Special Populations

Patients with renal or hepatic impairment

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

Elderly patients

Dose adjustment is not required in the elderly.

Pediatric patients

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

4.3 Contraindications

No contraindications.

4.4 Special warnings and special precautions for use

Hypokalaemia

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

Serum potassium levels

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

Oedema

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

QT Prolongation

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

The risk of interaction with X-rays

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

Intestinal perforation

The risk for intestinal perforation with the use of LOKELMA is currently unknown. No events of intestinal perforation have been reported with LOKELMA. Since intestinal perforation has been reported with polymers that act in the gastrointestinal tract, specific attention should be paid to signs and symptoms related to intestinal perforation.

Limitations of the clinical data

Patients on dialysis

LOKELMA has not been studied in patients receiving dialysis treatment.

Severe hyperkalaemia

There is limited experience in patients with serum potassium concentrations greater than 6.5 mmol/L.

Long-term exposure

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

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on LOKELMA

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

Effect of LOKELMA on other medicinal products

As LOKELMA is not absorbed or metabolised by the body and does not meaningfully bind other medicinal products, there are limited effects on other medicinal products. In a clinical drug-drug interaction study conducted in healthy subjects, co-administration LOKELMA with amlodipine, dabigatran, clopidogrel, atorvastatin, furosemide, glipizide, warfarin, losartan, or levothyroxine did not result in clinically meaningful drug-drug interactions. Consistent with co-

administration of dabigatran with other gastric acid modifiers, dabigatran C_{max} and AUC values were approximately 40% lower when co-administered with sodium zirconium cyclosilicate. No dose adjustments or separation of the time of dosing are required for these drugs.

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

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

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

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

4.6 Pregnancy and lactation

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

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

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

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Clinical trials

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

The most commonly reported adverse reaction was oedema related events which were reported by 5.7% LOKELMA patients; 1.7, 2.7, 5.2, and 14.3% of patients randomised to placebo,

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

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

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

Tabulated list of adverse reactions

The following convention was used for frequency of adverse drug reactions: Very common (≥1/10); Common (≥1/100 to <1/10); Uncommon (≥1/1,000 to <1/100); Rare (≥1/10,000 to <1/1,000); Very rare (<1/10,000), not known (cannot be estimated from the available data).

Table 1 List of adverse reactions in clinical studies

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

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

[b] Adverse reaction only in the maintenance phase

4.9 Overdose

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

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group (ATC code): V03AE10

Pharmacotherapeutic group: Drugs for treatment of hyperkalaemia and hyperphosphatemia

5.1 Pharmacodynamic properties

Mechanism of action

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

Pharmacodynamic effects

LOKELMA reduces serum potassium levels as soon as 1 hour after ingestion and serum potassium concentrations continue to decline over the 48-hour treatment period. Sodium zirconium cyclosilicate has no effect on serum calcium, magnesium, and sodium levels. In patients not continuing treatment, potassium levels increase. There is a close correlation between starting serum potassium levels and effect size; patients with higher starting serum potassium levels have greater reductions in serum potassium.

In a study of healthy subjects given LOKELMA 5 g or 10 g once daily for four days, dose-dependent reduction in serum potassium concentration and total urinary potassium excretion were accompanied by mean increases in faecal potassium excretion. No statistically significant changes in urinary sodium excretion were observed.

LOKELMA has also been shown to bind ammonium *in vitro* and *in vivo*, thereby removing ammonium and increasing serum bicarbonate levels. LOKELMA treated-patients experienced an increase of 1.1 mmol/L at 5 g once daily, 2.3 mmol/L at 10 g once daily, and 2.6 mmol/L at 15 g once daily in bicarbonate compared with a mean increase of 0.6 mmol/L for those receiving placebo. LOKELMA demonstrated a reduction in serum aldosterone levels (range: -30% to -31%) compared with the placebo group (+14%). No effect on systolic and diastolic blood pressure has been observed.

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

Clinical efficacy and safety

The potassium-lowering effects of LOKELMA have been demonstrated in three randomised, double-blind, placebo-controlled trials in patients with hyperkalaemia. All three studies tested the initial effect of LOKELMA to correct hyperkalaemia during a 48-hour period and two studies also tested maintenance of normokalaemia effect obtained. In addition, two open-label maintenance studies tested long-term safety of Lokelma. The maintenance studies included patients with chronic kidney disease (58%), heart failure (10%), diabetes mellitus (62%), and RAAS inhibitor therapy (68%). One thousand seven hundred sixty patients have received doses of LOKELMA; 507 exposed for at least 360 days. In the studies, LOKELMA reduced serum potassium and maintained normal serum potassium levels regardless of the underlying cause of hyperkalaemia, age, sex, race, comorbid disease, or concomitant use of RAAS inhibitors. No

dietary restrictions were imposed; patients were instructed to continue their usual diet without any specified alterations.

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

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

LOKELMA showed dose-dependent reductions in serum potassium at the 2.5 g, 5 g, and 10 g doses within hours of administration of the first dose (Table 2). Statistically significant reductions in potassium were observed 1 hour after the first 10 g dose of LOKELMA. Mean serum potassium reduction was -0.7 mmol/L and 86% of patients had normal potassium values within 48 hours at the 10 g dose. Patients with higher starting potassium levels had a greater response to LOKELMA. Patients with pre-treatment potassium levels in excess of 5.5 mmol/L (average baseline 5.8 mmol/L) saw an average decrease of 1.1 mmol/L at 48 hours while those with starting potassium levels at or below 5.3 mmol/L had an average decrease of 0.6 mmol/L at the highest dose. Potassium reduction was similar among patients with chronic kidney disease, heart failure, diabetes mellitus, and those taking RAAS inhibitor therapy (angiotensin receptor blockers, angiotensin converting enzyme inhibitors, aldosterone antagonists).

Table 2 Acute phase potassium change from baseline at 48 hours

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

*= p-value <0.05

Patients achieving normokalaemia (potassium levels between 3.5 and 5.0 mmol/L) were then re-randomised to active drug at the same dose level or placebo administered once daily for 12 days (Table 3). This phase of the study met the predefined efficacy endpoints at the 2.5 g,

5 g, and 10 g doses when compared with their respective placebo groups. Efficacy was consistent across pre-specified subgroups with heart failure, chronic kidney disease, and diabetes mellitus, or in patients on RAAS inhibitors. At the end of the treatment period, when LOKELMA was no longer administered, potassium increased to near baseline levels.

Table 3 Maintenance phase (12 days): Mean number of normokalaemic days

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

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

In the correction phase of the study, 258 patients with hyperkalaemia (baseline average 5.6, range 4.1-7.2 mmol/L) received 10 g of LOKELMA administered three times daily for 48 hours. Reductions in potassium were observed 1 hour after the first 10 g dose of LOKELMA. Median time to normokalaemia was 2.2 hours with 84% of patients achieving normokalaemia within 24 hours and 98% within 48 hours. Responses were larger in patients with more severe hyperkalaemia; serum potassium fell 0.8, 1.2, and 1.5 mmol/L in patients with baseline serum potassium <5.5, 5.5-5.9, and ≥6.0 mmol/L, respectively.

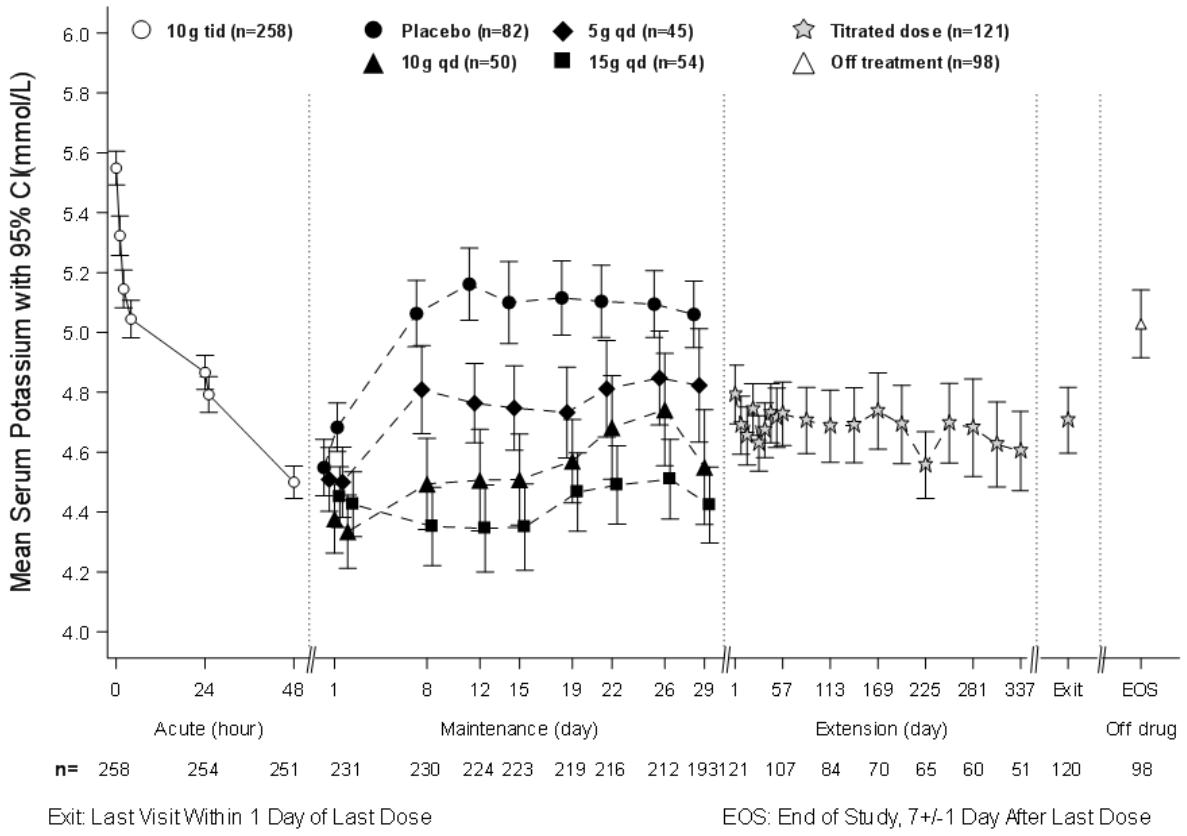
Patients who achieved normokalaemia (potassium levels between 3.5 and 5.0 mmol/L) were randomised in a double-blind fashion to one of three doses of LOKELMA (5 g (n=45), 10 g (n=51), or 15 g (n=56)), or placebo (n=85) administered once daily for 28 days (the double-blind randomised withdrawal phase).

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

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

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

Figure 1 Correction and maintenance phase: Mean serum potassium levels



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

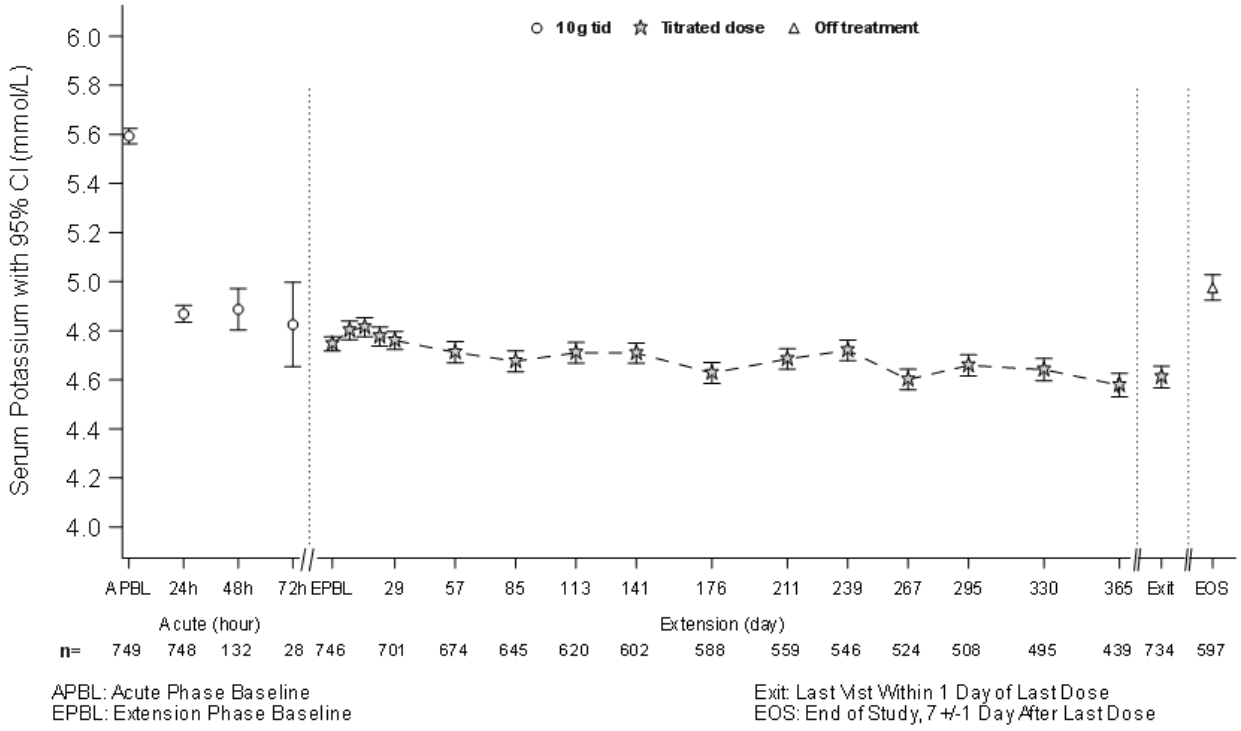
<u>A two-phase, multi-center, multi-dose, open-label safety and efficacy study</u>

The long term (up to 12 months) effects of LOKELMA were assessed in this study in 751 subjects with hyperkalaemia (baseline average 5.59 mmol/L; range 4.3, 7.6 mmol/L). Comorbid conditions included CKD (65%), diabetes mellitus (64%), heart failure (15%), and hypertension (83%). Use of diuretics and RAAS inhibitors was reported by 51 and 70% of subjects, respectively. During the correction phase, LOKELMA was administered 10 g TID for at least 24 hours and up to 72 hours. Subjects who achieved normokalaemia (3.5-5.0 mmol/L, inclusive) within 72 hours (n=746; 99%) entered the maintenance phase of the study. All subjects in the maintenance phase received LOKELMA at a starting dose of 5 g QD which could be increased in increments of 5 g QD (to a maximum of 15 g QD) or decreased (to a minimum of 5 g QOD) based upon the titration regimen.

Normokalaemia was achieved in 494/748 (66%), 563/748 (75%) and 583/748 (78%) of subjects after 24, 48 and 72 hours of correction phase dosing with an average reduction in serum potassium was -0.81 mmol/L, -1.02 mmol/L and -1.10 mmol/L at 24 (n=748), 48 (n=104) and 72 (n=28) hours, respectively. One hundred and twenty six patients had a baseline S-K ≥ 6.0 mmol/L (mean baseline potassium 6.28 mmol/L) and these patients had a mean reduction of -1.37 mmol/L at the end of the acute phase.

The proportion of subjects with a mean serum potassium ≤ 5.1 mmol/L across the Maintenance Phase Days 85-365 was 88% (95% CI 0.857, 0.908) and ≤ 5.5 mmol/L across the Maintenance Phase Days 85-365 was 99% (95% CI 0.976, 0.995). Normokalaemia was maintained while patients remained on drug and the mean serum potassium increased following discontinuation. Among those patients using RAAS inhibitors at baseline, 89% did not discontinue RAASi therapy, 74% were able to maintain the same dose during the maintenance phase and among those not on RAAS inhibitors at baseline, 14% were able to initiate this therapy.

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



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

A study in chronic kidney disease patients with hyperkalaemia

This study was a double-blind placebo-controlled dose-escalating study in 90 patients (60 LOKELMA patients; 30 controls) with baseline eGFR between 30-60 ml/min/1.73m^2 and hyperkalaemia (baseline serum potassium 5.2 mmol/L, range 4.6-6.0 mmol/L). Patients were randomised to receive escalating doses of LOKELMA (0.3 g, 3 g, and 10 g) or placebo,

administered three times a day with meals for two to four days. The primary endpoint was the rate of change in serum potassium from baseline throughout the initial 2 days of treatment. The trial met the primary efficacy endpoint at the 3 g and 10 g doses of LOKELMA compared to placebo. LOKELMA at the 10 g dose and the 3 g dose resulted in mean maximal reductions of 0.92 mmol/L and 0.43 mmol/L, respectively. Twenty-four hour urine collections showed that LOKELMA decreased urinary potassium excretion from baseline; -15.8 mmol/24 hours compared to placebo +8.9 mmol/24 hours ($p < 0.001$). Sodium excretion was unchanged relative to placebo (10 g TID, +25.4 mmol/24 hours compared to placebo +36.9 mmol/24 hours (NS)).

5.2 Pharmacokinetic properties

Absorption

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

Elimination

LOKELMA is eliminated via the faeces.

5.3 Preclinical safety data

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

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

None.

6.2 Incompatibilities

Not applicable.

6.3 Shelf-life

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

6.4 Special precautions for storage

Store at or below 30°C.

6.5 Nature and contents of container

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

Pack size: 30 sachets

6.6 Instructions for use, handling and disposal

No special requirements.

7. PRODUCT OWNER

AstraZeneca AB
SE-151 85, Södertälje, Sweden

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