Taiwan Food and Drug Administration

Assessment Report

Trade Name：
利控鉀口服懸液用粉劑 5 克 /LOKELMA 5g Powder for Oral Suspension
利控鉀口服懸液用粉劑 10 克 /LOKELMA 10g Powder for Oral Suspension

Active Ingredient：Sodium Zirconium Cyclosilicate

License Number：MOHW-PI 028710、MOHW-PI 028711

Applicant：臺灣阿斯特捷利康股份有限公司

Approval Date：2024.06.13

Indication：
適用於治療成人病人之高血鉀症。

Indicated for the treatment of hyperkalemia in adults.

1. Background Information

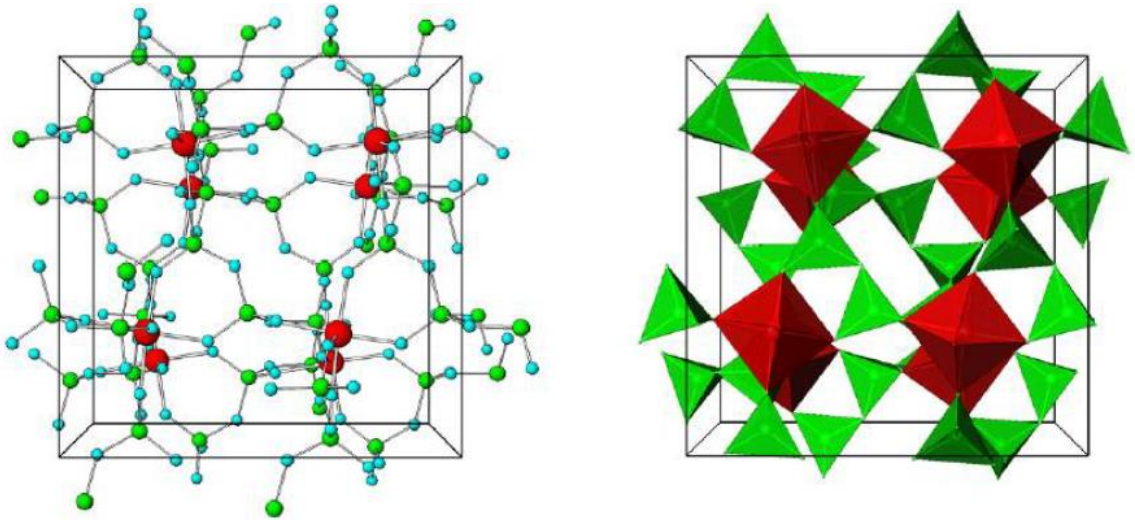
Trade Name	利控鉀口服懸液用粉劑 5 克 / LOKELMA 5g Powder for Oral Suspension 利控鉀口服懸液用粉劑 10 克 / LOKELMA 10g Powder for Oral Suspension
Active Ingredient(s)	Sodium Zirconium Cyclosilicate
Applicant	臺灣阿斯特捷利康股份有限公司
Dosage Form & Strengths	口服懸液用粉劑 5、10 克
Indication	適用於治療成人病人之高血鉀症。 Indicated for the treatment of hyperkalemia in adults
Posology	詳如仿單
Pharmacological Category **ATC Code**	V03AE10

2. Summary Report

2.1 Chemistry, Manufacturing and Controls Evaluation

2.1.1 Drug substance

The drug substance, sodium zirconium cyclosilicate, is chemically designated as sodium zirconium silicate hydrate and has the following structure:



It is a white to grey powder.. The molecular formula and the molecular weight range are $Na_{\sim 1.5}H_{\sim 0.5}ZrSi_3O_9 \bullet 2–3H_2O$ and 390.5 to 408.5 Daltons, respectively.

Adequate information of characterization of the drug substance has been provided. The molecular structure of sodium zirconium cyclosilicate has been confirmed by FTIR spectrum, nuclear magnetic resonance (^{29}Si-MAS-NMR) spectroscopy, synchrotron X-Ray powder diffraction and X-

Ray powder diffraction. Adequate specification has been presented for the drug substance and the test items include appearance, identification, potassium exchange capacity, impurities, elemental composition, pH, moisture content, particle size and elemental impurities. Batch analysis data from commercial scale batches of the drug substance are provided and the test results are within the specifications.

2.1.2 Drug product

The drug product is supplied for oral use as powder for oral suspension containing 5 g or 10 g of sodium zirconium cyclosilicate filled in sachets. No excipients used in the drug product formulation.

Adequate specification has been presented for the drug product and the test items includes appearance, identification, potassium exchange capacity, moisture content, particle size and average delivered weight. Batch analysis data from commercial scale batches of the drug product are provided and the test results are within the specifications. Analytical methods are described well and validated.

Stability studies of drug product under long-term condition (25°C/60% RH and 30°C/75% RH) and accelerated condition (40°C/75% RH) have been carried out. Up to 36 months of long-term and 6 months of accelerated stability data are submitted. No significant chemical or physical changes are observed for the drug product, the shelf life and storage condition of drug product can be granted for 36 months under the storage condition of below 30°C.

2.2 Preclinical Pharmacology/Toxicology Evaluation

Sodium zirconium cyclosilicate (ZS) is a non-absorbed cation-exchanger, which is designed to selectively capture potassium ions in exchange for sodium and hydrogen ions in the gastrointestinal tract, thereby reducing the plasma potassium concentration in adult patients with hyperkalemia. The non-clinical information of ZS, which will be reflected in the drug's labeling, including its genotoxicity, carcinogenicity, and developmental and reproductive toxicity, is summarized below.

ZS/ZS-9 exhibited no genotoxic potential in a standard battery of genotoxicity studies.

No carcinogenicity studies of ZS have been performed. Because ZS is not systemically absorbed, not genotoxic, and induced no hyperplastic or pre-neoplastic findings in the repeated-dose toxicity studies, carcinogenicity studies are deemed not warranted.

In a panel of DART studies, oral administration of ZS did not show effects on fertility, embryo-fetal development, and pre- and post-natal development at doses up to the maximum feasible dose of 6000 mg/kg/day in rats and rabbits, corresponding to 58 g/day and 116 g/day for a 60-kg person, or 1.9-and 3.9-fold MRHD (30 g/day), respectively.

2.3 Clinical Pharmacology Evaluation

2.3.1 General Pharmacodynamics and Pharmacokinetics

No systematic exposure of Lokelma was observed after dosing in healthy volunteers or hyperkelamia patients. Orally administered Lokelma retained in gut lumen and eliminated in the feces. In correction phase, for the 10 g TID dose of Lokelma, the serum potassium lowering effect started immediately, with a statistically significant difference from placebo noted for the mean change from baseline 1 hour after the first dose of study drug. For the 5 g TID dose of Lokelma, the first statistically significant difference from placebo was noted for the mean change from baseline 2 hours after the first dose of study drug. For the 2.5 g TID dose of Lokelma, the first statistically significant difference from placebo was noted for the mean change from baseline 4 hours after the first dose of study drug. Treatment with Lokelma resulted in clinically relevant and statistically significant dose-dependent reductions in serum potassium in patients with hyperkalemia.

2.3.2 Interaction Studies

Although Lokelma is not expected to influence the activities of CYP450s or transporters, it has been shown to affect the pH levels of gut lumen, which might alter the PK profiles of medications with pH-dependent absorption. Co-administration with 10 g Lokelma increased the C_{max} of atorvastatin and o-OH atorvastatin 69% and 37%, respectively. Co-administration with 10 g Lokelma showed 42.6% and 40.9% decreases in C_{max} and AUC of dabigatran 37%, respectively. Since it is difficult to list in detail the drugs whose pharmacokinetic performance is affected by pH, in general practice, Lokelma needs to be administered at least two hours apart from other oral medications.

2.3.3 Special Populations

Renal or hepatic impairments are not considered to impact the elimination of Lokelma. The dose regimens are primaryly based on the clinical outcomes of each individual patient, and no additional dose adjustments are recommended for special populations.

2.4 Clinical Efficacy and Safety Evaluation

2.4.1 Efficacy Results

In this NDA, five Phase 3, randomized, double-blind, placebo-controlled studies (ZS-003, ZS-004, D9480C00002, D9480C00006, and D9485C00001) were reviewed to evaluate the efficacy of Lokelma (Sodium Zirconium Cyclosilicate) for the treatment of hyperkalemia in adult patients.

ZS-003 enrolled patients with mild to moderate hyperkalemia (potassium value between 5.0 and 6.5 mmol/L as determined by i-STAT). In this study, two different SAPs and CSRs were used, but the study protocols were identical, with different primary endpoints for the US FDA and the EMA.

US FDA version:

(1) Acute: The estimates for the exponential rates of change in S-K from baseline to 48 hours were 10g: -0.00224; 5g: -0.00127, 2.5g: -0.00066, and 1.25g: -0.00013. The 10g TID, 5g TID, and 2.5g TID doses of Lokelma were statistically significantly superior to placebo ($p < 0.001$).
(2) SUBACUTE: The estimates for the exponential rates of change in S-K from baseline to 48 hours were 10g: -0.00844; 5g: -0.00368, 2.5g: 0.00031, and 1.25g: 0.00113. The 10g QD and 5g QD doses of Lokelma were statistically significantly superior to placebo ($p < 0.01$).

EMA version:

(1) ACUTE: The 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 Lokelma 10g TID, 5g TID, 2.5g TID, 1.25g TID, and placebo groups, respectively. The 10g TID, 5g TID, and 2.5g TID doses were statistically significantly superior to placebo ($p < 0.0001$).
(2) SUBACUTE: The total numbers of days normokalemic were statistically significantly greater in the Lokelma 10g QD (10.2 vs 8.2 days), 5g QD (9.0 vs 6.0 days), and 2.5g QD (8.6 vs 6.2 days) groups compared with their corresponding placebo controls ($p < 0.001$).

ZS-004 enrolled patients with hyperkalemia (i-STAT potassium ≥ 5.1 mmol/L). Patients who achieved normokalemia (potassium levels between 3.5 and 5.0 mmol/L) were randomized to receive Lokelma 5g, 10g, 15g or placebo QD for a maintenance phase. Serum potassium was statistically significantly lower during days 8-29 with all 3 Lokelma doses vs placebo (5g: 4.8 mmol/L, 10g: 4.5 mmol/L, and 15g: 4.4 mmol/L vs. placebo: 5.1 mmol/L; $p < 0.001$ for all comparisons).

D9480C00002 also enrolled patients with hyperkalemia (i-STAT potassium ≥ 5.1 mmol/L). Patients who achieved normokalemia (potassium levels between 3.5 and 5.0 mmol/L) were randomized to receive Lokelma 5g, 10g or placebo QD for a maintenance phase. The geometric means of S-K values for the 10g, 5g, and placebo were 4.8, 4.4, and 5.3 mmol/L, respectively, corresponding to a mean ratio of 0.904 between 5g and placebo and a ratio of 0.823 between 10 g and placebo. Both 5g and 10g doses were statistically significantly superior over placebo ($p < 0.001$).

D9480C00006 enrolled patients on *chronic hemodialysis*. Eligible patients were randomized to receive either Lokelma or placebo. In the Lokelma group, 5g, 10g or 15g QD was administered on non-dialysis days. A statistically higher proportion of responders (maintained a pre-dialysis S-K between 4.0 and 5.0 mmol/L on 3 out of 4 LIDI visits) in the Lokelma group (41.2%) compared to the placebo group (1.0%); the estimated odds ratio was 68.77 with $p < 0.001$.

D9485C00001 enrolled Chinese subjects with end-stage renal disease (ESRD) on *stable hemodialysis*. Eligible patients were randomized to receive either Lokelma or placebo. In the Lokelma group, 5g, 10g or 15g QD was administered on non-dialysis days. A statistically higher proportion of responders

(maintained a pre-dialysis S-K between 4.0 and 5.0 mmol/L on 3 out of 4 LIDI visits) in the Lokelma group (37.3%) compared with the placebo group (10.4%); the estimated odds ratio was 5.10 with $p < 0.001$.

2.4.2 Safety Results

During the maintenance phase of placebo-controlled studies, the overall rate of TEAEs was similar to placebo across all LOKELMA dose groups. No increase in the exposure adjusted event rate of TEAEs was observed in long-term LOKELMA treatment. Analyses of TEAEs by intrinsic factors and extrinsic factors did not suggest any clinically relevant differences between placebo and LOKELMA treatment groups.

Hypokalemia and Edema-related events were identified as an ADR. Both could be effectively managed by routine monitoring. LOKELMA demonstrated an overall safety profile, including gastrointestinal tolerability, generally similar to placebo, and no serious safety risks were identified with LOKELMA treatment. Furthermore, LOKELMA was well tolerated by patients on chronic hemodialysis and no new safety signals were identified.

In clinical studies conducted in countries with a predominantly Asian population, constipation with an estimated frequency of 8.9% occurred in patients receiving LOKELMA; and was resolved with dose adjustment or treatment discontinuation.

2.5 Bridging Study Evaluation

LOKELMA is not absorbed into systemic circulation after dosing. Consequently, pharmacokinetic properties of LOKELMA would not be altered by activities of metabolic enzymes or transporters. Ethnic differences were primarily assessed through pharmacodynamic results. Serum potassium lowering effects of LOKELMA were similar in Japanese and western population. The ethnic difference was negligible from PK point of view.

Studies D9480C002(HARMONIZE China), D9485C001(DIALIZE China) and D9482C001(long-term treatment in Japan) were submitted for BSE. Ethnic difference with clinical impact was not found. Bridging study was waived.

2.6 Conclusion

This multidisciplinary review recommends regular approval for LOKELMA (Sodium Zirconium Cyclosilicate) 5g and 10g Powder for Oral Suspension indicated for the treatment of hyperkalemia in adults.

3. Post-Marketing Requirements

NA