Public Assessment Report

LOKELMA

INFORMASI PRODUK

Nama obat	:	LOKELMA
Bentuk sediaan	:	Serbuk untuk suspensi oral
Zat aktif	:	Tiap sachet mengandung - Sodium zirconium cyclosilicate 5 g dan 10 g
Kemasan	:	Dus @ 30 Sachets
Pendaftar	:	PT. ASTRAZENECA INDONESIA
Produsen	:	ANDERSONBRECON INCORPORATED Rockford, United States of America, (Manufacturer, Primary Packaging Site, Secondary Packaging Site)
Kategori Registrasi	:	Registrasi baru dengan Zat Aktif Baru
Indikasi yang diajukan:	:	*Lokelma is indicated for the treatment of hyperkalaemia in adult patients.*
Posologi yang diajukan	:	Terlampir

PENGANTAR

Lokelma obat dengan zat aktif baru sodium zirconium cyclosilicate, yaitu senyawa anorganik non polymer dan tidak terabsorbsi dengan struktur mikrope yang menangkap kalium dalam pertukaran kation hidrogen dan natrium. Mengingat sodium zirconium cyclosilicate adalah zat aktif baru, saat ini evaluasi difokuskan pada data uji non klinik, klinik, dan mutu obat untuk pembuktian efikasi, keamanan, dan mutu obat lebih lanjut.

ASPEK MUTU

Lokelma (zirconium cyclosilicate) tersedia dalam bentuk serbuk untuk suspensi oral, mengandung zirconium cyclosilicate 5 g dan 10 g. Obat jadi tidak mengandung eksipien.

Zat Aktif

Zat aktif zirconium cyclosilicate memiliki nama kimia hidrogen natrium zirkonium (IV) silikat hidrat. Karena variabilitas alami dalam proses pembuatan zat aktif, diharapkan memiliki formula $Na_{\sim 1.5}H_{\sim 0.5}ZrSi_3O_9 \bullet 2–3\ H_2O$ dengan massa molekul relatif pada rentang 390.5 – 408.5 serbuk putih dan telah dilakukan karakterisasi,

Struktur zirconium cyclosilicate dikonfirmasi menggunakan difraksi serbuk sitokron, difraksi X-ray, 29Si magic angle spinning solid nuclear magnetic resonance studies (29Si-MAS-NMR*), fourier transform infrared spectroscopy, inductive coupled plasma-optical emission spectrometry, wave dispersive X-ray microprobe analysis dan thermo-gravimetric analysis.*

Spesifikasi zat aktif meliputi pengujian: pemerian, identifikasi (FT-IR, XRPD), kapasitas pertukaran kalium (kromatografi ion), *crystalline impurities* (XRPD), batas asetat (HPLC), kandungan Zr (WD-XRF), kandungan Si (WD-XRF), kandungan Na (WD-XRF), kandungan Hf (WD-XRF), pH (potensiometri), *moisture content* (TGA), ukuran partikel (difraksi laser) dan *elemental impurities* (ICP-MS)

Uji stabilitas zat aktif telah dilakukan dan menunjukkan obat stabil ketika disimpan pada suhu 25 ºC / 60% RH dan at 30 ºC / 75% RH. Hasil studi photostability menunjukkan zat aktif stabil ketika terpapar cahaya.

Studi degradasi paksa termasuk oksidasi paksa dengan hidrogen peroksida, kondisi asam dan basa, degradasi termal dan fotolisis juga dilakukan dengan hasil studi menunjukkan bahwa tidak terbentuk degradasi atau impurities baru.

Obat jadi

Obat jadi diproduksi dalam bentuk sediaan serbuk oral berwarna putih hingga keabuan. Obat jadi dapat langsung disuspensikan dalam air dengan pengadukan.

Proses pembuatannya terdiri dari dua langkah utama: pengisian dan penyegelan kemasan berisi zat aktif. Validasi proses telah dilakukan terhadap 3 bets skala produksi. Hasil validasi proses menunjukan kemampuan proses menghasilkan obat jadi yang memenuhi kriteria penerimaan yang ditetapkan.

Spesifikasi obat telah ditetapkan yaitu identifikasi (FT-IR, XRPD), kapasitas pertukaran kalium (ion chromatography), kadar Zr (WD-XRF), Kadar Si (WD-XRF), Kadar Na (WD-XRF), Kadar Hf(WD-XRF), *moisture content* (TGA), ukuran partikel (difraksi laser), *average delivered weight* dan *microbial limits* (Ph. Eur.). Parameter dalam spesifikasi dipilih berdasarkan karakterisitik fisikokima dan sifat zat aktif krital dengan mempertimbangkan antara lain hasil uji bets yang digunakan dalam uji klinik, data stabilitas jangka panjang. Metode analisa yang digunakan telah divalidasi. Hasil analisa bets memberikan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Data stabilitas dari 3 bets obat skala produksi telah dilakukan pada zona IVB, yaitu pada suhu 30°C/75% RH selama 36 bulan dan suhu 40°C/75% RH selama 6 bulan dengan hasil yang memenuhi spesifikasi yang dipersyaratkan.

Studi degradasi paksa yang dilakukan pada zat aktif dinilai dapat diterapkan pada produk jadi karena produk jadi tidak mengandung eksipien. Kompatibilitas dengan sistem kemasan divalidasi berdasarkan data stabilitas yang tersedia. Hasil studi photostability menunjukkan obat stabil ketika terpapar cahaya.

Kesimpulan
Dari aspek mutu, Obat Lokelma serbuk oral dapat dipertimbangkan untuk diterima.

ASPEK KHASIAT DAN KEAMANAN

Studi Non Klinik

Berdasarkan ringkasan hasil studi non klinik diinformasikan hal-hal sebagai berikut:

1. Farmakologi

   - Pengembangan non klinik dilakukan dengan menggunakan sodium zirconium cyclosilicate (ZS) tapi beberapa studi farmakologi dan toksikologi dengan durasi < 14 hari dilakukan pada non-protonated material (designated ZS-9). Perbedaan ZS dan Z-9 adalah kandungan ion sodium, ukuran partikel dnan pH pada larutan.

   - Data Farmakologi (non-GLP) menunjukkan nilai experimental potassium exchange capacity (KEC) saat uji rilis secara in vitro untuk sodium zirconium cyclosilicate adalah sekitar 3.2 ± 0.4 mEq/g atau rerata 125.5 mg/g.

   - Pengobatan dengan ZS-9 tidak mempengaruhi laju respirasi atau parameter EKG pada anjing bila diberikan selama 14 hari dengan dosis total harian hingga 4.479 mg/kg (1493 mg/kg/tid; studi 14250-10), yang setara dengan ~145g/hari dosis manusia. ZS juga tidak mempengaruhi parameter EKG kualitatif, denyut jantung, interval RR atau PR atau durasi QRS bila diberikan pada pemberian selama 28 hari pada dosis hingga 3000 mg/kg/hari atau selama 270 hari pada dosis hingga 2000 mg/kg/hari.

2. Farmakokinetik

   - Karena memiliki komposisi anorganik, Sodium Zirconium Cyclosilicate, tidak mengalami metabolisme enzimatik. Selain itu, karena sifatnya yang tidak larut dan ukuran partikelnya rata-rata 20 μm (97% >3 μm) bukan merupakan substrat untuk proses transport sehingga tidak memiliki efek metabolisme atau induksi sitokrom P450 dan secara sistemik tidak diserap.

   - Kurangnya penyerapan dikonfirmasi oleh analisis darah utuh dan urin anjing di mana tidak ada Zr yang dapat dideteksi setelah 9 bulan pemberian Sodium Zirconium Cyclosilicate dengan dosis harian 2000 mg/kg/hari, setara dengan dosis manusia dari ~65g/hari berdasarkan berat badan 60 kg.

   - Dalam studi keseimbangan massa tikus, 97-99% dosis Zr diekskresikan dalam tinja dalam waktu 48 jam setelah pemberian.

3. Toksikologi

- Studi toksisitas akut menunjukkan tidak ada efek samping yang tercatat setelah pemberian dosis tunggal 2000 mg/kg Sodium Zirconium Cyclosilicate tak terprotonasi (ZS-9) dalam air dengan volume dosis 10 ml/kg pada tikus atau anjing.
- Studi toksisitas dosis berulang pada tikus dan anjing dilakukan hingga durasi maksimum 180 hari dan 270 hari. Satu-satunya efek pemberian natrium zirkonium siklosilikat terkait dengan aktivitas farmakodinamik Sodium Zirconium Cyclosilicate, yaitu mengurangi penyerapan kalium dari saluran GI. Tikus mentoleransi natrium zirkonium siklosilikat hingga dosis maksimum 2000 mg/kg tid (6000 mg/kg/hari) hingga 26 minggu, dan anjing mentoleransi Sodium Zirconium Cyclosilic pada 1000 mg/kg/hari hingga 39 minggu. Tingkat dosis ini setara dengan tingkat dosis manusia sekitar 58 g/hari (tikus) dan 32 g/hari (anjing). Pada anjing pemberian dosis tertinggi mengakibatkan efek farmakodinamik, yaitu perkembangan hipokalemia yang signifikan secara klinis, perubahan degeneratif serta inflamasi sekunder pada ginjal, dan vakuolisasi lipid di korteks adrenal.
- Nilai NOAEL pada mencit yaitu 6000 mg/kg/day; 3000 mg/kg/day pada anjing; dan 6000 mg/kg/day pada kelinci.
- Sodium Zirconium Cyclosilic tidak menunjukkan potensi genotoksik berdasarkan *bacterial reverse mutation test*.
- Sodium Zirconium Cyclosilicate juga ditemukan hiperplastik atau pra-neoplastik dalam studi toksisitas kronis pada tikus dan anjing pada dosis setara manusia ~65g/hari dan karena kurangnya penyerapan sistemik dan tidak adanya potensi genotoksik, Sodium Zirconium Cyclosilic dianggap tidak mungkin menimbulkan bahaya karsinogenik.
- Sodium Zirconium Cyclosilicate tidak mempengaruhi fungsi reproduksi pada kedua jenis kelamin tikus hingga tingkat dosis maksimum 6000 mg/kg/hari, yang setara dengan tingkat dosis manusia sekitar 62 g/hari.

Berdasarkan data non klinik:
Hasil studi non klinik menunjukkan bahwa zirconium cyclosilicate tidak diabsorbsi secara sistemik, serta tidak bersifat karsinogenik dan mutagenik

Studi Klinik
Evaluasi dilakukan pada 5 studi pendukung, yaitu studi fase 2 (studi ZS-002); studi fase 3 (studi ZS-003 dan ZS-004 + studi *extension* ZS-004E), serta 1 studi jangka panjang dengan desain open-label tanpa pembanding (studi ZS-005).

1. Pada studi *dose escalation*, pemberian sodium zirconium cyclosilicate (ZS) 10g (n=24) 3 kali sehari (TID) menunjukkan efikasi yang terbaik dibandingkan dosis 3g (n=24) dan 0,3 g (n=12) vs. placebo (n=30) TID (studi ZS-002).
    - *mean maximal reduction serum potassium* [K+] (S-K) sampai 48 jam pada dosis 10g dan 3g sebesar 0,92 mmol/L (p<0,0001) dan 0,43 mmol/L (p=0,048), sedangkan dosis 0,3 g tidak memberikan penurunan S-K yang signifikan.
    - Parameter pengamatan S-K lain menunjukkan dose-dependent response dengan efek maksimal pada dosis 10g. ZS 10g vs. placebo menunjukkan hasil:
        - Waktu untuk mencapai penurunan S-K 0,5 mmol/L pertama berkurang secara signifikan (p=0,042).
        - Persentase subjek yang mencapai penurunan S-K >1,0 mmol/L pada 48 jam setelah 6 dosis: 33,3% vs. 6,7% (p=0,016).
        - Penurunan ekskresi kalium urin hingga hari ke-2: -23,11% vs. 30,88% (p<0,002
2. Pada studi dose ranging, pemberian ZS 10g dan 5g menunjukkan efikasi yang lebih baik dibanding dosis 2,5g, 1,25g vs. placebo (studi ZS-003).
    - Fase akut (48 jam pengobatan) pemberian 10g vs. 5g vs. 2,5g vs. 1,25g vs. placebo TID menunjukkan hasil:
        - Persentase subjek *normokalemic* (nilai S-K normal 3,5-5,0 mmol/L): 86,4% vs. 77,6% vs. 67,9% vs. 51,3% vs. 47,8 (p<0,0001)
        - *Mean* penurunan S-K dari *baseline* pada 48 jam setelah dosis pertama: -0,73 mmol/L vs. -0,54 mmol/L vs. 0,46 mmol/L vs. -0.30 mmol/L vs. -0.25 mmol/L
        - *Median* waktu mencapai penurunan nilai S-K 0,5 mmol/L (*time to 0.5 mmol/L decrease in S-K*

values): 22,8 jam (p<0,0001) vs. 23,5 jam (p=0,0137) vs. 21,4 jam (0,0067) vs. 24,1 jam (p=0,5278) vs. 24,8 jam.

- Fase subakut (tambahan 12 hari pengobatan setelah fase akut, sehari sekali/QD) *menunjukkan mean number of normokalemic days* pada ZS 10g, 5g dan 2,5g yang lebih baik dibandingkan *placebo*, yaitu 10,2 vs. 8,2 hari (p=0,0338), 9,0 vs. 6,0 hari (p=0,0002), dan 8,6 vs. 6,2 hari (p=0,0096), berurutan.

3. Pada pemberian ZS 10g TID (n=258) selama 48 jam pertama (6 dosis) kemudian subjek yang mencapai normokalemia dilanjutkan ke fase *maintenance* menerima ZS 5g (n=45) atau ZS 10g (n=51) atau ZS 15g (n=56) atau placebo (n=86) QD selama 28 hari, menunjukkan efikasi ZS yang lebih baik dari placebo (studi ZS-004). ZS 5g vs. 10g vs. 15g vs. *placebo* menunjukkan hasil:

   - *Mean* S-K 4,7544 mmol/L vs. 4,5081 mmol/L vs. 4,3742 mmol/L vs. 5,0603 mmol/L (p<0,05)
   - *Mean number of normokalemic days* 13,4 hari vs. 13,9 hari vs.16,8 hari vs. 7,4 hari (p<0,05)
   - *Median time to relapse in S-K values* hanya dapat diukur pada ZS 5g vs. placebo yaitu 29 hari vs. 19 hari.
   - Studi *extension* selama 11 bulan dengan penambahan/penurunan 5g QD atau minimal 5g every other day (QOD) berdasarkan pengukuran i-STAT kalium menunjukkan proporsi subjek dengan nilai S-K $\leq$ 5,1 mmol/L pada rentang 77,1% hingga 87,5% studi ZS-004E, n=121)
   - Pada pemberian obat ZS 10g TID sampai normokalemia dilanjutkan 5g QD selama 12 bulan dengan penambahan/penurunan 5g QD atau minimal 5g QOD berdasarkan pengukuran i-STAT kalium menunjukkan proporsi subjek dengan nilai S-K < 5,1 mmol/L pada rentang 76,7% hingga 87,2% (studi ZS-005, n=746).

4. Keamanan menunjukkan bahwa obat dengan dosis yang diajukan (ZS 5g dan 10g) dapat ditoleransi dengan baik.

   - Pada fase akut, *treatment emergent adverse events* (TEAEs) GIT yang dilaporkan terkait dengan obat studi sebanyak 3,2% (ZS 5g TID) dan 2,1% (ZS 10 g TID) dengan kejadian >1% adalah adalah diare, mual, dan muntah (studi ZS-002, 003, 004).
   - Pada fase *maintenance*, TEAEs dilaporkan sebanyak 34,5% (ZS 5g QD) dan 31,6% (ZS 10g QD) dengan kejadian >1% adalah dispepsia, konstipasi, muntah (studi ZS-003, 004).
   - Pada studi *extension*, AE terkait obat adalah *muscle spasms* (2,4%), *edema perifer* (1,6%), elektrokardiogram *QT* memanjang (1,6%), dan hipomagnesemia (1,6%) (studi ZS004E). Pada studi jangka panjang, TEAE terkait dengan obat adalah sembelit (3,1%), mual (1,7%), dan *edema perifer* (1,7%) (studi ZS-005).

KEPUTUSAN
Mempertimbangkan data khasiat dan keamanan tersebut di atas, diputuskan registrasi zat aktif baru lokelma serbuk untuk suspensi oral disetujui dengan **perbaikan indikasi** sebagai berikut:

Indication
LOKELMA is indicated for the treatment of hyperkalemia in adults.
LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action

Lampiran
Posologi yang diajukan:
Posology
Posology and method of administration
Posology
Adults, including the elderly
Correction phase
The recommended starting dose of Lokelma is 10 g, administered three times a day orally as a suspension in water. When normokalaemia is achieved, the maintenance regimen should be followed (see below).
Typically, normokalaemia is achieved within 24 to 48 hours. If patients are still hyperkalaemic after 48 hours of treatment, the same regimen can be continued for an additional 24 hours. If normokalaemia is not achieved after 72 hours of treatment, other treatment approaches should be considered.
Maintenance phase
When normokalaemia has been achieved, 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.
Serum potassium levels should be monitored regularly during treatment. Monitoring frequency will depend upon a variety of factors including other medications, progression of chronic kidney disease and dietary potassium intake.
If severe hypokalaemia should occur, Lokelma should be discontinued and the patient re-evaluated.

Patients on chronic haemodialysis
For patients on dialysis Lokelma should only be dosed on non-dialysis days. The recommended starting dose is 5 g once daily. To establish normokalaemia (4.0-5.0 mmol/L), the dose may be titrated up or down weekly based on the pre-dialysis serum potassium value after the long inter-dialytic interval (LIDI). The dose could be adjusted at intervals of one week in increments of 5 g up to 15 g once daily on non-dialysis days. It is recommended to monitor serum potassium weekly while the dose is adjusted; once normokalaemia is established, potassium should be monitored regularly (e.g. monthly, or more frequently based on clinical judgement including changes in dietary potassium or medication affecting serum potassium).

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/hepatic impairment No changes from the normal doses are required for patients with renal or hepatic impairment

Paediatric population
The safety and efficacy of Lokelma in children and adolescents (No data are available. Method of administration For oral use. The suspension can be taken with or without food. For instructions on preparation of the suspension, see section 6.6

Public Assessment Report

LOKELMA

PRODUCT INFORMATION

Name of the drug	:	LOKELMA
Dosage form	:	Powder for oral suspension
Active substance	:	Each sachet contains - Sodium zirconium cyclosilicate 5 g and 10 g
Packaging	:	Box @ 30 Sachets
Applicant	:	PT. ASTRAZENECA INDONESIA
Manufacturer	:	ANDERSONBRECON INCORPORATED Rockford, United States of America, (Manufacturer, Primary Packaging Site, Secondary Packaging Site)
Registration Category	:	New registration with New Active Substance
Proposed Indication	:	*Lokelma is indicated for the treatment of hyperkalaemia in adult patients.*
Proposed Posology	:	Attached

INTRODUCTION

Lokelma is a drug with a new active substance,sodium zirconium cyclosilicate, which is a non-polymer and non-absorbable inorganic compound with a microp structure that captures potassium in the exchange of hydrogen and sodium cations. Considering that sodium zirconium cyclosilicate is a new active substance, currently the evaluation is focused on non-clinical, clinical and drug quality test data to further prove the efficacy, safety and quality of the drug.

QUALITY ASPECTS

Lokelma (zirconium cyclosilicate) is available in powder form for oral suspension, containing 5 g and 10 g of zirconium cyclosilicate . The finished medicine does not contain excipients.

Active substance

The active substance zirconium cyclosilicate has the chemical name sodium zirconium hydrogen (IV) silicate hydrate. Due to natural variability in the active substance manufacturing process, it is desirable to have a formula
Na~1.5H~0.5ZrSi3O9 • 2–3 H2O with a relative molecular mass in the range of 390.5 – 408.5 white powder and has been characterized,

The structure of zirconium cyclosilicate was confirmed using cytochrome powder diffraction, X-ray diffraction, 29Si magic angle spinning solid nuclear magnetic resonance studies (29Si-MAS-NMR*), fourier transform infrared spectroscopy, inductive coupled plasma-optical emission spectrometry, wave dispersive X-ray microprobe analysis and thermo-gravimetric analysis.*

Active substance specifications include testing: description, identification (FT-IR, XRPD), potassium exchange capacity (ion chromatography), *crystalline impurities* (XRPD), acetate limit (HPLC), Zr content (WD-XRF), Si content (WD-XRF), Na content (WD-XRF), Hf content (WD-XRF), pH (potentiometry), *moisture content* (TGA), particle size (laser diffraction) and *elemental impurities* (ICP-MS)

The stability test of the active substance has been carried out and shows that the drug is stable when stored at 25 ºC / 60% RH and at 30 ºC / 75% RH. The results of the photostability study show that the active substance is stable when exposed to light.

Forced degradation studies including forced oxidation with hydrogen peroxide, acidic and alkaline conditions, thermal degradation and photolysis were also carried out with the study results showing that no new degradation or impurities were formed.

Drug Product

The drug product is produced in the form of a white to gray oral powder dosage form. The drug product can be directly suspended in water with stirring.

The manufacturing process consists of two main steps: filling and sealing the packaging containing the active substance. Process validation has been carried out on 3 production scale batches. Process validation results show the ability of the process to produce drug products that meet the specified acceptance criteria.

Drug specifications have been determined, namely identification (FT-IR, XRPD), potassium exchange capacity (ion chromatography), Zr content (WD-XRF), Si content (WD-XRF), Na content (WD-XRF), Hf content (WD -XRF), *moisture content* (TGA), particle size (laser diffraction), *average delivered weight* and *microbial limits* (Ph. Eur.). The parameters in the specifications are selected based on the physicochemical characteristics and properties of the crystal active substance by considering, among other things, the test results of the batch used in clinical trials, long-term stability data. The analytical method used has been validated. The results of the batch analysis provide results that meet the required specifications.

Stability data from 3 batches of production scale drugs has been carried out in zone IVB, namely at a temperature of 30°C/75% RH for 36 months and a temperature of 40°C/75% RH for 6 months with results that meet the required specifications.

Forced degradation studies carried out on active substances are considered applicable to finished products because the finished products do not contain excipients. Compatibility with the packaging system is validated based on available stability data. The results of the photostability study showed that the drug was stable when exposed to light.

Conclusion
From the quality aspect, Lokelma oral powder can be considered acceptable.

EFFECTIVE AND SAFETY ASPECTS

Non-Clinical Studies

Based on the summary of non-clinical study results, the following information is provided:

1. Pharmacology
    - Non-clinical development was carried out using sodium zirconium cyclosilicate (ZS) but several pharmacological and toxicological studies with a duration of <14 days were carried out on non-protonated material (designated ZS-9). The differences between ZS and Z-9 are the sodium ion content, particle size and pH of the solution.
    - Pharmacological data (non-GLP) shows that the experimental potassium exchange capacity (KEC) value during the in vitro release test for sodium zirconium cyclosilicate is around 3.2 ± 0.4 mEq/g or an average of 125.5 mg/g.
    - Treatment with ZS-9 did not affect respiration rate or ECG parameters in dogs when administered for 14 days at a total daily dose of up to 4479 mg/kg (1493 mg/kg/tid; study 14250-10), which is equivalent to a ~145g/day dose man. ZS also does not affect qualitative ECG parameters, heart rate, RR or PR intervals or QRS duration when administered for 28 days at doses up to 3000 mg/kg/day or for 270 days at doses up to 2000 mg/kg/day.
2. Pharmacokinetics
    - Because it has an inorganic composition, Sodium Zirconium Cyclosilicate, does not undergo enzymatic metabolism. In addition, due to its insoluble nature and an average particle size of 20 μm (97% >3 μm), it is not a substrate for the transport process so it has no metabolic or cytochrome P450 induction effects and is not absorbed systemically.
    - Lack of absorption was confirmed by whole blood and urine analysis of dogs in which no Zr could be detected after 9 months of administration of Sodium Zirconium Cyclosilicate at a daily dose of 2000 mg/kg/day, equivalent to a human dose of ~65g/day based on a body weight of 60 kg.
    - In rat mass balance studies, 97–99% of a dose of Zr was excreted in feces within 48 hours of administration.

3. Toxicology

- Acute toxicity studies showed no recorded side effects following administration of a single dose of 2000 mg/kg unprotonated Sodium Zirconium Cyclosilicate (ZS-9) in water at a dose volume of 10 ml/kg in rats or dogs.
- Repeated dose toxicity studies in mice and dogs were carried out for a maximum duration of 180 days and 270 days. The only effect of administering sodium zirconium cyclosilicate is related to the pharmacodynamic activity of Sodium Zirconium Cyclosilicate, namely reducing potassium absorption from the GI tract. Rats tolerated sodium zirconium cyclosilicate up to a maximum dose of 2000 mg/kg tid (6000 mg/kg/day) for up to 26 weeks, and dogs tolerated Sodium Zirconium Cyclosilicate at 1000 mg/kg/day for up to 39 weeks. These dose levels are equivalent to human dose levels of approximately 58 g/day (rats) and 32 g/day (dogs). In dogs administration of the highest dose resulted in pharmacodynamic effects, namely the development of clinically significant hypokalemia, degenerative changes and secondary inflammation in the kidneys, and lipid vacuolization in the adrenal cortex.
- The NOAEL value in mice is 6000 mg/kg/day; 3000 mg/kg/day in dogs; and 6000 mg/kg/day in rabbits.
- Sodium Zirconium Cyclosilic did not show genotoxic potential based on *the bacterial reverse mutation test*.
- Sodium Zirconium Cyclosilicate was also found to be hyperplastic or pre-neoplastic in chronic toxicity studies in rats and dogs at human equivalent doses of ~65g/day and due to the lack of systemic absorption and absence of genotoxic potential, Sodium Zirconium Cyclosilicate is considered unlikely to pose a carcinogenic hazard.
- Sodium Zirconium Cyclosilicate did not affect reproductive function in either sex of rats up to a maximum dose level of 6000 mg/kg/day, which is equivalent to a human dose level of approximately 62 g/day.

Based on non-clinical data:
The results of non-clinical studies show that zirconium cyclosilicate is not absorbed systemically, and is not carcinogenic or mutagenic.

Clinical Studies
Evaluation was carried out on 5 supporting studies, namely phase 2 study (ZS-002 study); phase 3 studies (studies ZS-003 and ZS-004 + *extension*study ZS-004E), as well as 1 long-term study with an open-label design without a comparison (study ZS-005).

1. In the *dose escalation* study, administration of sodium zirconium cyclosilicate (ZS) 10g (n=24) 3 times daily (TID) showed the best efficacy compared to doses of 3g (n=24) and 0.3 g (n=12) vs. placebo (n=30) TID (study ZS-002).
    - *mean maximal reduction in serum potassium* [K+] (SK) up to 48 hours at doses of 10g and 3g were 0.92 mmol/L ($p<0.0001$) and 0.43 mmol/L ($p=0.048$), while doses of 0, 3 g did not provide a significant decrease in SK.
    - Other SK observation parameters showed a dose-dependent response with maximum effect at a dose of 10g. ZS 10g vs. placebo shows the results:
        - The time to achieve the first 0.5 mmol/L SK reduction was significantly reduced ($p=0.042$).
        - Percentage of subjects achieving a SK reduction of >1.0 mmol/L at 48 hours after 6 doses: 33.3% vs. 6.7% ($p=0.016$).
        - Decreased urinary potassium excretion until day 2: -23.11% vs. 30.88% ($p<0.002$
2. In the dose ranging study, administration of ZS 10g and 5g showed better efficacy than doses of 2.5g, 1.25g vs. placebo (study ZS-003).
    - Acute phase (48 hours of treatment) administration of 10g vs. 5g vs. 2.5g vs. 1.25g vs. TID placebo shows the results:
        - Percentage of *normokalemic*subjects (normal SK value 3.5-5.0 mmol/L): 86.4% vs. 77.6% vs. 67.9% vs. 51.3% vs. 47.8 ($p<0.0001$)
        - *Mean* decrease in SK from *baseline* at 48 hours after first dose: -0.73 mmol/L vs. -0.54 mmol/L vs. 0.46 mmol/L vs. -0.30 mmol/L vs. -0.25 mmol/L
        - *Median* time to 0.5 mmol/L decrease in SK values (*time to 0.5 mmol/L decrease in SK values*): 22.8 hours ($p<0.0001$) vs. 23.5 hours ($p=0.0137$) vs. 21.4 hours (0.0067) vs. 24.1 hours ($p=0.5278$) vs.

24.8 hours.

- The subacute phase (additional 12 days of treatment after the acute phase, once a day/QD) *showed a better mean number of normokalemic days* at ZS 10g, 5g and 2.5g compared to *placebo*, namely 10.2 vs. 8.2 days (p=0.0338), 9.0 vs. 6.0 days (p=0.0002), and 8.6 vs. 6.2 days (p=0.0096), sequentially.

3. When giving ZS 10g TID (n=258) for the first 48 hours (6 doses) then subjects who achieved normokalemia were continued to the *maintenance* phase receiving ZS 5g (n=45) or ZS 10g (n=51) or ZS 15g (n=56) or placebo (n=86) QD for 28 days, showing better efficacy of ZS than placebo (study ZS-004). ZS 5g vs. 10g vs. 15g vs. *placebo* shows the results:

   - *Mean* SK 4.7544 mmol/L vs. 4.5081 mmol/L vs. 4.3742 mmol/L vs. 5.0603 mmol/L ($p<0.05$)
   - *Mean number of normokalemic days* 13.4 days vs. 13.9 days vs. 16.8 days vs. 7.4 days ($p<0.05$)
   - *Median time to relapse in SK values* can only be measured on ZS 5g vs. placebo i.e. 29 days vs. 19 days.
   - *Extension* study for 11 months with addition/decrease of 5g QD or at least 5g every other day (QOD) based on i-STAT potassium measurements showed the proportion of subjects with SK values $\leq$ 5.1 mmol/L in the range of 77.1% to 87.5% study ZS-004E, n=121)
   - When administering the drug ZS 10g TID until normokalemia followed by 5g QD for 12 months with the addition/decrease of 5g QD or at least 5g QOD based on i-STAT potassium measurements shows the proportion of subjects with SK values < 5.1 mmol/L in the range of 76.7% to 87.2% (study ZS-005, n=746).

4. Safety demonstrated that the drug at the proposed doses (ZS 5g and 10g) was well tolerated.

   - In the acute phase, reported GIT*treatment emergent adverse events* (TEAEs) related to the study drug were 3.2% (ZS 5 g TID) and 2.1% (ZS 10 g TID) with an incidence of >1% being diarrhea, nausea, and vomiting (studies ZS-002, 003, 004).
   - In the *maintenance*phase, TEAEs were reported in 34.5% (ZS 5g QD) and 31.6% (ZS 10g QD) with an incidence of >1% being dyspepsia, constipation, vomiting (studies ZS-003, 004).
   - In the *extension* study, drug-related AEs were *muscle spasms* (2.4%), *peripheral edema* (1.6%), electrocardiogram *QT* prolongation (1.6%), and hypomagnesemia (1.6%) (study ZS004E). In long-term studies, TEAEs associated with the drug were constipation (3.1%), nausea (1.7%), and *peripheral edema* (1.7%) (study ZS-005).

DECISION
Considering the efficacy and safety data mentioned above, it was decided that the registration of the new active substance Lokelma powder for oral suspension was approved with the following **improvements in indications :**

Indications
LOKELMA is indicated for the treatment of hyperkalemia in adult patients.
LOKELMA should not be used as an emergency treatment for life-threatening hyperkalemia because of its delayed onset of action

Attachment
Proposed posology:
Posology
Posology and method of administration
Posology
Adults, including the elderly
Correction phase
The recommended starting dose of Lokelma is 10 g, administered three times a day orally as a suspension in water. When normokalaemia is achieved, the maintenance regimen should be followed (see below).
Typically, normokalaemia is achieved within 24 to 48 hours. If patients are still hyperkalaemic after 48 hours of treatment, the same regimen can be continued for an additional 24 hours. If normokalaemia is not achieved after 72 hours of treatment, other treatment approaches should be considered.
Maintenance phase
When normokalaemia has been achieved, 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.
Serum potassium levels should be monitored regularly during treatment. Monitoring frequency will depend upon a variety of factors including other medications, progression of chronic kidney disease and dietary potassium intake.
If severe hypokalaemia should occur, Lokelma should be discontinued and the patient re-evaluated.

Patients on chronic haemodialysis
For patients on dialysis Lokelma should only be dosed on non-dialysis days. The recommended starting dose is 5 g once daily. To establish normokalaemia (4.0-5.0 mmol/L), the dose may be titrated up or down weekly based on the pre-dialysis serum potassium value after the long inter-dialytic interval (LIDI). The dose could be adjusted at intervals of one week in increments of 5 g up to 15 g once daily on non-dialysis days. It is recommended to monitor serum potassium weekly while the dose is adjusted; once normokalaemia is established, potassium should be monitored regularly (e.g. monthly, or more frequently based on clinical judgement including changes in dietary potassium or medication affecting serum potassium).

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/hepatic impairment No changes from the normal doses are required for patients with renal or hepatic impairment

Paediatric population
The safety and efficacy of Lokelma in children and adolescents (No data are available. Method of administration For oral use. The suspension can be taken with or without food. For instructions on preparation of the suspension, see section 6.6