אוגוסט 2025

רופא/ה נכבד/ה
רוקח/ת נכבד/ה שלום רב,

<u>פרסום עדכון בעלוני התכשיר:</u>
<u>Lokelma 5 g, 10 g, Powder for oral suspension</u>

חברת אסטרהזניקה ישראל מבקשת להודיע על עדכון העלון לרופא ועלון לצרכן בתאריך אוגוסט 2025 בהתאם להוראות משרד הבריאות.

בהודעה זו מצוינים רק הסעיפים בהם נעשו <u>שינויים מהותיים</u> בעלון לרופא ובעלון לצרכן.
התוספות סומנו בצבע כחול, החמרות סומנו בצהוב והמחיקות סומנו בצבע אדום עם קו מחיקה.

<u>הרכב:</u>

SODIUM ZIRCONIUM CYCLOSILICATE 5, 10 G/SACHET

<u>התוויה:</u>

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

<u>עדכונים מהותיים בעלון לרופא:</u>

[...]

4.4 Special warnings and precautions for use

<u>Serum potassium levels</u>

Serum potassium should be monitored when clinically indicated, including after changes are made to medicinal products that affect the serum potassium concentration (e.g. renin-angiotensin-aldosterone system (RAAS) inhibitors or diuretics) and after the Lokelma dose is titrated.

Monitoring frequency will depend upon a variety of factors including other medicinal products, progression of chronic kidney disease and dietary potassium intake.

<u>Hypokalaemia</u>

Hypokalaemia may be observed (see section 4.8). Dose titration as described under maintenance posology may be required in such cases to prevent moderate to severe hypokalaemia. In patients with severe hypokalaemia, Lokelma should be discontinued and the patient re-evaluated.

<u>Worsening of pre-existing heart failure</u>

Patients with pre-existing heart failure, particularly those in whom an increased sodium intake may lead to fluid overload and decompensation, should be monitored for manifestations of worsening heart failure. These may include increased dyspnoea,

oedema and rapid weight gain, and should be managed as per standard clinical practice (see section 4.8).

[...]

4.8 Undesirable effects

Summary of the safety profile

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

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%), nausea (1.6%), diarrhoea (0.9%), abdominal pain/distension (0.5%) 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 established.

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

In a pooled analysis of three placebo-controlled clinical studies of Lokelma in non-dialysis patients, some patients with pre-existing heart failure experienced worsening of heart failure, which occurred at a frequency of 13.6% (30/220) on Lokelma and 5.7% (12/209) on placebo. Most cases resolved with appropriate clinical management without withdrawing Lokelma (see section 4.4).

Tabulated list of adverse reactions

The safety profile of Lokelma was evaluated in clinical trials involving 1,760 patients with 507 patients exposed for one year.

The adverse reactions identified from controlled trials and post-marketing reports are shown in Table 1. Adverse reactions listed below are classified according to frequency and system organ class (SOC). The following convention was used for frequency of adverse 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 trials and post-marketing reports

System Organ class	Very Common	Common
Metabolism and nutrition disorders Gastrointestinal disorders		Hypokalaemia Constipation
General disorders and administration site conditions		Oedema related events
Cardiac disorders	Worsening of pre-existing heart failure	

[...]

5.1 Pharmacodynamic properties

[...]

Study 6 - PRIORITIZE HF

This was a randomised, double-blind, placebo-controlled study aimed to assess if a treatment regimen containing Lokelma would allow Renin Angiotensin Aldosterone System Inhibitor (RAASi) therapies to be up-titrated to target doses at 3 months vs placebo in patients with heart failure and hyperkalaemia or at high risk of developing hyperkalaemia. The primary endpoint of the study was proportion of subjects in the following 4 categories at 3 months: No Angiotensin Converting Enzyme Inhibitors (ACEi)/Angiotensin Receptor Blocker (ARB)/Angiotensin Receptor Blocker/Neprilysin Inhibitors (ARNI) or at less than target dose and no Mineralocorticoid Receptor Antagonist (MRA); ACEi/ARB/ARNI at target dose and no MRA; MRA at less than target dose; MRA at target dose.

Heart failure patients with New York Heart Association (NYHA) Class II-IV with Left Ventricular Ejection Fraction (LVEF) ≤40%, estimated glomerular filtration rate (eGFR) 20-59 mL/min/1.73 m^2 and serum potassium 4.0-5.5 mmol/L were randomised to receive Lokelma or placebo (1:1) for 3 months. RAASi up-titration to guideline-recommended doses was encouraged but not mandated, and Lokelma or placebo dose titrations were performed in parallel to prevent hyperkalaemia.

The study was terminated prematurely during the Covid-19 pandemic due to recruitment challenges and difficulties to ascertain adequate safety monitoring when patients were not able to attend study and laboratory check visits. This resulted in 182 patients randomised as opposed to the planned 280 patients. The premature termination of the study precludes any firm conclusions on the primary and other efficacy measures.

Study 7 - REALIZE-K

This was a Phase 4, prospective, double-blind, randomised-withdrawal trial aimed to determine the efficacy and safety of Lokelma in optimising MRA therapy in patients with heart failure with reduced ejection fraction. The primary endpoint was the occurrence of optimal response, defined as the composite of serum potassium in the normal range (3.5-5.0 mmol/L), on a spironolactone dose of ≥25 mg/daily, without the need of rescue therapy for hyperkalaemia.

This study enrolled adults with established heart failure diagnosis ≥ 3 months duration, LVEF ≤40% with NYHA Class II-IV symptoms who were receiving treatment with an ACEi/ARB/ARNI and a beta-adrenergic receptor blocker (unless contraindicated) at stable

dose for ≥4 weeks. Participation was permitted for those untreated with a MRA and those receiving spironolactone or eplerenone <25 mg once daily.

Patients were screened and entered an open label run in phase with two cohorts. Cohort 1 included patients who had evidence of prevalent hyperkalaemia (defined as serum potassium 5.1-5.9 mmol/L) and eGFR ≥30 mL/min/1.73 m^2. Patients in this cohort received Lokelma to correct potassium to normal range, after which spironolactone was initiated or up-titrated per protocol. Cohort 2 included patients who were at high risk for hyperkalaemia (defined as either a history of serum potassium >5.0 mmol/L within the prior 36 month and eGFR ≥30 mL/min/1.73 m^2 OR serum potassium 4.5-5.0 mmol/L with eGFR 30-60 mL/min/1.73m^2 OR serum potassium 4.5-5.0 mmol/L and age >75 years. These patients had spironolactone initiated or up-titrated towards the target dose; those developing hyperkalaemia received Lokelma to correct potassium to normal range, while those who failed to become hyperkalaemic within 4 weeks were discontinued from the study.

In this trial, use of Lokelma led to a greater occurrence of optimal response for the primary endpoint compared with placebo (OR 4.45 [95% CI 2.89-6.86], p<0.001, estimated percentages 71% vs 36%). These results were consistent when patients receiving 15 g of Lokelma at randomisation were excluded from the analysis. Lokelma also improved secondary endpoints vs placebo: the occurrence of normokalaemia on the randomised dose of spironolactone and without rescue therapy for hyperkalaemia (HK) (OR 4.58 [95% CI 2.78-7.55], p<0.001; estimated percentages 58% vs 23%); the occurrence of spironolactone ≥25 mg/daily dose (OR 4.33 [95% CI 2.50-7.52], p<0.001; estimated percentages 81% vs 50%); time to first HK episode (serum K^+ >5.0 mmol/L) (HR 0.51 [95% CI 0.37-0.71], p<0.001); and time to first decrease or discontinuation of spironolactone dose due to HK (HR 0.37 [95% CI 0.17-0.73], p=0.006).

Study 8 - STABILIZE-CKD

This was a Phase 3, randomised withdrawal, double-blind, parallel-group, placebo-controlled study aimed to assess whether Lokelma, as an adjunct to ACEi/ARB therapy, is superior to placebo in slowing Chronic kidney disease (CKD) progression over time in patients with hyperkalaemia or at risk of hyperkalaemia. Co-primary endpoints were eGFR total slope (from randomisation to end of treatment) and eGFR chronic slope (from 12 weeks after randomisation to end of treatment).

The study enrolled patients with eGFR 25-59 mL/min/1.73 m^2, urine albumin-to-creatinine ratio (uACR) 200-5000 mg/g, and hyperkalaemia (serum potassium [sK+] >5.0 to ≤6.5 mmol/L) on adequate/limited ACEi/ARB therapy or normokalaemia on limited ACEi/ARB therapy. Patients with NYHA class III to IV congestive heart failure at the time of screening or previous history of severe or symptomatic heart failure were excluded from the study.

The study included a screening period, an initiation phase (with up to 72 hr open-label Lokelma for the participants to maintain or achieve normokalaemia), a 3-month run-in phase (where lisinopril or valsartan were expected to be up-titrated to maximal tolerated doses under open-label Lokelma potassium management), an originally planned 24-month randomised blinded maintenance phase (1:1 blinded Lokelma or matching placebo, and both lisinopril or valsartan and Lokelma/placebo were titrated and monitored for efficacy and safety assessments), and a follow-up visit.

The trial was terminated early due to recruitment challenges, resulting in a reduced sample size of 760 randomised patients as opposed to the planned 1360 patients, and shortened

post-randomisation follow-up duration (median ~8 - 9 months, as opposed to the planned 24 months). This precludes any conclusions on eGFR slope and hard renal outcomes.

In a pooled analysis of placebo-controlled clinical studies of Lokelma in non-dialysis patients (PRIORITIZE-HF, REALIZE-K, STABILIZE-CKD), more patients with pre-existing heart failure experienced worsening of heart failure on Lokelma comparing with the ones on placebo (see section 4.8).

[...]

עדכונים מהותיים בעלון לצרכן:

2. לפני השימוש בתרופה

אין להשתמש בתרופה אם:

- אתה רגיש (אלרגי) לחומר הפעיל אשר מכילה התרופה.

אזהרות מיוחדות הנוגעות לשימוש בלוקלמה

ניטור
לפני התחלת הטיפול בתרופה, הרופא או האחות יבדקו את רמות האשלגן בדמך:

- על מנת לוודא כי אתה מקבל את המינון המתאים. המינון יעלה או ירד בהתאם לרמת האשלגן בבדיקות הדם.
- ייתכן והטיפול יופסק במידה ורמות האשלגן בדמך נמוכות מדי.
- ספר לרופא או לאחות אם אתה לוקח תרופות כלשהן העשויות לשנות את רמות האשלגן בדמך, כיוון שיתכן שיהיה צורך לשנות את מינון הלוקלמה. תרופות אלו כוללות תרופות משתנות (תרופות המגבירות את ייצור השתן), תרופות המעכבות את האנזים ההופך אנגיוטנסין (ACE) כגון אנאלפריל (Enalapril), תרופות חוסמות קולטנים לאנגיוטנסין כגון ואלסארטן (Valsartan) (תרופות לטיפול ביתר לחץ דם ובעיות לבביות) ומעכבי רנין כגון אליסקירן (Aliskiran) (תרופות לטיפול ביתר לחץ דם).

במהלך הטיפול בלוקלמה, יש לעדכן את הרופא או האחות אם:

- יש לך הפרעה בפעילות החשמלית של קצב הלב (הארכת מקטע QT), מאחר ולוקלמה מורידה את רמות האשלגן בדמך וזה עשוי להשפיע על קצב הלב.
- עליך לעבור צילום רנטגן, מאחר ולוקלמה יכולה להשפיע על תוצאות הבדיקה.
- אתה סובל מכאב פתאומי או חריף בבטן, מאחר וזה עלול להיות סימן לבעיה שנצפתה עם תרופות הפועלות במערכת העיכול.
- יש לך אי ספיקת לב קיימת. אצל מטופלים מסוימים, תרופה זו עלולה להחמיר מצב זה. סימנים ותסמינים להחמרה של אי ספיקת הלב עשויים לכלול: החמרה בקוצר נשימה; נפיחות ברגליים או בקרסוליים; עלייה פתאומית במשקל. אם אתה חווה אחד מהסימנים או התסמינים הללו, פנה לרופא מיד.

[...]

4. תופעות לוואי

כמו בכל תרופה, השימוש בלוקלמה עלול לגרום לתופעות לוואי בחלק מהמשתמשים. אל תיבהל למקרא רשימת תופעות הלוואי. ייתכן ולא תסבול מאף אחת מהן.

תופעות לוואי שכיחות מאוד (very common) – תופעות שמופיעות ביותר ממשתמש אחד מעשרה:

- החמרה של אי ספיקת לב קיימת.

תופעות לוואי שכיחות (common) – תופעות שמופיעות ב-1-10 משתמשים מתוך 100:

- התחלה של תחושת עייפות, חולשת שרירים או התכווציות שרירים, ייתכן וזה סימן לרמות נמוכות מדי של אשלגן בדם. פנה מיידית לרופא אם תסמינים אלו מחמירים.
- הצטברות נוזלים ברקמות, המובילה לנפיחות במקומות שונים בגוף (לרוב ברגליים ובקרסוליים).
- עצירות.

[...]

העלון המעודכן נשלח למשרד הבריאות לצורך פרסומו במאגר התרופות שבאתר משרד הבריאות: www.health.gov.il וניתן לקבלו מודפס על ידי פנייה לבעל הרישום:

אסטרהזניקה (ישראל) בע"מ, רח' עתירי ידע 1 כפר סבא 4464301.

טלפון 073-2226099 פקס 09-7406527

בכבוד רב,
אריאל מימון
רוקחת ממונה
אסטרהזניקה (ישראל) בע"מ