NCPE Assessment Summary

Sodium zirconium cyclosilicate

(Lokelma ®)

HTA ID: 24039

July 2026

Applicant: AstraZeneca Pharmaceuticals (Ireland) DAC

Sodium zirconium cyclosilicate for the treatment of hyperkalaemia in adult patients*

* Reimbursement is sought in the following subpopulation: adult patients with serum potassium levels ≥ 5.5mmol/L who have advanced chronic kidney disease (stage 3 to 5) and/or heart failure and are being treated with renin angiotensin aldosterone system inhibitors

NCPE
National Centre for Pharmacoeconomics, Ireland

The National Centre for Pharmacoeconomics (NCPE) has issued a recommendation regarding the cost-effectiveness of Sodium zirconium cyclosilicate (Lokelma ®).

Following assessment of the Applicant's submission, the NCPE recommends that sodium zirconium cyclosilicate (Lokelma®), for treatment of hyperkalaemia in patients with serum potassium levels ≥ 5.5 mmol/L who have advanced chronic kidney disease (stage 3 to 5) and/or heart failure and are being treated with renin angiotensin aldosterone system inhibitors, not be considered for reimbursement unless cost effectiveness can be improved relative to existing treatments*

The Health Service Executive (HSE) asked the NCPE to carry out an evaluation of the Applicant's (AstraZeneca Pharmaceutical [Ireland] DAC) Health Technology Assessment of sodium zirconium cyclosilicate (Lokelma®). The NCPE uses a decision framework to systematically assess whether a technology is cost-effective. This includes comparative clinical effectiveness and health related quality of life benefits, which the new treatment may provide and whether the cost requested by the pharmaceutical company is justified.

Following the recommendation from the NCPE, the HSE examines all the evidence which may be relevant for the decision; the final decision on reimbursement is made by the HSE. In the case of cancer drugs the NCPE recommendation is also considered by the National Cancer Control Programme (NCCP) Technology Review Group.

About the National Centre for Pharmacoeconomics

The NCPE are a team of clinicians, pharmacists, pharmacologists and statisticians who evaluate the benefit and costs of medical technologies and provide advice to the HSE. We also obtain valuable support from clinicians with expertise in the specific clinical area under consideration. Our aim is to provide impartial advice to help decision makers provide the most effective, safe and value for money treatments for patients. Our advice is for consideration by anyone who has a responsibility for commissioning or providing healthcare, public health or social care services.

Summary

In September 2025, AstraZeneca Pharmaceuticals (Ireland) DAC submitted a dossier which investigated the comparative clinical effectiveness, cost-effectiveness and budget impact of sodium zirconium cyclosilicate (SZC)/(Lokelma®). SCZ is licensed for the treatment of hyperkalaemia (HK) in adult patients. However, the Applicant submitted a dossier which considered a subpopulation of the licensed population only. This considered the treatment of HK in patients with serum potassium (S-K) levels ≥ 5.5 mmol/L who have advanced chronic kidney disease (CKD) (stage 3 to 5) and/or heart failure (HF) and are being treated with renin angiotensin aldosterone system inhibitor (RAASi) therapy. The Applicant is also seeking reimbursement for the treatment of patients receiving haemodialysis. Patients receiving haemodialysis were not considered in the cost-effectiveness analysis and are therefore outside the scope of the NCPE evaluation. AstraZeneca Pharmaceuticals (Ireland) DAC is seeking reimbursement of SZC on the Hospital and High Tech Drug Arrangement.

HK refers to an elevation of S-K levels that can result from increased potassium intake, insufficient renal clearance of potassium or a shift in potassium from the intracellular to the extracellular space (e.g. due to tissue injury). Patients with CKD, diabetes mellitus and HF are particularly at risk of HK and these conditions often co-exist. Medicines that reduce renal potassium elimination such as RAASis are commonly prescribed in these patient groups as they reduce the risk of kidney failure and cardiovascular mortality and morbidity. HK can limit the optimal use of RAASi therapy in these patients.

Symptoms of HK are non-specific and generally include malaise and muscle weakness or signs of cardiac arrhythmias such as palpitations, bradycardia, or tachycardia. Severe HK represents an acute emergency that must be corrected immediately due to the potential for fatal cardiac arrhythmias. A normal S-K level typically ranges from 3.5 to 5.0mmol/L. There is no universal consensus definition of what S-K level constitutes HK and no standardised definition for grading the severity of HK. The European Resuscitation Council defines HK as mild (S-K level: 5.5 to 5.9 mmol/L), moderate (S-K level: 6.0 to 6.4 mmol/L), or severe (S-K level: ≥ 6.5 mmol/L).

SZC is available as a powder for oral suspension. It preferentially captures potassium in exchange for hydrogen and sodium cations in the gastrointestinal tract to increase faecal potassium excretion and lower S-K levels. For patients who are not on chronic haemodialysis, the recommended dose of SZC is 10g three times a day until normokalaemia is achieved (correction phase). If patients are still hyperkalaemic after 48 hours of treatment the same regimen can be continued for an additional 24 hours. When normokalaemia has been achieved, the minimal effective dose of SZC to prevent recurrence of HK should be established (maintenance phase). A maintenance-phase starting dose of 5g once daily is recommended, with possible titration up to 10g once daily, or down to 5g once every other day, as needed, to maintain a normal S-K level.

In the acute HK setting (correction phase dosing) the Applicant anticipates that SZC will be given following emergency treatments such as IV calcium gluconate, IV insulin in glucose, and nebulised salbutamol (i.e. SZC will be an add-on to standard of care). In the chronic HK setting (maintenance phase dosing), the Applicant considers the comparator to be usual care, defined as the management of HK which consists primarily of RAASi dose reduction (down-titration) or discontinuation of RAASi therapy.

1. Comparative effectiveness of **sodium zirconium cyclosilicate**

Clinical evidence supporting the efficacy and safety of SZC for the treatment of HK in adult patients is informed by a number of randomised controlled trials (RCTs) including ZS-003 (conducted in patients with mild to moderate HK) and ZS-004. Longer term data (up to 12 months) is available from the open label extension of ZS-004 and ZS-005 (a single arm study). Efficacy data from ZS-004 and ZS-005 are used to inform the cost-effectiveness model (CEM) and these studies are described below.

ZS-004 was a phase III, double-blind, RCT evaluating the safety and efficacy of SZC versus placebo in participants with HK (S-K level ≥ 5.1 mmol/L) treated in an outpatient setting. The trial included an initial open-label, correction phase where all participants (n=258) received SZC 10g three times daily for 48 hours. Participants who achieved normokalaemia in the correction phase entered the 28-day maintenance phase where they were randomised in a

4:4:4:7 ratio to receive one of three SZC doses once daily (5g, 10g or 15g) or placebo once daily. There were no protocol-mandated dietary or RAASi restrictions required for participants. Concomitant use of alternative potassium lowering therapies including emergency treatments (e.g. IV calcium gluconate, IV insulin in glucose, and nebulised salbutamol) was prohibited.

The mean age of participants was 64.0 years at baseline. The majority of participants were male (57.8%) and white (83.3%). The mean baseline S-K level was 5.6 mmol/L; 46.1% of participants had a S-K level < 5.5 mmol/L, 38.8% had a S-K level of 5.5 to 5.9 mmol/L, and 15.1% had a S-K level ≥ 6.0 mmol/L. Regarding aetiologies of HK, 69.4% of participants had CKD with an estimated glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2, 36.4% had HF, and 65.9% had diabetes mellitus. The majority of participants (69.8%) were on RAASi therapy. In the correction phase, the median time to normokalaemia was 2.2 hours with 66% of participants achieving normokalaemia at 24 hours and 88% at 48 hours. The primary endpoint was met as there was a statistically significant difference in the mean S-K level during Days 8 to 29 of the maintenance phase in each SZC group compared with placebo (4.5 mmol/L, 4.8 mmol/L and 5.1 mmol/L for the 10g, 5g and placebo groups, respectively). Outcomes in the SZC 15g group are not discussed in this summary, as this dosage regimen is not licensed.

ZS-005 trial was a phase III, open-label, single-arm trial which assessed the ability of SZC to restore normokalaemia in an outpatient setting. Participants initially received SZC 10g three times daily for 24 to 72 hours (correction phase). Participants who achieved normokalaemia were eligible for a subsequent 12-month maintenance phase. Similar to ZS-004, there were no protocol-mandated dietary or RAASi restrictions required for participants and concomitant use of alternative potassium-lowering therapies (including emergency treatments) was prohibited. Baseline characteristics were broadly aligned with those reported for ZS-004. A total of 751 participants were treated in the correction phase with normokalaemia being achieved in 66%, 75% and 78% of participants after 24, 48 and 72 hours, respectively. During the maintenance phase, the majority of participants (88%) maintained normokalaemia (mean S-K level ≤ 5.1 mmol/L) from Days 85 to 365. Among those participants using RAASi at baseline (n=483), 74% were able to maintain the same dose. RAASi down-titration and discontinuations occurred in 14% and 11% of participants,

respectively.

The Review Group note that there is no direct comparative evidence for SZC versus usual care (defined as the down-titration of discontinuation of RAASi therapy) in the chronic HK setting. In addition, the clinical evidence from the ZS-004 and ZS-005 trials does not reflect the treatment pathway for patients with HK in Irish clinical practice. Both trials present the use of SZC as a monotherapy in the outpatient setting with only one-sixth of participants having S-K levels ≥ 6.0 mmol/L. Clinical opinion suggests that, for patients with S-K levels ≥ 6.0 mmol/L, SZC will be used as an add-on to acute HK treatments administered in the emergency department. The trials also enrolled large numbers of patients with S-K levels < 5.5 mmol/L. These patients may not be treated for HK in clinical practice. Furthermore, these trials did not capture the impact of SZC on clinically meaningful outcomes such as mortality, cardiovascular or renal morbidity and health related quality of life. Finally, there is no evidence on the efficacy and safety of SZC beyond 12 months.

Several other randomised studies have also been conducted in specific patient populations. These include:

- DIALIZE, a phase IIIb double blind placebo-controlled study evaluating SZC in the management of HK in patients with end stage renal disease receiving haemodialysis.
- ADAPT, a randomised, open-label, crossover study of SZC to control interdialytic HK following an increase of dialysate potassium.
- REALIZE-K, a phase IV, double-blind, placebo-controlled, randomised-withdrawal trial which assessed the efficacy and safety of SZC to enable optimal dosing of spironolactone in patients with HF with reduced ejection fraction.

2. Safety of **sodium zirconium cyclosilicate**

In the ZS-004 trial, the incidence of treatment-emergent adverse events (TEAEs) during the correction phase was 7.8%; the most common were gastrointestinal disorders including diarrhoea (1.2%), constipation (0.8%), and nausea (0.8%). All were considered mild to moderate in severity. During the maintenance phase, oedema was reported in 2.4% of participants in the placebo group, 2.2% of participants in the SZC 5g group and 5.9% of participants in the SZC 10g group. None of the oedema events were considered related to

study treatment, and most were mild or moderate in severity. Constipation was more common in the placebo group (7.1%) compared to the SZC 5g group (0%) or SZC 10g group (2.0%). Upper respiratory tract infections were less common in the placebo group (1.2%) compared to the SZC 5g group (6.7%) or SZC 10g group (2.0%). Hypokalaemia (S-K level < 3.5mmol/L) occurred in no participants in the placebo and SZC 5g groups and in 9.8% of participants in the SZC 10g group. All cases of hypokalaemia were mild (S-K levels ranging from 3.0 to 3.4 mmol/L) and resolved after the dose of study drug was reduced. Serious adverse events (SAEs) occurred in no participants taking placebo, 11.1% of participants in the SZC 5g group and 3.9% of participants in the SZC 10g group. None of the SAEs were deemed to be related to the study treatment.

The safety profile of SZC in ZS-005 was consistent with previous studies. Adverse events (AEs) occurred in 4.1% and 65.5% of participants in the correction and maintenance phases, respectively. In the 12-month maintenance phase, the most common AEs were hypertension (11.0%), peripheral oedema (9.7%), urinary tract infection (7.9%), nausea (7.5%), constipation (6.4%), anaemia (5.9%), hypokalaemia (5.8%), and upper respiratory infection (5%). SAEs occurred in 21.6% of participants in the maintenance phase; pneumonia (1.9%), congestive cardiac failure (1.5%), chest pain (1.5%), osteomyelitis (1.1%), and acute renal failure (1.1%) were the most frequently reported. Discontinuations due to TEAEs occurred in 13.7% of participants in the maintenance phase.

3. Cost effectiveness of **sodium zirconium cyclosilicate**

The population in the cost effectiveness model (CEM) consists of adult patients with S-K level ≥ 5.5mmol/L who have advanced CKD (CKD stage 3 to 5) and/or HF who are being treated with RAASi therapy. This is a subpopulation of the licensed population. There are three distinct cohorts in the CEM, namely patients with both CKD and HF (henceforth referred to as the CKD + HF cohort), patients with CKD but no HF (CKD only cohort) and patients with HF but no CKD (HF only cohort). A number of baseline characteristics (including age, sex, weight and eGFR) were derived from the ZS-004 and ZS-005 trials. Baseline characteristics not available from the SZC trials (including morbidity profiles, modifiable risk factors and concomitant therapies) were derived from external sources.

Methods

The Applicant implemented a patient microsimulation model. All patients enter the CEM with HK (defined as a S-K level ≥ 5.5mmol/L) and are assumed to be receiving optimal RAASi therapy. Treatment effects were applied directly to the fluctuations of S-K levels as well as changes in RAASi use. S-K levels were also assumed to have a further direct influence on RAASi use. Three RAASi states (optimal dosing, suboptimal dosing, no usage) were modelled to capture change in RAASi use over time.

To simulate the fluctuations of S-K levels over time, S-K levels of each patient are sampled per-cycle according to a mixed effects model fitted to data from the ZS-004 and ZS-005 trials. All patients experience an acute HK event once their S-K ≥ 5.5mmol/L. Other clinical events (hospitalisation, major adverse cardiovascular events (MACE), and death) are captured, with baseline risks assumed equal between treatment arms. These risks are subsequently modified based on S-K levels and RAASi status. CKD and HF progression was also modelled, with rates of CKD progression influenced by RAASi status. A major limitation of the model structure was that change in RAASi use had no impact on S-K levels. Therefore, the impact of usual care in terms of managing S-K levels is not modelled. To address this concern the Applicant added functionality in the CEM to apply a fixed reduction in S-K levels to account for RAASi down-titration or discontinuation. This reduction was based on results of a meta-analysis by Ng et al. which found that mineralocorticoid therapy (a type of RAASi) was associated with an increase in S-K levels in patients with CKD. This functionality was not implemented in the Applicant base case.

The relationship between S-K levels and risk of clinical events (MACE, hospitalisation and death) was based on an analysis of the SPARK study while treatment-specific changes in RAASi use according to different S-K thresholds were informed by ZORA. SPARK is a UK-based retrospective observational study. The ZORA study was an observational cohort study from the US, Japan, and Spain. The Applicant used results from a re-analysis of the ZORA study, excluding data from Spain. Other key treatment effectiveness parameters including baseline risk of clinical events and risk of clinical events linked to RAASi status came from a variety of external sources. It is unclear whether these studies were identified in a systematic manner. Furthermore, combining data from multiple RCTs and observational studies in the CEM introduces a high level of uncertainty due to substantial heterogeneity

across the studies in terms of design, patient populations, study treatments and definition of clinical events.

The Review Group were concerned with the modelling of the usual care arm (RAASi down-titration or discontinuation) in the Applicant base case:

- The long-term S-K trajectories for usual care are informed by short-term data from the placebo arm of the ZS-004 trial which is not representative of usual care in clinical practice.
- The impact of RAASi down-titration and discontinuation in managing S-K levels has not been modelled.

Consequently, the number of acute HK events in the usual care arm greatly exceeds the number in the SZC arm. As a result, the Applicant's cost-effectiveness results are primarily driven by costs associated with treating the high number of acute HK events. The Review Group present an exploratory base case where the fixed reduction to S-K levels was applied to account for RAASi down-titrations or discontinuations. This reduction was only applied to patients whose extrapolated S-K trajectories were informed by the short-term data from the placebo arm of the ZS-004 (patients in the usual care arm and patients in the SZC arm who have discontinued treatment). The Review Group did not apply this reduction to patients on-treatment in the SZC arm as the impacts of RAASi modification on S-K were likely captured in the modelled S-K trajectories, which were informed by ZS-005 where patients were treated with SZC for up to one year.

The Review Group also implemented a number of other changes in the NCPE exploratory base case including removal of a 52-week stopping rule for SZC as this stopping rule is not included in the licence. To avoid double-counting, an additional mortality benefit associated with RAASi use in patients with HF was removed as this benefit was already accounted for in the HF mortality estimates. In addition, health related quality of life values (utilities) for patients in the CKD + HF cohort were based on the lower of the two CKD stage or New York Heart Association class utility values. The Review Group considered that Applicant's base case multiplicative approach (CKD stage utility x NYHA class utility) may underestimate health related quality of life of patients with both CKD and HF.

Results

Deterministic incremental cost-effectiveness ratios (ICERs) generated under the Applicant and NCPE exploratory base case assumptions are shown in Table 1 and Table 2, respectively. In the Applicant base case SZC is dominant as it is less costly and more effective than usual care. The results are primarily driven by costs associated with treating the high number of acute HK events in the usual care arm.

Table 1: Applicant base case incremental cost-effectiveness results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
CKD + HF cohort[b]					
SZC	104,740	2.14	-	-	-
Usual care	121,902	1.71	-17,162	0.42	SZC Dominates[a]
CKD only cohort[c]					
SZC	102,847	3.10	-	-	-
Usual care	129,206	2.63	-26,359	0.47	SZC Dominates[a]
HF only cohort[d]					
SZC	91,012	4.02	-	-	-
Usual care	101,470	2.76	-10,458	1.26	SZC Dominates[a]

CKD: chronic kidney disease, HF: heart failure, HK: hyperkalaemia; ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SZC: sodium zirconium cyclosilicate

Note: Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.

[a] SZC dominates usual care as it is less costly and more effective. The Review Group note that the negative incremental costs are driven by the high number of acute HK events in the usual care arm

[b] CKD + HF cohort : SZC remains dominant in the PSA using 500 iterations (Incremental costs: -€15,039; incremental QALYs: 0.44)

[c] CKD only cohort: SZC remains dominant in the PSA using 500 iterations (Incremental costs: -€23,520; incremental QALYs: 0.48)

[d] HF only cohort: SZC remains dominant in the PSA using 500 iterations (Incremental costs: -€12,283; incremental QALYs: 1.29)

Table 2: NCPE exploratory base case results

Treatments	Total costs (€)	Total QALYs	Incremental costs (€)	Incremental QALYs	ICER (€/QALY)
CKD + HF[a]					
SZC	86,108	2.38	-	-	-
Usual care	69,004	2.06	17,105	0.31	54,531
CKD only[b]					
SZC	92,127	2.89	-	-	-
Usual care	73,832	2.55	18,296	0.34	53,594
HF only[c]					
SZC	64,153	3.47	-	-	-
Usual care	46,588	3.1	17,566	0.37	46,931

CKD: chronic kidney disease, HF: heart failure, ICER: incremental cost-effectiveness ratio; QALY: quality-adjusted life year; SZC: sodium zirconium cyclosilicate

Note: Figures in the table are rounded, and so calculations may not be directly replicable. Discount rate of 4% applied to costs and outcomes.

[a] CKD + HF cohort: Corresponding probabilistic ICER using 500 iterations is €56,368/QALY

[b] CKD only cohort: Corresponding probabilistic ICER using 500 iterations is €53,621/QALY

[c] HF only cohort: Corresponding probabilistic ICER using 500 iterations is €46,331/QALY.

Sensitivity analysis

In the Applicant base case, the probability of cost effectiveness for SZC versus usual care at willingness-to-pay thresholds of €45,000 per QALY and €20,000 per QALY is 100% at both thresholds in all cohorts. In the NCPE exploratory base case the corresponding probabilities are 0% at the €20,000 per QALY threshold in all cohorts, and 2%, 9%, and 35% at the €45,000 per QALY thresholds for the CKD and HF, CKD only, and HF only cohorts, respectively.

It should be noted that in the NCPE exploratory base case considerable uncertainties remain. In particular, the reductions in S-K levels after RAASi down-titration or discontinuation (informed by Ng et al.) in patients being treated with usual care may not be generalisable to the population in the CEM. The risk of RAASi down-titration or discontinuation informed by ZORA is estimated based on a single S-K measurement at the time of a HK event and therefore does not account for differences in S-K levels over time as a result of treatment for HK. The risk of clinical events in patients with both CKD and HF are also likely to be underestimated and there are general concerns with the modelling of mortality. The use of data from multiple external sources introduces a high level of uncertainty.

The Review Group conducted a Price-ICER analysis under the NCPE exploratory base case. A discount of 29%, 27% and 13% on the price to wholesaler of SZC (inclusive of Framework Agreement rebate) would be required for SZC to meet the €45,000 per QALY threshold in the CKD + HF cohorts, CKD only cohorts and HF only cohorts, respectively. A discount of 82%, 79%, and 59% is required to meet the €20,000 per QALY threshold for each respective cohort.

4. Budget impact of SZC

The price to wholesaler of one pack of SZC 5g sachets (pack size: 30) is €245. Treatment course cost estimates account for discontinuations (based on the ZS-005 trial) and are based on the assumption that all patients who discontinue are retreated with SZC if their S-K levels ≥ 5.5 mmol/L. It is uncertain whether these assumptions will be reflective of clinical practice. The mean lifetime treatment cost per patient in the NCPE exploratory base case is €17,332, €19,202 and €23,460 in the CKD + HF, CKD only and HF only cohorts, respectively. It should be noted that the higher costs in the HF only cohort is reflective of the

underestimated mortality rates and hence higher retreatment costs.

The Applicant submitted a budget impact model (BIM) estimating the population of eligible patients and the proportion expected to receive treatment with SZC. Many of the inputs are very uncertain and there is therefore considerable uncertainty associated with budget impact estimates. The eligible patient population in the BIM consists of those with advanced CKD and/or HF, who are receiving RAASi, have HK (S-K level ≥ 5.5 mmol/L) and are at risk of receiving suboptimal RAASi therapy. Patients receiving dialysis were included in the BIM though these patients were excluded from the CEM. The Applicant anticipated the market share of SZC to be 10% in year one increasing to 20% in year five.

The Applicant assumed a maximum treatment duration of 52 weeks with annual discontinuation informed by the ZS-005 trial. Contrary to the approach taken in the CEM, the Applicant assumed no retreatment in the BIM. Under these assumptions the Applicant estimated the five-year cumulative gross and net drug-budget impacts to be €17.12 million each.

A scenario removing the 52-week stopping rule and assuming retreatment was also provided. This broadly aligns with the assumptions in the NCPE exploratory base case. In this scenario the resulting five-year cumulative gross and net drug-budget impacts are an estimated €22.87 million each. When patients receiving dialysis are excluded from the BIM, the five-year cumulative gross and net drug-budget impacts are an estimated €22.61 million each.

Patient Organisation Submission

No patient organisation submissions were received during the course of the assessment.

5. Conclusion

The NCPE recommends that SZC, for treatment of HK in patients with S-K levels ≥ 5.5 mmol/L who have advanced CKD (stage 3 to 5) and/or HF and are being treated with RAASi, not be considered for reimbursement unless cost effectiveness can be improved relative to existing

treatments*

The full licensed population is broader than the subpopulation used to inform the cost-effectiveness analysis and the budget-impact estimates. As part of the reimbursement decision--making process, the HSE may wish to consider how access for this subpopulation might be facilitated.

*Next steps: The NCPE Assessment Report (and) recommendation, will be considered by the HSE when making their decision on reimbursement, while also having regard to the criteria specified in the Health (Pricing and Supply of Medical Goods) Act 2013.
Further information on this process may be found here.