Single Technology Appraisal

Sodium zirconium cyclosilicate for the treatment of persistent hyperkalaemia with a serum potassium level between 5.5 mmol/litre and 5.9 mmol/litre (partial review of TA599) [ID6439]

Committee Papers

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

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Contents:

The following documents are made available to stakeholders:

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NICE National Institute for Health and Care Excellence

Sodium zirconium cyclosilicate for the treatment of persistent hyperkalaemia with a serum potassium level between 5.5 mmol/litre and 5.9 mmol/litre (partial review of TA599) [ID6439]

Draft guidance comments form

Consultation on the draft guidance document – deadline for comments end of day on 26 November 2025 Please submit via NICE Docs.

	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	AstraZeneca UK Ltd.

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	N/A
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	N/A
Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
1	**AstraZeneca feel that the NICE Committee have taken into account the majority of the relevant evidence presented during the appraisal so far, with one key exception:**

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	• Clinical expert opinion on the ZORA validates the study outcomes. Clinical expert opinions state that patients with the same S-K level will be less likely to down-titrate or discontinue RAASi therapy when prescribed sodium zirconium cyclosilicate (SZC), versus patients prescribed no potassium binder. • The ZORA study, clinical experts and additional new evidence presented by AstraZeneca demonstrate that patients are less likely to down-titrate or discontinue RAASi therapy if they are prescribed SZC versus patients prescribed no potassium binder. AstraZeneca have therefore provided new evidence and analyses, as requested by NICE in the draft guidance. See Document [ID6439] SZC_HK_TA599 partial review_Addendum.
2	NICE have asked whether the summaries of clinical and cost effectiveness provide reasonable interpretations of the evidence? **AstraZeneca believe that the summaries in the draft guidance do not provide appropriate representation for the strength of the data presented in the submission.** **Firstly, NICE have requested additional information or evidence that justifies the correlation between serum potassium levels and risk of adverse outcomes, independent of RAAS inhibitor use.** • The SPARK study was conducted specifically to address concerns raised by the committee in TA599[1] in relation to the above correlation. This study adds to those conducted previously which have found a relationship between increased S-K levels and the incidence of long-term clinical outcomes, adjusted for 38 known confounders, including co-medications, comorbidities and RAASi usage, which has been raised as a key concern by the Committee. • NICE state that there may be a relationship between hyperkalaemia and adverse outcomes mediated by reductions in RAASi use, but that there is substantial uncertainty whether there is a causal effect between hyperkalaemia and adverse outcomes that is independent of RAASi use. However, the SPARK study, in addition to other published literature,[2-7] clearly demonstrate the association between S-K levels and adverse outcomes. The SPARK study has been conducted in alignment with the NICE RWE framework[8] and controls for all known confounders, including RAASi use. It is therefore deemed an appropriate and robust data set to demonstrate the association between S-K levels and adverse outcomes. • The impact of RAASi down-titration and discontinuation on patient S-K is accounted for in the model separately, through an S–K reduction of 0.115 mmol/L and 0.230 mmol/L respectively, in alignment with committee preferred assumptions in TA599.[1, 9] • In addition, e-values were calculated to quantify the strength of the unmeasured confounder needed to reverse the observed relationship between S-K and adverse outcomes. Results demonstrated that an unmeasured confounder would need to be simultaneously highly correlated with the clinical outcome and imbalanced between S–K

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	groups to reverse or nullify these findings. For MACE, mortality, and hospitalisations, the CI e-values corresponding to the IRR reported above were [redacted], [redacted] and [redacted], respectively, therefore it is highly unlikely for any remaining unknown confounder to nullify the relationship. • In addition, NICE provide comment on the James et al. (2021)[10] study from the EAG and clinical experts, however, NICE fail to recognise that unlike SPARK, it is not well designed to answer the decision problem. James et al. (2021)[10] assesses long-term S–K variability and time spent in specific S–K cut-offs, whilst the SPARK study aimed to analyse the relationship between individual S–K measurements and the risk of significant clinical outcomes. It is important to note that the James et al. (2021)[10] study does not call into question the association between S-K and adverse outcomes but rather re-confirms the relationship between adverse outcomes and an elevated SK (>5.0 mmol/L), demonstrating the same U-shaped curve recognised by international guidelines[11, 12] and reported by other studies.[3, 13] **Secondly, the NICE committee have requested evidence that justifies the differential stopping or down titration of RAAS inhibitor treatment between the SZC and SoC arm; and an analysis of the rates of stopping or down-titrating RAAS inhibitor treatment per time-unit spent in each serum potassium category (accounting for individuals switching categories).** • The ZORA study and re-analysis clearly demonstrate that patients receiving SZC are less likely to down-titrate or discontinue RAASi inhibitor therapy, versus patients receiving no potassium binder. This has been supported by clinical experts, who stated during the committee meeting that for a given serum potassium level, healthcare professionals may feel more comfortable maintaining RAASi treatment if someone is prescribed a potassium binder. • A reanalysis of the ZORA dataset to accommodate the committee request was explored. Determining exact dates of down-titration and discontinuation cannot be done for this dataset, as RAASi prescriptions generally last at least 30 days (sometimes more), and patients often have stockpiled amounts from earlier treatment cycles, so exact down-titration and discontinuation dates cannot be captured. Additionally, measurements of S-K values during follow-up are limited. Therefore, reanalysis of ZORA to produce an analysis for the rates of stopping or down titrating RAASi treatment per time-unit spent in each serum potassium category was not possible. • As the request of the NICE committee could not be accommodated, AstraZeneca have provided additional data in the accompanying addendum to support decision making. Despite the additional data shared, AstraZeneca feel that that ZORA data has not be accurately assessed and the strength of the data has not been recognised by the Committee.
3	NICE have asked whether the provisional recommendations provide a sound and a suitable basis for guidance to the NHS? **Treatment duration with SZC is varied in NHS clinical practice, particularly across primary and secondary care. As such, AstraZeneca do not believe the recommendations are sound**

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	and a suitable basis for guidance to the NHS, as the NICE Committee have not considered this variation in practice when prescribing SZC and managing hyperkalaemia in patients with CKD stage 3b to 5 and/or HF. • The NICE committee have stated a preferred assumption for lifelong treatment duration for SZC subject to an annual stopping rate), however evidence provided throughout the submission and clinical expert opinion during ACM highlights that there is substantial variation in treatment duration in UK clinical practice. • Treatment duration with SZC is varied in NHS clinical practice, particularly across primary and secondary care, as demonstrated by evidence submitted by AstraZeneca and clinical expert opinion. Although lifetime treatment duration may be reflective of more specialist management, some patients may be treated more episodically in primary care, therefore, the Committees preferred assumption of lifetime treatment is not reflective of care across the UK • AstraZeneca therefore do not believe the Committees assumption of lifetime duration is sound and suitable basis for guidance to the NHS. Despite the data and clinical opinion provided, AstraZeneca are concerned that the Committees decision doesn't take into account the variation in clinical practice across the UK and therefore isn't a reasonable interpretation of the evidence. As a result, AstraZeneca have provided additional data to further support and demonstrate the variation of care seen in primary care setting, provided in the accompanying addendum. **Patients with persistent HK and S-K <6.0 mmol/L have no appropriate treatment options and as such face serious unmet need, unable to manage their HK and maintain an optimal dose of RAASi therapy. A cost-effective willingness to pay threshold of £30,000 per QALY gained with SZC vs. current SoC would be more appropriate.** • Hyperkalaemia is a debilitating and potentially life-threatening condition. In the UK, potassium binders such as SZC are recommended by NICE as an option for treating hyperkalaemia for people with persistent hyperkalaemia and CKD stage 3b to 5 or HF if they have confirmed S-K ≥ 6.0 mmol/L and because of hyperkalaemia are not taking optimised dosage of RAASi treatment. • However, for patients with persistent HK and S-K of ≥5.5–<6.0 mmol/L, current treatment options remain limited to non-pharmaceutical interventions, most commonly down-titration/discontinuation of RAAS inhibitor therapy. • In patients with comorbid CKD or HF, down-titration/ discontinuation of RAASi therapy is associated with worsened long-term health outcomes (hospitalisation, death and end stage kidney disease) compared with patients that maintain RAASi usage.[14-16] • Clinical experts state that waiting until a patient gets to an S-K of ≥6.0 mmol/L puts patients at risk and undue pressure on the NHS, as such, HCPs will continue to down-titrate and discontinue RAASi therapy in this patient population without appropriate treatment to address the treatment need (section B.1.3.7 of the Company Submission).

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	• Therefore, evaluating SZC at the £30K willingness to pay threshold is more reflective of the high unmet need, takes into account the uncaptured benefits of the benefit of SGLT2s (detailed in section B.3.9 of the Company Submission) and the conservative assumptions carried through from TA599 (such as an additional 50% reduction in S-K in the SoC arm following a hyperkaliaemic event) (section B.3.3.3 of Company Submission, response B.2 of EAG clarification questions).
References	1. NICE. Sodium zirconium cyclosilicate for treating hyperkalaemia. NICE technology appraisal [TA599]. 2019. 2. Palaka E, Grandy S, Darlington O, McEwan P, van Doornewaard A. Associations between serum potassium and adverse clinical outcomes: A systematic literature review. Int J Clin Pract. 2020;74(1):e13421. 3. Luo J, Brunelli SM, Jensen DE, Yang A. Association between Serum Potassium and Outcomes in Patients with Reduced Kidney Function. Clin J Am Soc Nephrol. 2016;11(1):90-100. 4. Qin L, McEwan P, Evans M, Bergenheim K, Horne L, Grandy S. #325 Association Between Serum Potassium and Clinical Outcomes in UK Patients with Heart Failure (Poster). European Society of Cardiology2017. 5. Qin L, McEwan P, Evans M, Bergenheim K, Horne L, Grandy S. MO067 The relationship between serum K+ and incidence rates of major adverse cardiovascular events and mortality in UK patients with CKD. (Oral presentation). Nephrol Dial Transplant. 2017;32(3):ii73-4. 6. Collins AJ, Pitt B, Reaven N, Funk S, McGaughey K, Wilson D, Bushinsky DA. Association of Serum Potassium with All-Cause Mortality in Patients with and without Heart Failure, Chronic Kidney Disease, and/or Diabetes. Am J Nephrol. 2017;46(3):213-21. 7. McEwan P, Qin L, Evans M, Horne L, Palaka E, Grandy S. TH-PO1106 Associations Between Serum Potassium and Clinical Outcomes in Patients with CKD in a Real-World Setting (Poster). American Society of Nephrology2017. 8. NICE. NICE real-world evidence framework. Available at: https://www.nice.org.uk/corporate/ecd9/resources/nice-realworld-evidence-framework-pdf-1124020816837. Accessed: 20 December 2024. 9. Ng KP, Arnold J, Sharif A, Gill P, Townend JN, Ferro CJ. Cardiovascular actions of mineralocorticoid receptor antagonists in patients with chronic kidney disease: A systematic review and meta-analysis of randomized trials. Journal of the Renin-Angiotensin-Aldosterone System. 2015;16(3):599-613. 10. James G KJ, Mellström C, Ford KL, Jenkins NC, Tsang C, Evans M, McEwan P. Serum potassium variability as a predictor of clinical outcomes in patients with cardiorenal disease or diabetes: A retrospective UK database study. Clinical Kidney Journal. 2022;15(4):758-70. 11. Mancia G, Kreutz R, Brunström M, Burnier M, Grassi G, Januszewicz A, et al. 2023 ESH Guidelines for the management of arterial hypertension The Task Force for the management of arterial hypertension of the European Society of Hypertension: Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA). J Hypertens. 2023;41(12):1874-2071. 12. Stevens PE, Ahmed SB, Carrero J. KDIGO 2024 Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. Kidney Int. 2024;105(4s):S117-s314. 13. Linde C, Qin L, Bakhai A, Furuland H, Evans M, Ayoubkhani D, et al. Serum potassium and clinical outcomes in heart failure patients: results of risk calculations in 21 334 patients in the UK. ESC Heart Fail. 2019;6(2):280-90. 14. Epstein M. Hyperkalemia constitutes a constraint for implementing renin-angiotensin-aldosterone inhibition: the widening gap between mandated treatment guidelines and the real-world clinical arena. Kidney International Supplements 2016;6:20-28.

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	15. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oetreicher N, Knipsel J. Evaluation of the Treatment Gap Between Clinical Guidelines and the Utilisation of Renin-Angiotension-Aldosterone System Inhibitors. Am J Managed Care. 2015;21:S212-S20. 16. Humphrey TJL, James G, Wittbrodt ET, Zarzuela D, Hiemstra TF. Adverse clinical outcomes associated with RAAS inhibitor discontinuation: analysis of over 400 000 patients from the UK Clinical Practice Research Datalink (CPRD). Clin Kidney J. 2021;14(10):2203-12.

Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Single technology appraisal

Sodium zirconium cyclosilicate for treating hyperkalaemia – partial review of TA599 [ID6439]

Addendum

Company evidence submission

November 2025

File name	Version	Contains confidential information	Date
[ID6439] SZC_HK_TA599 partial review_Addendum [CON]	Final	Yes	26th November 2025

Summary of evidence provided in this addendum

Following the first committee meeting on 8th October, the NICE Committee could not determine the most plausible ICER for SZC in patients with persistent HK < 6.0 mmol/L without further analyses. Therefore, the NICE Committee requested the following:

- Additional information or evidence justifying the correlation between serum potassium (S-K) levels and risk of adverse outcomes, independent of RAASi use
- Evidence that justifies the differential stopping or down titration of RAAS inhibitor treatment between the 2 arms; and an analysis of the rates of stopping or down titrating RAAS inhibitor treatment per time-unit spent in each S-K category, rather than per baseline S-K category (accounting for individuals switching categories over time)
- Updated model functionality to include an analysis in which people in the standard care (SoC) arm take sodium zirconium cyclosilicate (SZC) if their S-K is 6.0 mmol/litre or more. If not possible, a scenario in which the maximum S-K level in the model is capped at 6.0 mmol/litre
- Removal of RRT costs from Kent et al. (2015) estimates for chronic kidney disease stage 4 and 5. If not possible, exploration of other suitable sources (including NHS reference costs) to populate health state costs for chronic kidney disease that does not include RRT costs

In response to the NICE Committee conclusion in the draft guidance, AstraZeneca have also provided new evidence from Prescribing Episode Statistics (PES) data, for patients who have 12, 24 and 36 months of follow-up data available, to demonstrate treatment duration with SZC in clinical practice.

This document therefore provides additional evidence following the committee's request for further information, specifically sharing additional evidence on:

- Further evidence to justifies the differential stopping or down titration of RAAS inhibitor treatment between SZC and SoC arm.
- Updated model functionality to include an analysis in which people in the SoC arm take SZC if their S-K is 6.0 mmol/litre or more.
- CKD health state costs that do not include RRT costs.
- Further evidence to support CS base case on treatment duration with SZC.

Additional evidence to support SPARK study outcomes

NICE request:

- *Additional information or evidence justifying the correlation between serum potassium levels and risk of adverse outcomes, independent of RAASi use*

Additional evidence from the company

The SPARK study, in addition to other published literature,[1-6] clearly demonstrates the association between S-K levels and adverse outcomes. The SPARK study is a robust data set as it has been conducted in alignment with the NICE RWE framework[7] and controls for all known confounders, including RAASi use.

In addition, e-values were calculated to quantify the strength of the unmeasured confounder needed to reverse the observed relationship between S-K and adverse outcomes. Results demonstrated that an unmeasured confounder would need to be simultaneously highly correlated with the clinical outcome and imbalanced between S–K groups to reverse or nullify these findings. For MACE, mortality, and hospitalisations, the CI e-values corresponding to the IRR reported above were [redacted], [redacted] and [redacted], respectively, therefore it is highly unlikely for any remaining unknown confounder to nullify the relationship.

Other than the SPARK study, clinical opinion and the wealth of current published literature[1-6] highlighted in the Company submission, AstraZeneca are not aware of any other additional data sources that justify the correlation between S-K levels and the risk of adverse outcomes. AstraZeneca therefore feel that the data provided to NICE is robust and reflects the evidence base, clearly demonstrating the correlation between S-K levels and risk of adverse outcomes, independent of RAASi use. For further details, please see the company's comments on the in the DG stakeholder form shared.

Additional evidence to support ZORA study outcomes

NICE request:

- *Evidence that justifies the differential stopping or down titration of RAAS inhibitor treatment between the 2 arms; and an analysis of the rates of stopping or down titrating RAAS inhibitor treatment per time-unit spent in each serum potassium category, rather than per baseline serum potassium category (accounting for individuals switching categories over time).*

Additional evidence from the company

A reanalysis of the ZORA dataset to accommodate the Committee's request was explored. However, upon investigating, it has not been possible to determine the exact dates of down-titration and discontinuation from this dataset, as RAASi prescriptions generally last at least 30 days (sometimes more), and patients often have stockpiled amounts from earlier treatment cycles, so exact down-titration and discontinuation dates were not captured in ZORA. Additionally, measurements of S-K values during follow-up are limited. Therefore, reanalysis of ZORA to produce an analysis for the rates of stopping or down titrating RAASi treatment per time-unit spent in each S-K category is not possible. However, AstraZeneca understand why the NICE committee have requested such data and have therefore found alternative data sources to demonstrate the link.

There are differential rates of RAASi down-titration and discontinuation across each potassium stratification in clinical practice for two primary reasons. The first reason is that for patients with identical S-K, patients on SZC have their S-K controlled by the SZC, whereas patients on SoC are having their S-K controlled by RAASi down-titration/discontinuation which is less predictable. The second reason is that clinicians are more likely to maintain RAASi in patients on SZC, as the binder gives them confidence that patients can be protected against hyperkalaemia due to the predictable effect on S-K and the potential option to increase the dose. The latter point can be demonstrated through CONTINUITY.

The CONTINUITY study was a Phase 4, randomised, open-label, multicentre pragmatic trial conducted at 39 sites across six European countries. Eligible participants were adults with CKD (any stage) who were admitted to hospital with documented HK (S-K >5.0 to ≤6.5 mmol/L) and at hospitalisation were not receiving a potassium binder. All patients were treated for their hyperkaliaemic event during their hospital admission and at discharge were either randomised to receive continued treatment for their hyperkalaemia with SZC, or receive no S-K binder. At discharge, clinicians, who had been unblinded as to whether the patient would continue to receive SZC after discharge, made decisions regarding optimisation of RAASi therapy.

At discharge, the group treated with SZC, patients were [redacted] to be prescribed RAASi therapy ([redacted] patients were prescribed ACE/ARBs, and [redacted] patients were prescribed MRAs) compared to those not on a binder. Patients were also [redacted] to be prescribed an optimal dose of RAASi therapy, defined as ≥50% of guideline directed medical therapy dose. A summary of the key data from CONTINUITY is shown in Table 1.[8]

This additional evidence alleviates uncertainty around the ZORA analysis, as it definitively shows an increased probability of SZC patients being prescribed RAASi therapy directly following a hyperkaliaemic event verses SoC in a matched analysis. This relationship was also supported the opinion of the clinical experts at the first committee meeting.

Table 1: CONTINUITY summary data[8]*

	SZC (N=[redacted])	SoC (N=[redacted])
Number and percentage of patients without RAASI, n (%)	[redacted]	[redacted]
Number and percentage of patients with RAASI, n (%)		
Number and percentage of patients on ACE/ARBs		
Number and percentage of patients on MRAs		
Number and percentage of patients on ACE/ARBs and MRAs		
Percentage of patients with ≥50% GDMT of at least one RAASi therapy, n (%)		

Abbreviations: ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; GDMT: guideline directed medical therapy; MRA: mineralocorticoid receptor antagonist; RAASi: Renin-angiotensin-aldosterone system inhibitor

* Further information relating to the CONTINUITY study methodology and results can be found in Astrazeneca. Data on File: CONTINUITY. 2025.[8]

Updated model functionality

NICE Committee request:

- *Updated model functionality to include an analysis in which people in the standard care arm take sodium zirconium cyclosilicate if their serum potassium is 6.0 mmol/litre or more. If not possible, a scenario in which the maximum serum potassium level in the model is capped at 6.0 mmol/litre.*

Additional evidence from the company

Following the committee's request for an updated model, which treats patients in the SoC arm with SZC if their S-K is 6.0 mmol/L or more, AstraZeneca have updated the cost-effectiveness model. A copy has been shared as an Excel document.

In the updated model version, SoC arm patients are initiated on treatment and retreated for an 84-day treatment cycle in an approach consistent with the SZC arm, but with a threshold for treatment set at an S-K of 6.0 mmol/L, rather than 5.5mmol/L. The modelled SZC arm remains consistent with the original model submitted as part of this appraisal. For transparency, an adaptation log for how the model was updated has also been shared.

Base-case results with the updated model, applying the company base case and assumptions are presented in Table 2 for the mixed CKD & HF population. The ICER decreases slightly relative to the base case analysis, as the increase in costs for the SoC arm don't fully offset the additional QALY gains.

Table 2. Results for the mixed CKD & HF population

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
SZC	£45,546	6.938	4.128	£3,872	0.538	0.313	£12,355
SoC	£41,673	6.401	3.815	-	-	-	-

Abbreviations: ICER: incremental cost-effectiveness ratio; Inc.: incremental; LYG: life-years gained; QALYs: quality-adjusted life years; SoC: Standard care; SZC: sodium zirconium cyclosilicate.

CKD health state costs

NICE Committee request:

- *Removal of RRT costs from Kent et al. (2015) estimates for chronic kidney disease stage 4 and 5. If not possible, exploration of other suitable sources (including NHS reference costs) to populate health state costs for chronic kidney disease that does not include RRT costs.*

Additional evidence from the company

The company base case submitted to NICE used costs from Kent et al. (2015)[9], specifically from Table 3 of the paper. These costs taken from the study were inflated to a 2023 cost year using PSS Pay and Prices Index[10], as detailed in the company submission.

These costs have been recalculated using table 2 and supplemental table S4 from Kent et al. (2015), and includes all events listed with the exclusion of dialysis and transplant. This was deemed the most suitable method for stratifying costs by CKD stage, after communication with the publication corresponding author. These costs were then inflation adjusted using the PSS Pay and Prices Index[10] to a 2023 cost year for consistency with the original submission. See Table 3 for CKD costs in the company submission and the updated costs (dialysis and transplant costs removed), with accompanying ICERs for each scenario.

The model conservatively includes the mortality specific costs for CKD within the costs for each health state, which disproportionately favours the SoC arm due to that arm having significantly higher rates of mortality. The costs used in the original submission from Kent et al. are overestimated due to the inclusion of dialysis and transplant costs, however as patients consistently spend more time in each respective health state (CKD stage 3a-5) if treated with SZC vs SoC, due to a combination of lower CKD stage progression, and lower mortality rates from lower average S-K and increased RAASi use. This overestimate disproportionately impacts the SZC arm, so the original base case costs used can be considered as conservative.

Table 3: CKD health state costs

	Kent et al. (original)[9]	Kent et al. (dialysis and transplant costs removed)[9]
CKD stage 3a	£1,354	£657
CKD stage 3b	£1,354	£657
CKD stage 4	£4,741	£733
CKD stage 5	£16,623	£1,014
ICER for the mixed CKD & HF population	£12,495	£12,097

Abbreviations: CKD: chronic kidney disease; HF: heart failure; ICER: incremental cost-effectiveness ratio.

Treatment duration with sodium zirconium cyclosilicate

The committee's preferred base case is to apply a lifelong treatment duration for sodium zirconium cyclosilicate (subject to an annual stopping rate). However, the company have collected additional evidence to demonstrate the variation in treatment duration across the NHS, specifically using patient episode statistics (PES) data.

Additional evidence from the company

As stated in the draft guidance form, treatment duration with SZC is varied in NHS clinical practice, particularly across primary and secondary care. As such, AstraZeneca do not believe the recommendations are sound and a suitable basis for guidance to the NHS, as the NICE Committee have not considered this variation in practice when prescribing SZC and managing hyperkalaemia in patients with CKD stage 3b to 5 and/or HF.

Although AstraZeneca believe the data provided in the original submission coupled with the clinical opinion heard during the Committee Meeting, evidences the variation in care seen in the UK, AstraZeneca have provided an additional data analysis to support.

The following data has been derived from prescribing episode statistics (PES) data for primary care prescriptions of SZC. PES contains NHS patient level longitudinal prescribing data, covering every prescription from primary care in England for the past six years. This is the most appropriate and reflective data available for the chronic hyperkaliaemic population currently being assessed in this appraisal, as secondary care statistics will also include patients treated in the acute setting, where treatment duration is far lower.

The data provided demonstrates the number of patients that are 'Simply Active' on treatment with SZC, where 'Simply Active' is defined as being on treatment in that respective month. The requirement for patient inclusion in this dataset is for patients who have started SZC treatment in primary care at least 36 months prior to the data cut end month of July 2025 (the most recent month of data available), so patients could have the ability to be on treatment in each observed month. The PES data is likely an overestimate of total time on treatment for S-K ≥5.5 - <6.0, as the data is reflective of the more severe S-K ≥6.0 population currently reimbursed. Additionally, we know that a significant proportion of patients will not be continued on SZC in primary care following discharge from secondary care. Full population figures are provided in the accompanying DoF[11], along with a 12-month and 24-month analysis which shows similar results.

At the end of the 36-month analysis only [redacted]% of patients remained on treatment, with [redacted]% being continuously treated patients, and [redacted]% being restarted patients. It is noteworthy that in the PES population only [redacted]% reinitiated treatment over the 36-month data-cut showing that in practice treatment with SZC is not often restarted after discontinuation. Continuous and restart patients are disaggregated by month in the DoF[11].

The active treatment by month observed in PES over 36 months is shown in Figure 1, overlaid with the active treatment observed in the cost-effectiveness model, for the company and EAG preferred base cases. The curves for the PES data and company base case deviate at two timepoints; prior to Month 4 where patients only discontinue treatment in the cost-effectiveness model due to the natural rate of treatment discontinuation, and at month 4, where most patients will discontinue treatment following the initial 3-month treatment cycle. Patients will then reinitiate treatment in the company base case cost-effectiveness model and from month 6 both, curves are relatively consistent, with both curves gradually separating out to month 36. The active patient curve for the EAG base case is consistently and significantly higher than what is observed in clinical practice. This trend is consistent across the 12-month and 24-month data-cuts,[11] demonstrating minimal change in real world treatment practice over the past three years.

Figure 1: Proportion of Simply Active patients on SZC, 36 months[8]

Abbreviations: EAG: external assessment group; CEM: cost-effectiveness model; PES: prescribing episode statistics; SZC: sodium zirconium cyclosilicate.

An area under the curve analysis has been conducted to find the average time on treatment for patients in both the company and EAG base case analyses, for a comparison against the PES statistics, this is presented in Table 4. The average percentage of time spent on treatment in the first three years of the company base case analysis is conservative with regard to observed clinical practice using PES statistics (% higher), whilst the time on treatment in the EAG preferred base case is almost triple (% higher) to that observed in clinical practice. Results for the 12-month and 24-month data-cuts, shown in the accompanying DoF[11] also show a consistent trend, with the company base case aligning more closely with clinical practice, and the EAG preferred base case being significantly higher.

Table 4: Average time spent on treatment[8]

	Average time on treatment in first 36 months	Percentage increase vs PES statistics
PES statistics	%	-
Company base case	%	%
EAG preferred base case	%	%

Abbreviations: EAG: external assessment group; PES: prescribing episode statistics.

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11. Astrazeneca. Data on File: Prescribing Episode Statistics. 2025.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	NHS England Cardiac Services Clinical Reference Group Renal Services Clinical Reference Group

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	Example 1

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We are concerned that this recommendation may imply that ……..	
Cardiac Services CRG feedback	
1	There is a risk that this guidance may be interpreted that there are safety issues with the use of K binders between K 5.5 and 5.9mmol/l and the recommendation should include the text that the decision is based on uncertainty of QALY evidence.
2	Failure to approve for use for heart failure or CKD patients with K 5.5-5.9mmol/l may lead to failure to uptitrate or premature RAASi discontinuation with subsequent increased risk of worsening heart failure, end-stage renal disease, and mortality, outcomes with major QALY losses.
3	Uptitration of HF medication is usually carried out under the supervision of heart failure specialist nurses. Due to caution, is unlikely that continued uptitration above K levels of 5.5 will recommended, leaving a significant proportion of patients undertreated with long term consequences.
4	Has the committee taken this recent meta-analysis into account? Huang N, Xu Y, Liu C, Liu Y, Fan Y, Li Z, Zhang D, Mao H, Chen W. Novel Potassium Binders in Reduction of Hyperkalemia and Optimization of RAAS Inhibitors Treatment in Patients with Chronic Kidney Disease or Heart Failure: A Systematic Review and Meta-analysis. Drugs. 2025 Aug;85(8):1013-1031. doi: 10.1007/s40265-025-02198-6. Epub 2025 Jun 21. PMID: 40542996; PMCID: PMC12321686.
5	Has the committee taken into account these published cost-effectiveness studies? 1. Alcázar-Arroyo R, Crespo-Leiro MG, Bover J, Oliva J, Sequera-Mutiozabal M, Gradari S, Martínez-López A, López-Chicheri B, Vidal-Vilar N, Aceituno S, Cobo M. Cost-effectiveness of sodium zirconium cyclosilicate for the treatment of hyperkalemia in patients with chronic kidney disease or heart failure in Spain. Nefrologia (Engl Ed). 2024 Sep-Oct;44(5):709-720. doi: 10.1016/j.nefroe.2024.10.001. Epub 2024 Oct 28. PMID: 39472184. 2. Tian L, Fu S, Li M, Zhao X, Li H. Cost-effectiveness analysis of sodium zirconium cyclosilicate for treating hyperkalemia among Chinese patients. Front Public Health. 2023 Dec 7;11:1196789. doi: 10.3389/fpubh.2023.1196789. PMID: 38145082; PMCID: PMC10740179.
Renal CRG feedback	
1	Patient groups most at risk of hyperkalaemia are those with CKD, diabetes mellitus and heart failure. The recognised standard pillars of care include 2 pharmacological groups, Renin-Angiotensin-Aldosterone System inhibitors (RAASi) and mineralocorticoid receptor antagonists (MRAs). Approximately 10% of out-patients develop hyperkalaemia after initiating RAASi therapy (Palmer, B.F. and D.J. Clegg, Diagnosis and treatment of hyperkalemia. Cleve Clin J Med, 2017. 84(12): p. 934-942). and combining these therapy groups increases the risk of developing hyperkalaemia further.

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	In patients with serum potassium levels 5.5-6mmol/L we are concerned that RAASi or MRAs cannot be optimised without the option of prescribing sodium zirconium cyclosilicate so dose reduction or discontinue of these therapies is required. This limits treatment in this group of patients increasing risk of mortality particularly as a healthy, low potassium diet is notoriously hard to achieve.
2	There is evidence that the incidence of CKD increases as the level of deprivation increases and more people of ethnic minority groups are living in areas of higher deprivation. ethnicity report UKKA final (1) By optimising RAASi and MRA therapies in patients with a serum potassium 5.5-5.9 mmol/L using sodium zirconium cyclosilicate therapy will enable personalised care and may reduce the risk of CKD and reduce the disparity across deprived groups and ethnic groups.
3	The government's 10-year health plan includes the principle of moving patient care from hospital to community. Prescribing Sodium zirconium cyclosilicate in patients with a serum potassium 5.5-5.9 mmol/L to optimise RAASi and MRA therapy for patients in primary care and patients unable to dialyse successfully would both support this principle.
4.	Prescribing sodium zirconium cyclosilicate in patients with a serum potassium 5.5-5.9 mmol/L will enable continuation of their RAASi and MRAs therapies in primary care reducing the risk of chronic kidney disease progression and hospitalisation due to heart failure. This would support the government's 10-year health care plan principle of moving patient care from sickness to prevention.

Insert extra rows as needed

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Renal Pharmacy Group, part of the UK Kidney Association

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Name of commentator person completing form:	[redacted]

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..
1	We are concerned that without the option of lokelma for use when a patient's potassium levels are 5.5-6mmol/L, healthcare professionals will continue to reduce the dose of RASi or discontinue

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	completely thus causing a potential doubling of mortality as shown in the Epstein 2015 paper. (Epstein M, et al. *Am J Manag Care.* 2015;21(11):S209–S222). Approximately 10% of out-patients develop hyperkalaemia after initiating RAASi therapy (Palmer, B.F. and D.J. Clegg, Diagnosis and treatment of hyperkalemia. Cleve Clin J Med, 2017. 84(12): p. 934-942). From patients we hear how difficult it is to follow a low potassium diet and maintain a healthy diet.
2	With the government's 10 year health care plan principle of moving care from hospital to community, waiting until the potassium is >6mmol/L will require patients to be seen in an acute hospital setting which against this principle and also has an associated cost for this acute admission episode. Enabling earlier use of lokelma could reduce this cost and enable care in the community.
3	With the government's 10 year health care plan principle of moving from treatment to prevention, not enabling patients to continue with their RAASi therapies if they suffer with a hyperkalaemia episode will reverse the prevention and cause more care to be treatment due to progression of chronic kidney disease and hospitalisation due to heart failure.
4	KDIGO 2024 chronic kidney disease guidelines state that hyperkalaemia associated with use of RASi can often be managed by measures to reduce the serum potassium levels rather than decreasing the dose or stopping RASi, thus supporting the principle of earlier use of lokelma. A low potassium diet is hard to achieve and is not compatible with the at least five fruit and vegetable portions a day NHS message.
5	Some areas of England have the ability to prescribe lokelma in primary care, whereas others do not. Not changing the level of potassium at which to prescribe lokelma risks widening this inequality for use of well established disease modifying medications such as RAASi. It is well known that CKD affects the most poorest sectors of society and this inequality needs to be reduced. Kidney health inequalities - Kidney Research UK. From the UKKA disparities report, as the level of deprivation increases, the incidence of kidney failure increases. There is no evidence of a threshold effect: even amongst the least deprived quintiles, there is an increased rate of kidney failure for people in quintile 4 compared to quintile 5.Disparities Report | UK Kidney Association. Those in the most deprived quintiles are less able to follow a low potassium diet as potassium is highest in many processed foods.
6	

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1	I believe that this recommendation is sound guidance for the NHS given the available evidence. The frequency of hyperkalaemia increases inversely with its severity, therefore patients with mild hyperkalaemia represent the highest frequency group. On this basis, lowering the threshold for initiation of sodium zirconium cyclosilicate for patients with mild hyperkalaemia (5.5 – 5.9 mmol/l) would have a major impact on NHS services in both primary and secondary care.
2	I believe that the summaries of the evidence related to clinical and cost effectiveness are clear and have included additional studies not presented in the submission. Identifying 'persistent hyperkalaemia' requires serial blood monitoring and it is difficult to interpret findings if the data set is not robust. Conclusions based on single results or baseline results are also difficult to interpret and risks bias.
3	With regard to patients with chronic kidney disease, I agree that limiting treatment duration to 12 weeks is likely to result in a rebound of hyperkalaemia if RAAS inhibitor treatment is ongoing and particularly if it has been up-titrated.
4	Dialysis patients were included in the scope of this submission, but have been excluded from this guideline on the basis that this would be regarded as emergency treatment. Dialysis patients were also excluded from NICE TA599. This patient group is at highest risk for hyperkalaemia and there are some circumstances where potassium binders may be life-saving (e.g. bridge to vascular access procedure). Exclusion of dialysis patients in both NICE treatment guidelines (with exception during pandemic) pertaining to the use of this effective technology could be perceived to be discriminatory.
5	
6	

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	Please read the checklist for submitting comments at the end of this form. We cannot accept forms that are not filled in correctly. The Appraisal Committee is interested in receiving comments on the following: • has all of the relevant evidence been taken into account? • are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence? • are the provisional recommendations sound and a suitable basis for guidance to the NHS? NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations: • could have a different impact on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology; • could have any adverse impact on people with a particular disability or disabilities. Please provide any relevant information or data you have regarding such impacts and how they could be avoided or reduced**.**
Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	Princess of Wales Hospital- Dr Aaron Wong, Cardiologist

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NICE National Institute for Health and Care Excellence

Sodium zirconium cyclosilicate for the treatment of persistent hyperkalaemia with a serum potassium level between 5.5 mmol/litre and 5.9 mmol/litre (partial review of TA599) [ID6439]

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Disclosure Please disclose any funding received from the company bringing the treatment to NICE for evaluation or from any of the comparator treatment companies in the last 12 months. [Relevant companies are listed in the appraisal stakeholder list.] Please state: • the name of the company • the amount • the purpose of funding including whether it related to a product mentioned in the stakeholder list • whether it is ongoing or has ceased.	Received speaker fees and consultations fees from Astra Zeneca (AZ). Invited by AZ to give lectures to healthcare professionals in Asia (Hong Kong, Taiwan, Singapore, Malaysia), Middle East, India, and Europe. Combination of promotional and non-promotional talks. Received around £20k of honorarium in the last 12 months from AZ. At the time of writing this report, there are no further scheduled and agreed speakers' engagement with AZ.
Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	No link to tobacco industry.
Name of commentator person completing form:	Aaron Wong

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
	NICE has not made a positive recommendation for SZC or patiromer with persistent HK with S-K 5.5-<6.0 due to lack of clinical data linking S-K and long term clinical outcomes. Lack of clinical evidence to adequately demonstrate the SZC usage allows reinitiation, up titration or maintenance/optimisation of RAASi dosage, and inadequate clinical evidence to demonstrate the relationship between RAASi dosage and clinical outcomes.

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1	HK has been demonstrated to increase mortality when S-K rises above 5.0 in patients with HF, CKD and diabetes mellitus (Collins AJ, Pitt B, Reaven N, et al. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *Am J Nephrol*. 2017;46(3):213-221. P. Rossignol *et al. Eur J Heart Fail*, 2020;22(8):1378-1389, took another step further, by assessing the interplay between hyperkalemia and RAASi use, dose and discontinuation, and their association with all-case or CV death in patients with chronic heart failure. 9222 patients from the ESC-HFA-EORP Heart failure Long Term registry were included in the analysis. They concluded that HK is a risk marker for RAASi discontinuation, which lead to adverse outcome in patients with chronic heart failure. Therefore, the long term benefit of K binder is not only limit to reduce risk of HK-related mortality and admission, but link to percentage of optimal RAASi doses prescribed, which translate into cardiovascular outcome (Mortality and hospitalization for heart failure). Patients with S-K of 5.5-<6.0 represents a vulnerable group. A cohort of patients who are likely to have their RAASi (GDMT) reduced or discontinued (Epstein M, Reaven NL, Funk SE, et al. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care*. 2015;21(suppl 11):S212-S220. Such practice will contradict international guidelines and expert opinions, where RAASi doses are recommended to be up titrated to maximal tolerable dose; and down titration or discontinuation of RAASi should be the last resort. Recommendation from NICE for not treating HK with S-K between 5.5-5.9 will create confusion and hesitancy to deliver optimal cardiac and renal care in the UK. (Burton JO, Coats AJS, Kovesdy CP, et al. An international Delphi consensus regarding best practice recommendations for hyperkalaemia across the cardiorenal spectrum. *Eur J Heart Fail.* 2022;24(9):1467-1477.)
2	I have concern that by not recommending treatment for HK for patients with S-K of 5.5-<6.0 will leave a therapeutic gap in patients with HF and CKD. Where patients are likely to worsen (Epstein M, Reaven NL, Funk SE, et al. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care.* 2015;21(suppl 11):S212-S220. and readmitted (Svensson MK, Murohara T, Lesén E, et al. Hyperkalemia-related reduction of RAASi treatment associates with more subsequent inpatient care February 27, 2024. *Nephrol Dial Transplant.* 2024. https://doi.org/10.1093/ndt/gfae016
3	In addition to the HARMONIZE Extension trial (Spinowitz BS, Fishbane S, Pergola PE, et al. Sodium zirconium cyclosilicate among individuals with hyperkalemia: a 12-month phase 3 study. *Clin J Am Soc Nephrol.* 2019;14(6):798-809), REALIZE K, randomised control trial demonstrated that SZC can allow patients to initiate and maintain on guideline directed RAASi (Kosiborod MN, et al. *J Am Coll Cardiol*. 2025;85(10):971-984), these findings are consistent with the real world evidence, ZORA Meta-analysis (Rastogi A et al, Clin Kidney J. 2024 Mar 25;17(5):sfae083.doi: 10.1093/ckj/sfae083. eCollection 2024 March. Therefore, there are clinical evidence to show that SZC usage allows optimisation of RAASi.
4	The appraisal has not taken into the account of costs of leaving treatment gap of those with S-K of 5.5-<6.0. Patients will need to visit GP more frequently for S-K monitoring, likely to present to GP

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	or hospital with worsening Sx and severe hyperkalaemia. May the committee consider looking at cost effectiveness paper published in Europe for reference? (Roberto AA et al. Nefrologia (Engl Ed). 2024 Sep-Oct;44(5):709-720.doi: 10.1016/j.nefroe.2024.10.001. Epub 2024 Oct 28.), similar cost effectiveness were also observed in Singapore in patients with S-K>5.5, treated with SZC (Chay et al. Nephrology 2024. DOI: 10.1111/nep.14284) and in Kuwait (Gihan H Elsisi et al. Journal of Medical Economics 2024, 27:1, 253-265, DOI: 10.1080/13696998.2024.2314930)
5	
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Insert extra rows as needed

Checklist for submitting comments

- Use this comment form and submit it as a Word document (not a PDF).
- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
- Combine all comments from your organisation into one response. We cannot accept more than one set of comments from each organisation.
- Do not paste other tables into this table – type directly into the table.
- In line with the NICE Health Technology Evaluation Manual (sections 5.4.4 to 5.4.21), if a comment contains confidential information, it is the responsibility of the responder to provide two versions, one complete and one with the confidential information removed (to be published on NICE's website), together with a checklist of the confidential information. Please underline all confidential information, and separately highlight information that is submitted as 'confidential [CON]' in turquoise, and all information submitted as 'depersonalised data [DPD]' in pink. If confidential information is submitted, please submit a second version of your comments form with that information replaced with asterixis and highlighted in black.
- Do not include medical information about yourself or another person from which you or the person could be identified.
- Do not use abbreviations.
- Do not include attachments such as research articles, letters or leaflets. For copyright reasons, we will have to return comments forms that have attachments without reading them. You can resubmit your comments form without attachments, it must send it by the deadline.
- If you have received agreement from NICE to submit additional evidence with your comments on the draft guidance document, please submit these separately.

Note: We reserve the right to summarise and edit comments received during consultations, or not to publish them at all, if we consider the comments are too long, or publication would be unlawful or otherwise inappropriate.

Comments received during our consultations are published in the interests of openness and transparency, and to promote understanding of how recommendations are developed. The comments are published as a record of the comments we received, and are not endorsed by NICE, its officers or advisory committees.

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Organisation name – Stakeholder or respondent (if you are responding as an individual rather than a registered stakeholder please leave blank):	[Insert organisation name]

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Please disclose any past or current, direct or indirect links to, or funding from, the tobacco industry.	None
Name of commentator person completing form:	Steven Oliver

Comment number	**Comments** Insert each comment in a new row. Do not paste other tables into this table, because your comments could get lost – type directly into this table.
Example 1	We are concerned that this recommendation may imply that ……..

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1	Non=steroidal mineralocorticoid receptor antagonists (like fineronone) are also regularly used to reduce the risk of kidney function decline. They are also associated with hyperkakalaemia. The evidence focuses on RAAS inhibitors.
2	When discussing the control of potassium levels in the 5.1 to 5.9 range there was no recognition of the psychological impact. Control of levels by diet is difficult and if levels are increasing due to taking medicines rather than diet it can lead to great uncertainty. GP's have difficulty gauging how often to test patients in the absence of clear symptoms. GP would appreciate clear guidance on what to advise a patient with a level at say 5.9. Unnecessary Emergency department admissions an blood tests may happen in the absence of guidance.
3	In economic modelling it only seemed to take into account dialysis (RRT) costs. Other costs could include emergency admissions, inpatient stays, pressure on primary care including visits and blood tests,
4	There seemed to be no mention of side effects from the long terms use of Sodium zirconium cyclosilicate.
5	
6	

Insert extra rows as needed

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- Complete the disclosure about funding from the company and links with, or funding from, the tobacco industry.
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- Do not include medical information about yourself or another person from which you or the person could be identified.
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Single Technology Appraisal

Sodium zirconium cyclosilicate for the treatment of persistent hyperkalaemia with a serum potassium level between 5.5 mmol/litre and 5.9 mmol/litre (partial review of TA599) [ID6439]

Comments on the draft guidance received through the NICE website

Name	[redacted]
Organisation	CSL Vifor
Conflict	N/A
Comments on the DG:	

Has all of the relevant evidence been taken into account?
No.
The current Lokelma Summary of Product Characteristics (SmPC) from the European Medicines Agency (EMA)1 includes 3 additional randomised, double-blind, placebo-controlled studies of sodium zirconium cyclosilicate in patients with heart failure (PRIORITIZE HF and REALIZE-K) or chronic kidney disease (STABILIZE-CKD). All 3 studies included patients within the scope of this review i.e. with serum potassium levels between 5.5 mmol/litre and 5.9 mmol/litre.
The SmPC states that 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 (13.6% (30/220)) comparing with the ones on placebo (5.7% (12/209)). Most cases resolved with appropriate clinical management without withdrawing Lokelma.
'Worsening of pre-existing heart failure' has been added to the table listing adverse reactions in clinical trials and post marketing reports, with a frequency of 'Very Common (≥ 1/10)'.
In addition, 'Worsening of pre-existing heart failure' has been added to the 'Special warnings and precautions for use' section of the SmPC stating that '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'.

1 Lokelma EMA Summary of Product Characteristics
https://www.ema.europa.eu/en/documents/product-information/lokelma-epar-product-information_en.pdf

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

In the event that the UK Lokelma SmPC is updated to reflect the current EMA document it may be prudent to ensure the summaries of clinical and cost effectiveness in the NICE guidance are consistent with the product labelling.
Given its frequency, it would be appropriate to capture the costs and consequences of worsening of heart failure associated with sodium zirconium cyclosilicate in the adverse event section of the economic model.

Are the recommendations sound and a suitable basis for guidance to the NHS?

In addition to addressing the areas of uncertainty identified in the draft guidance, the impact of worsening heart failure associated with sodium zirconium cyclosilicate treatment should be considered when formulating guidance on its use in patients with pre-existing heart failure.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of age, disability, gender reassignment, pregnancy and maternity, race, religion or belief, sex or sexual orientation?

No.

EAG addendum

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Sodium zirconium cyclosilicate for treating hyperkalaemia (partial review of TA599) [ID6439]: EAG critique of the company draft guidance response

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 171850

Completed 9th January 2026

CONTAINS CONFIDENTIAL DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

1 BACKGROUND

Following the National Institute for Health and Care Excellence (NICE) first appraisal committee meeting (ACM1), NICE published draft guidance and invited comments on this guidance from stakeholders.[1] In addition to comments on the draft guidance, the company (AstraZeneca) provided an addendum which it considered provided:

1. additional information or evidence relating to the correlation between serum potassium (S-K) levels and risk of adverse outcomes, independent of renin-angiotensin-aldosterone system inhibitor (RAASi) use
2. additional information or evidence relating to the differential stopping or down titration of RAASi treatment between sodium zirconium cyclosilicate (SZC) and standard of care (SoC) arm and an analysis of the rates of stopping or down titrating RAASi treatment per time-unit spent in each S-K category, rather than per baseline S-K category (accounting for individuals switching categories over time)
3. updated model functionality to include an analysis in which people in the SoC arm take SZC if their S-K is 6.0 mmol/litre or more
4. additional information or evidence relating to chronic kidney disease (CKD) health state costs that do not include renal replacement therapy (RRT) costs
5. additional information or evidence relating to support company submission (CS) base case on treatment duration with SZC.

The EAG critique of the addendum proved by the company is provide in Sections 2.1 to 2.5. The updated cost-effectiveness results using the EAG base case assumptions and scenarios are shown in Section 3.

2 EAG CRITIQUE OF INFORMATION PROVIDED IN THE COMPANY ADDENDUM

2.1 Correlation between S-K levels and risk of adverse outcomes, independent of RAASi use

The company has not provided any additional evidence to the SPARK study[2] evidence previously provided.

As stated in the original EAG report, the EAG considers that the SPARK study does not provide robust evidence of a correlation between persistent S-K and adverse outcomes or how reducing S-K levels with a potassium binder would affect the risk of adverse outcomes.

2.2 *Differential stopping or down titration of RAASi treatment SZC and SoC arm and an analysis of the rates of stopping or down titrating RAASi treatment per time-unit spent in each S-K category, rather than per baseline S-K category (accounting for individuals switching categories over time)*

For patients with identical S-K, the company considers that the probability of down-titrating/discontinuing RAASi will differ by SZC treatment status because as stated in the company addendum (page 4):

1. Patients who receive SZC have their S-K controlled through treatment whereas patients who receive SoC have their S-K controlled by RAASi down-titration/discontinuation RAASi which is "less predictable".
2. Clinicians are more likely to maintain RAASi dosages for patients receiving SZC as they are more confident that patients are protected against hyperkalaemia (as demonstrated in the CONTINUITY trial[2,3]).

The EAG considers that:

1. It is not clear what the company mean when they describe the control of S-K as being "less predictable" for patients receiving SoC and why this would impact RAASi use for patients with the same S-K. The EAG agrees that patients receiving SoC are more likely to experience an increase in S-K over time than patients treated with SZC and subsequently have a higher probability of RAASi discontinuation/down-titration. However, this argument only supports the assumption that SZC impacts RAASi use through changing/stabilising S-K as opposed to any independent effect.

   The committee considered that the EAG's approach "did not account for changes in S-K levels over time" (draft guidance, page 15). The EAG highlights that in the cost effectiveness model, the probability of RAASi discontinuation/down-titration differs according to a patient's S-K in each model cycle (which decreases once patients initiate SZC and increases if they discontinue). The effect of changes to S-K over time on RAASi use are therefore accounted for. The company's assumption that mean S-K remains constant over time (from Day 29 onwards for patients receiving SZC and Day 4 onwards for patients receiving SoC) may underestimate the benefit of SZC if S-K is expected to increase over time for patients receiving SoC but stabilise for patients treated with SZC. However, the EAG considers that the effect of changes to S-K over time on RAASi use should be modelled explicitly rather than assuming SZC impacts RAASi use without changing S-K.

2. CONTINUITY trial data suggests that after hyperkalaemia has been treated with SZC in hospital, [redacted]. The company consider that CONTINUITY trial data demonstrates that SZC treatment impacts the willingness of clinicians to prescribe RAASi and therefore patients with identical S-K can be expected to have different probabilities of RAASi discontinuation/down-titration if treated with SZC or not.

   CONTINUITY trial data captures RAASi use for patient who attend hospital and have S-K levels between S-K >5.0 to ≤6.5 mmol/L but are not currently receiving SZC. The EAG questions whether this evidence can be used to support different probabilities of RAASi down-titration/discontinuation for patients with persistent SK ≥5.5 to <6.0mmol/L who are already receiving RAASi. Even if it is accepted that a behavioural effect exists, the difference in RAASi use between CONTINUITY trial cohorts is much

smaller than the difference in RAASi discontinuation probabilities between ZORA study[4] cohorts.

The EAG cautions that the comparison of RAASi use at discharge between CONTINUITY trial cohorts is descriptive only, so it is unclear if observed differences are statistically significant. Furthermore, baseline patient characteristics were not reported so it is not known if differences in RAASi use reflect differences in S-K, CKD stage or other relevant characteristics.

The EAG considers that the company has not provided robust evidence that SZC impacts RAASi use independent of S-K. The EAG therefore maintains the view that the probability of RAASi down-titration/discontinuation in the cost effectiveness model should differ by S-K group only (not both SZC treatment status and S-K group).

2.3 Updated model functionality to include an analysis in which people in the SoC arm take SZC if their S-K is 6.0 mmol/litre or more

The company did not provide any information as to how the clinical benefit of SZC treatment (decrease in S-K) was modelled for patients receiving SoC when S-K ≥6.0 mmol/L. In the cost effectiveness model provided by the company, it appears that upon initiation of SZC (when S-K ≥6.0 mmol/L), S-K decreases to the average S-K for patients initially treated with SZC. The EAG considers that this a reasonable assumption as the average S-K value is similar to that for patients receiving SZC in TA599.[5]

As expected, the change in cost effectiveness results is small given that [redacted] patients in the SoC arm experience S-K levels ≥6.0mmol/L. As noted in Section 6.4.1 of the original EAG report, if average S-K levels are expected to increase over time, a substantially higher proportion of patients may be eligible to receive SZC. Scenarios that explored different S-K trajectories over time for patients treated with SoC would therefore be informative.

2.4 CKD health state costs health state costs that do not include RRT costs

At the request of the NICE appraisal committee, CKD health state costs have been recalculated by the company with the exclusion of dialysis and transplant costs.

The EAG considers that the approach taken by the company to recalculate health state costs was reasonable.

The updated cost-effectiveness results using the EAG base case assumptions and scenarios are shown in Section 3 (only the CKD and mixed heart failure (HF)/CKD populations are affected by the new costs so the HF only population is not shown).

2.5 Treatment duration with SZC

The NICE committee's preferred base case is to apply a lifelong treatment duration for SZC (subject to an annual stopping rate). However, the company has collected additional evidence to demonstrate the variation in treatment duration across the NHS, specifically using patient episode statistics (PES) data.

The company consider that a lifetime SZC treatment duration is not appropriate as it does not reflect the variation in treatment duration observed in clinical practice. However, the company has not explained why their base case assumption of a 12-week SZC treatment duration (applied to all patients) better reflects patient heterogeneity than assuming a lifetime treatment duration.

The company provided PES data for primary care prescriptions of SZC in the NHS for patients with S-K ≥6.0 mmol/L. The company consider that over 36 months, the average time on treatment in the company base case approximates the average time on treatment from the PES data.

No information was provided by the company as to the S-K value of patients when they initiated SZC, their S-K value when SZC was discontinued and the reason for discontinuation (e.g., starting dialysis or death). The company appear to assume that all patients in the dataset have received SZC for persistent/chronic hyperkalaemia on the basis that data is from primary care settings. However, the substantial decrease in the proportion of patients remaining on treatment at month 2 ([redacted]%) suggests that a large proportion of patients may have received SZC for, or after, an acute HK event. It is not clear from the information presented whether the dataset includes patients who were treated for acute hyperkalaemia in the secondary care setting and subsequently were prescribed SZC in the primary care setting to ensure normokalaemia is achieved.

The high rate of SZC discontinuation (and low rate of reinitiation) observed in the PES data is contrary to the clinical advice received by the EAG and the Committee that upon discontinuation of SZC, S-K will increase and patients may return to persistent hyperkalaemia. Without further information that confirms the population in the PES data received SZC for persistent hyperkalaemia only and an explanation as to why so many patients discontinued SZC early on in follow-up, the EAG considers that a lifetime treatment duration is more appropriate than a fixed 12-week treatment duration.

3 SCENARIO ANALYSES

NICE requested the following scenario analyses from the EAG:

1. deterministic cost effectiveness results for CKD population with new company CKD health state costs

2. deterministic cost effectiveness results for mixed CKD and HF population with new company CKD health state costs.

The results of the scenario analyses are provided in Table 1 and Table 2.

Table 1 Deterministic cost effectiveness results for CKD population with new company CKD health state costs: SZC versus standard care

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£15,583**	**-**
R1a) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: SZC values								
R1b) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: standard care values								
R2) Lifetime SZC treatment duration								
R3) Probability of up-titration informed by ZORA study subgroup analysis								
R4) Eligible to return to “max” RAASi state 4 weeks after discontinuation/down-titration								
S1) S-K has no effect on the risk of MACE, hospitalisation or mortality								
B1. EAG exploratory base case (R1a, R2-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£37,633**	**£22,050**
B2. EAG exploratory base case (R1b, R2-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£58,100**	**£42,517**
C1. B1+S1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£47,829**	**£32,246**
C2. B2+S1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£90,298**	**£74,715**

CG=clinical guideline; CKD=chronic kidney disease; EAG=External Assessment Group; ICER=incremental cost effectiveness ratio; MACE=major adverse cardiovascular event; QALYs=quality-adjusted life year; RAASi=renin–angiotensin–aldosterone system inhibitors; S-K=serum potassium; SZC=sodium zirconium cyclosilicate

Table 2 Deterministic cost effectiveness results for mixed CKD and HF population with new company CKD health state costs: SZC vs standard care

Scenario/EAG revisions	SZC		Standard care		Incremental		ICER (£/QALY)	Change from base case
	Cost	QALYs	Cost	QALYs	Cost	QALYs		
A1. Company base case	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£12,097**	**-**
R1a) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: SZC values								
R1b) Probabilities of RAASi down-titration/discontinuation for each S-K group equivalent by treatment: standard care values								
R2) Lifetime SZC treatment duration								
R3) Probability of up-titration informed by ZORA study subgroup analysis								
R4) Eligible to return to “max” RAASi state 4 weeks after discontinuation/down-titration								
S1) S-K has no effect on the risk of MACE, hospitalisation or mortality								
B1. EAG exploratory base case (R1a, R2-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£29,475**	**£17,378**
B2. EAG exploratory base case (R1b, R2-R4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£45,895**	**£33,798**
C1. B1+S1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£36,758**	**£24,661**
C2. B2+S1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	**£70,523**	**£58,426**

CG=clinical guideline; CKD=chronic kidney disease; EAG=External Assessment Group; HF=heart failure; ICER=incremental cost effectiveness ratio; MACE=major adverse cardiac event; QALY=quality adjusted life year; RAASi=renin–angiotensin–aldosterone system inhibitor; S-K=serum potassium; SZC=sodium zirconium cyclosilicate

4 REFERENCES

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal

Sodium zirconium cyclosilicate for treating hyperkalaemia – partial review of TA599 [ID6439]

Addendum

Company evidence submission

January 2026

File name	Version	Contains confidential information	Date
[ID6439] Updated NICE scenarios addendum post ACM2	Final	Yes	23rd January

NICE request 16th January (post ACM 2)

For the evaluation of sodium zirconium cyclosilicate (SZC) for hyperkalaemia [ID6439], the Committee was able to determine its preferred approach from the external assessment group (EAG) or company base case/scenarios, with the exception of the assumption on differential renin-angiotensin-aldosterone system inhibitor (RAASi) down titration between the treatment arms (Table 1). For this assumption, the Committee have asked whether a scenario can be run in which the company's rates by treatment arm are run for the first three treatment cycles (to reflect that there may be a difference at the point of initiation) and then to apply the ZORA no-binder (standard of care [SoC]) rates in both modelled treatment arms for the remainder of the model.

Table 1. Updated NICE Committee assumptions

Assumption	
Differential RAASi discontinuation by treatment arm	New approach requested. Use company differential rates by treatment arm using ZORA data first 3 model cycles (12-weeks) then use EAG single rate across both treatment arm rest of model duration using SoC estimates from ZORA
Treatment duration	Use EAG assumption – lifelong with annual stopping rate
SZC treatment in standard care arm	Use company post-consultation scenario- assumes people in SZC move to standard care arm if SZC above 6
S-K effect on adverse outcomes	Company base case using SPARK data
RAASi model algorithm	Keep as company/EAG base case- at baseline all people receiving optimal dose and after discontinuation return to optimal dose
CKD health state costs	Use company post-consultation scenario Kent data with RRT costs removed
Probability of up-titration	Use EAG assumption based on ZORA re-analysis not Luo
Time for return to "max" RAASi state	Use EAG assumption eligible to return to max RAASi state after 4-weeks

Abbreviations: CKD: Chronic kidney disease; EAG: External assessment group; NICE: National Institute for Health and Care Excellence; RAASi: Renin-angiotensin-aldosterone system inhibitors; RRT: Renal replacement therapy; SoC: Standard of care; S-K: Serum potassium; SZC: Sodium zirconium cyclosilicate.

Summary of the scenarios provided in this addendum

Based on the request from the National Institute for Health and Care Excellence (NICE) made on the 16th January 2026, AstraZeneca has provided an updated scenario that completely aligns with the updated Committee assumptions, adapting the model to include differential RAASi discontinuation from ZORA for the first 12-weeks, and then SoC estimates for both arms for the remainder of model (Table 2). Due to the perceived levels of uncertainty from the Committee around the differential RAASi discontinuation by treatment arm, AstraZeneca have provided two similar alternative scenarios which are both clinically plausible and in line with the evidence base provided to date to aid the Committees decision making. These scenarios have been run in the Committee's preferred model and are as follows:

- Additional scenario 1: Removal of the differential RAASi discontinuation from ZORA for the first 12-weeks, and applying SZC estimates for both arms for the duration of the model, as aligned to the EAG base case (Table 3);
- Additional scenario 2: Differential RAASi discontinuation between arms is applied for the first 168 days (6 x 28 cycles) following treatment initiation, which most closely aligns with the 180-day treatment duration in ZORA (Table 4).

NICE request: Differential RAASi discontinuation by treatment arm for first 12-weeks, SoC estimates for the remainder of the model

As requested by NICE, Table 2 presents the scenario aligned with all the Committee preferred assumptions (Table 1), where the differential rates by treatment arm are applied from ZORA for 12-weeks after SZC initiation, with the ZORA SoC rates applied to both patients on SZC and SoC thereafter. ZORA SZC rates are also applied for 12-weeks for patients initiating SZC in the SoC arm (when serum potassium [S-K] ≥6.0).

Table 2. RAASi discontinuation by treatment arm: differential ZORA rates for 12-weeks (applied when patients initiate treatment) followed by SoC rate application for both arms for the remainder of model

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
SZC	£35,681	6.574	3.912	£6,123	0.311	0.182	£33,725
SoC	£29,558	6.263	3.731	-	-	-	-

Abbreviations: ICER: Incremental cost-effectiveness ratio; Inc.: Incremental; LYG: Life-years gained; QALYs: Quality-adjusted life years; RAASi: Renin-angiotensin-aldosterone system inhibitors; SoC: Standard care; SZC: Sodium zirconium cyclosilicate.

Additional scenario 1: RAASi discontinuation rates based on SZC estimates for full model duration

An additional scenario has been provided where the differential RAASi discontinuation from ZORA for the first 12-weeks is removed, and the SZC estimates are applied for both arms for the model duration, as aligned to the EAG base case (Table 3).

There is a clear clinical logic for using the discontinuation rates from ZORA's SZC arm for modelled patients receiving SZC. In real-world settings and in ZORA, patients on SZC benefit from consistent and predictable potassium control, which directly enables clinicians to maintain RAASi therapy with greater confidence, a pattern mirrored in the observed lower discontinuation rates in this group. Applying SoC discontinuation rates to patients on continued SZC would ignore that key benefit and underestimate the real impact of proactive potassium binder use.

While the Committee noted uncertainty between the rates, it's critical to recognise that the SZC arm reflects clinical behaviour when potassium can be reliably managed outside hospital, a scenario increasingly common with modern primary care and supported by NICE's policy direction to move proactive management into the community. This was validated by clinicians during the Committee meeting who strongly advised that discontinuation rates are different when potassium binders are available vs SoC. Additionally, there is no data showing that SoC rates apply to patients maintained on SZC.

Therefore, using the SZC arm rates for both groups is not only more consistent with expert experience but better represents the intended effect and value of SZC in routine National Health Service (NHS) care.

Table 3. RAASi discontinuation based on SZC rate for both arms for full model duration

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
SZC	£37,494	6.948	4.131	£6,836	0.426	0.247	£27,679
SoC	£30,658	6.521	3.884	-	-	-	-

Abbreviations: ICER: Incremental cost-effectiveness ratio; Inc.: Incremental; LYG: Life-years gained; QALYs: Quality-adjusted life years; RAASi: Renin-angiotensin-aldosterone system inhibitors; SoC: Standard care; SZC: Sodium zirconium cyclosilicate.

Additional scenario 2: Differential RAASi discontinuation between arms is applied for the first 168 days

An additional scenario has been provided where the SZC rates of down-titration and discontinuation are applied for the first 168-days after SZC initiation across the SZC and SoC arms (6 x 28-day model cycles) to most closely align with the treatment duration observed in the ZORA analysis. Following this, the ZORA SoC rate is applied for patients on treatment in alignment with the Committee base case (Table 4). Since the ZORA study collected data for 180 days, the RAASi discontinuation rate is relevant for this time period and so it is more accurate to be modelled for this length of time, rather than selecting 12-weeks. Combining scenarios 1 and 2 yield the same results presented in Table 3, as SZC rates of down-titration and discontinuation will be applied to both arms for the model duration. For this reason, a combined analysis has not been presented.

Table 4. RAASi discontinuation by treatment arm: differential ZORA rates for 168-days (applied when patients initiate treatment) followed by SoC rate application for both arms for the remainder of model

Technology	Total costs (£)	Total LYG	Total QALYs	Inc. costs (£)	Inc. LYG	Inc. QALYs	ICER (£)
SZC	£35,826	6.604	3.930	£6,229	0.332	0.194	£32,093
SoC	£29,597	6.271	3.736	-	-	-	-

Abbreviations: ICER: Incremental cost-effectiveness ratio; Inc.: Incremental; LYG: Life-years gained; QALYs: Quality-adjusted life years; RAASi: Renin-angiotensin-aldosterone system inhibitors; SoC: Standard care; SZC: Sodium zirconium cyclosilicate.

Additional uncertainty

The current assumption of lifetime treatment in the Committee preferred scenario directly conflicts with existing inputs included in the model for a 12-week treatment duration. There is an assumption that 7% of SZC prescriptions would be wasted due to misalignment with wholesale pack size (30 sachets) and model treatment cycle length (28 days). This was a highly conservative assumption carried over from TA599, and in practice pharmacists can prescribe the correct number of sachets for

prescription length. The inclusion of this assumption is not relevant for lifetime treatment as misalignment between the 30-sachet pack size and 84-day treatment length would no longer occur. The breakdown of treatment doses is also highly conservative for lifetime treatment. The model assumes that [redacted]% of maintenance phase prescriptions will be for the 10g dose, however long-term prescriptions for chronic patients with S-K ≥5.5 - <6.0 would primarily be 5g doses, so the proportion of 10g doses in practice will be far lower. It is noteworthy that the assumption of only 5g dosing being used in the maintenance phase is in alignment with the NICE budget impact assessment. Finally, the current EAG base case model assumption for lifetime treatment allows patients who discontinue SZC due to the annual stopping rate, to later reinitiate treatment. This assumption is implausible, as it is highly unlikely that patients who discontinue SZC due to adverse events and other factors causing them to stop treatment will later reinitiate. These assumptions have a significant impact on overall treatment cost, and in turn a very large impact on the incremental cost-effectiveness ratio (ICER).

Conclusion

Following the inclusion of the Committee preferred assumptions in the model and the updated request for RAASi down-titration (Table 1), the updated ICER is £33,725 (presented in Table 2).

AstraZeneca appreciate the request from the Committee to provide an alternative scenario for RAASi discontinuation. However, given the perceived uncertainty in the evidence base, AstraZeneca have provided two similar clinically plausible scenarios to aid the Committees decision making. These additional scenarios have also been run in the Committee preferred model, with an ICER of £27,679 when SZC rates of down-titration and discontinuation from ZORA are used in alignment with the EAG preferred base case, and an ICER of £32,093 when SZC rates of down-titration and discontinuation are applied for 168 days following treatment initiation in alignment with the ZORA analysis. Additional reasons have also been presented for why the current model assumptions being used to apply a lifetime treatment duration are implausible and highly conservative for the current base case ICER.

Given the clinically plausible and additional evidence-based scenarios presented, AstraZeneca believe that the £33,725 scenario requested by the Committee represents the upper bound of the most likely ICER value, and so the evidence supports that SZC is a cost-effective treatment option for patients with persistent hyperkalaemia with a serum potassium of ≥5.5 to <6.0 mmol/litre.

