**National Institute for Health and Care Excellence**

**Health Technology Evaluation**

# Sodium zirconium cyclosilicate for treating hyperkalaemia (partial review of TA599) ID6439
# Response to stakeholder organisation comments on the draft remit and draft scope

**Please note:** Comments received in the course of consultations carried out by NICE 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 submissions that NICE has received, and are not endorsed by NICE, its officers or advisory committees.

**Comment 1: the draft remit and proposed process**

| Section | Stakeholder | Comments [sic] | Action |
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| Appropriateness of an evaluation and proposed evaluation route | AstraZeneca | The evaluation outlined in the draft scope is not appropriate. AstraZeneca has requested a partial review of the existing guidance for sodium zirconium cyclosilicate (SZC) to treat hyperkalaemia (HK) [TA599]. The purpose of this partial review is to assess SZC in the population of patients with persistent HK and a serum potassium level (S–K) of ≥5.5 to <6.0 mmol/L. As SZC is not currently recommended for use in this population, they represent the population of patients with the greatest unmet need and AstraZeneca is therefore seeking a partial review to the existing recommendations in TA599.<br>The partial review should not extend to the population in which a positive recommendation within TA599 already exists. AstraZeneca now has clinical and economic evidence which addresses the uncertainties and concerns which remained following the original appraisal of TA599 and therefore will now enable NICE to broaden the current recommendations.<br>As mentioned in the FAD for TA599, clinical trials show that SZC lowers S–K when used in outpatient care, however, in the original assessment of SZC, a number of uncertainties were raised by NICE and the EAG, which meant that the cost-effectiveness of SZC in the treatment of patients with persistent HK | Comments noted. The remit has been amended to “To appraise the clinical and cost effectiveness of sodium zirconium cyclosilicate within its marketing authorisation for treating persistent hyperkalaemia in adults with a serum potassium level between 5.5 to 6.0 mmol/L or who need dialysis”. |

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| | | and an S–K of <6.0 mmol/L could not be established. The main uncertainties raised were that:<br>• There was a paucity of clinical data linking S-K levels and long-term clinical outcomes (mortality, hospitalisations, major adverse cardiac events [MACE])<br>• Clinical evidence did not adequately demonstrate that SZC usage allows reinitiation, up-titration or maintenance of optimum RAASi dosage<br>• Clinical evidence did not adequately demonstrate the relationship between RAASi dosage and long-term clinical outcomes<br>Within this resubmission for SZC in HK, AstraZeneca intends to present additional observational evidence to address these uncertainties, and thus demonstrate the benefit of expanding reimbursement of SZC to persistent HK patients with an S–K of ≥5.5 to <6.0 mmol/L. Note that this evidence takes into account NICE's original concerns, updated analytic techniques and is aligned with NICEs RWE framework. This evidence will address the uncertainties specifically in patients with a S-K of ≥5.5 to <6.0 mmol/L. AstraZeneca has not generated new evidence in patients in whom a positive recommendation already exists. | |
| | UK Renal Pharmacy Group | It would be helpful to review the Patiromer TA at the same time – this would give choice for patients and prevent market monopoly for one company. | Comments noted. It is beyond the scope to appraise patiromer in this evaluation. No action needed. |
| Wording | AstraZeneca | The wording of the remit does not reflect the intended scope of this targeted review of TA599. The clinical and cost effectiveness of SZC in patients with HK and S–K of ≥6.0 mmol/L has already been determined within the previous appraisal. This targeted review is intended to re-evaluate the population of patients for whom treatment was not recommended in TA599, namely, | Comments noted. The remit has been amended to "To appraise the clinical and cost effectiveness of |

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| | | patients with HK and an S–K of ≥5.5 to <6.0 mmol/L. AstraZeneca has generated evidence to specifically address the concerns raised during TA599 for those with S–K of ≥5.5 to <6.0 mmol/L and has not generated new evidence or conducted economic modelling for the population that already has a positive reimbursement decision from NICE. | sodium zirconium cyclosilicate within its marketing authorisation for treating persistent hyperkalaemia in adults with a serum potassium level between 5.5 to 6.0 mmol/L or who need dialysis". |
| | UK Renal Pharmacy Group | Wording of the remit is concise as reflects the drug license. The drug is licensed for patients on dialysis and there is trial evidence this is safe so would request this is clearly stated here too. | Comments noted. The remit has been amended to "To appraise the clinical and cost effectiveness of sodium zirconium cyclosilicate within its marketing authorisation for treating persistent hyperkalaemia in adults with a serum potassium level between 5.5 to 6.0 mmol/L or who need dialysis". The wording reflects the population for a targeted review of TA599. |
| Timing issues | AstraZeneca | Currently there are limited treatment options available for the management of patients with HK who have an S–K of <6.0 mmol/L within the NHS. These | Comments noted. NICE has scheduled this topic into its work |

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| | | patients receive standard of care (SOC), and no selective potassium binder such as SZC is available in the NHS for these patients.<br><br>This SOC treatment is no longer aligned with updated international treatment guidelines (Kidney Disease: Improving Global Outcomes [KDIGO] 2024 and European Society of Cardiology [ESA] 2021 guidance) which recommend the prescription of potassium binders prior to modification of renin–angiotensin–aldosterone system inhibitors (RAASi) dosage. Therefore, the current NICE recommendations do not represent best-practice, evidence-based management of patients with hyperkalaemia.<br><br>The current restriction in the NICE recommendation creates an unmet need in patients with S–K of ≥5.5 to <6.0 mmol/L, despite the availability of licensed therapies. | programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/awaiting-development/gid-ta11561. No action needed. |
| | UK Renal Pharmacy Group | Reasonably urgent as patients with CKD are being managed within primary care and use of potassium binders will aid their effective care. The previous NICE guidance requires widening to allow earlier use and treatment to be started within primary care. This update will help healthcare professionals be able to adapt and match the 21st century way patients are managed across the care pathway. Many patients are managed in primary care, with secondary care giving advice and, in some cases, not seeing them for long periods of time. This change will allow people who are living with heart failure and chronic kidney disease, to more readily access treatments that can help manage persistent hyperkalaemia.<br><br>Allowing use in dialysis patients and continuation of prescribing within primary care would allow patients to obtain their medications from a single source to reduce confusion. | Comments noted. NICE has scheduled this topic into its work programme. For further details, see the NICE website: https://www.nice.org.uk/guidance/awaiting-development/gid-ta11561. No action needed. |

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| Additional comments on the draft remit | AstraZeneca | N/A | Comment noted. No action needed. |

**Comment 2: the draft scope**

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| Background information | AstraZeneca | ***NICE text:*** "The European Resuscitation Council classifies HK as mild (serum potassium level of 5.5 to 5.9 mmol/L), moderate (6.0–6.4 mmol/L) or severe (6.5 mmol/L and above)."<br>***Response:*** Whist this is an accurate description of HK classification, AstraZeneca feels it is important to note that these classifications are arbitrary and do not represent the clinical burden experienced by patients. This is particularly the case in patients who have modified RAASi dosage in response to HK, and thus may be at increased risk of cardio-renal adverse events.<br><br>***NICE text:*** "This evaluation will review and replace the recommendations in TA599"<br>***Response:*** Please see comment in the 'Appropriateness' row above. The purpose of this targeted review is to assess SZC in the population of patients with HK and an S–K of ≥5.5 to <6.0 mmol/L. AstraZeneca has generated evidence to specifically address the concerns raised during TA599 for those with S–K of ≥5.5 to <6.0 mmol/L and has not generated new evidence or conducted economic modelling for the population that already has a positive reimbursement decision from NICE. | Comments noted. The background section provides a broad overview. The remit has been amended to "To appraise the clinical and cost effectiveness of sodium zirconium cyclosilicate within its marketing authorisation for treating persistent hyperkalaemia in adults with a serum potassium level between 5.5 to 6.0 mmol/L or who need dialysis". This change has been reflected in the background information. |

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| | UK Renal Pharmacy Group | I think the use for dialysis patients could be included | Comments noted. The background section provides a broad overview. The remit has been amended to “To appraise the clinical and cost effectiveness of sodium zirconium cyclosilicate within its marketing authorisation for treating persistent hyperkalaemia in adults with a serum potassium level between 5.5 to 6.0 mmol/L or who need dialysis”. This change has been reflected in the background information. |
| Population | AstraZeneca | The population of interest is patients with persistent HK and an S–K of ≥5.5 to <6.0 mmol/L, the population of patients for whom treatment was not recommended in TA599.<br>This company submission will focus specifically on the comorbid patient population comprising patients with HK and chronic kidney disease (CKD; stage 3b–5) or heart failure (HF) with a S-K of ≥5.5 and <6.0 mmol/L. HK occurs predominantly in patients with an underlying degree of CKD or HF due to disease pathophysiology and the wide use of cardio-renal protective medicines, such as RAASi, which significantly increase the risk of developing HK due to their mechanism of action. | Comments noted. The population has been amended to “People with persistent hyperkalaemia and a serum potassium level between 5.5 to 6.0 mmol/L” and “People with persistent |

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| | | As mentioned in the 'Appropriateness' row above, this resubmission will focus on patients with persistent HK with an S–K of ≥5.5 to <6.0 mmol/L that currently does not have a positive recommendation from NICE. | hyperkalaemia who need dialysis". |
| | UK Renal Pharmacy Group | As far as I am aware it is | Comment noted. No action needed. |
| Subgroups | AstraZeneca | ***NICE text:*** "people with acute hyperkalaemia"<br>***Response:*** SZC is already recommended for use by NICE in patients with life threatening acute HK (TA599). This population is therefore not within the scope of this resubmission. AstraZeneca has not generated new evidence nor conducted economic modelling in the population of patients with acute life-threatening HK given that this population has already received a positive reimbursement decision from NICE.<br>***NICE text:*** "people with chronic kidney disease", "people with heart failure"<br>***Response:*** AstraZeneca's value proposition will be specifically adults with HK and comorbid CKD or HF. No other subgroups will be provided. This population is consistent with the original approach in TA599.<br><br>***NICE text:*** "people with acidosis"<br>***Response:*** The clinical trial programme for SZC did not evaluate people with acidosis and no additional observational evidence has been collected on this sub-population. No subgroups of people with acidosis were presented during TA599 for the same rationale. | Comments noted. The population has been amended to "People with persistent hyperkalaemia and a serum potassium level between 5.5 to 6.0 mmol/L" and "People with persistent hyperkalaemia who need dialysis". No action needed. |
| Comparators | AstraZeneca | It is appropriate to use standard of care as a comparator in this appraisal. Patients with HK with a S–K ≥5.5 and <6.0 mmol/L are managed with lifestyle interventions for the background maintenance of S–K. This may include low | Comments noted. The scope has been |

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| | | potassium diet and down-titration or discontinuation of concomitant medications, such as RAASi.<br>Patiromer is not recommended by NICE for those ≥5.5 to <6.0 mmol/L and therefore doesn't represent standard care for the population of interest to this submission – persistent HK patients with an S–K of ≥5.5 to <6.0 mmol/L. As such, patiromer is not a relevant comparator and should be excluded from the scope. | amended to include only standard care. |
| | UK Renal Pharmacy Group | Yes | Comment noted. No action needed. |
| Outcomes | AstraZeneca | The outcomes listed are appropriate. AstraZeneca recommends that major adverse cardiac events (MACE) should be included as a key outcome to consider in this appraisal. This outcome is relevant because patients with HK who are forced to discontinue or modify dosage of RAASi are likely to be at increased risk of MACE. | Comments noted. Major adverse cardiac events has been included under 'adverse effects of treatment'. |
| | UK Renal Pharmacy Group | Perhaps include use of SGLT2i. | Comments noted. The "use of sodium-glucose cotransporter 2 (SGLT2) inhibitors" has been added to the outcomes in the scope. |
| Equality | AstraZeneca | No equality considerations identified. | Comment noted. No action needed. |

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| | UK Renal Pharmacy Group | I think the importance as I said higher up of many patients are managed in primary care, with secondary care giving advice and, in some cases, not seeing them for long periods of time. A change to allowing at a lower potassium and more within primary care, will allow people who are living with heart failure and chronic kidney disease, to more readily access treatments that can help manage persistent hyperkalaemia. | Comments noted. No action needed. |
| Other considerations | AstraZeneca | No additional comments. | Comment noted. No action needed. |
| | UK Renal Pharmacy Group | N/A | Comment noted. No action needed. |
| Questions for consultation | AstraZeneca | ***Where do you consider sodium zirconium cyclosilicate will fit into the existing care pathway for hyperkalaemia?***<br>In UK clinical practice, patients with persistent HK were historically managed in the outpatient setting in the hospital. However, following an update to the existing recommendations in TA599 in January 2022, continuation of SZC can take place within primary care. AstraZeneca proposes that SZC could now be prescribed and managed across the full NHS system, either in primary or secondary care.<br>Similarly to those patients currently treated with SZC in line with the current NICE recommendations, patients with a S-K of between 5.5 and 6.0 mmol/L would be treated with SZC as an alternative to the need to down-titrate and/or discontinue their RAASi therapies. It is also expected that treatment with SZC would results in normokalaemia sooner and therefore enable re-initiation/uptitration of any RAASi therapies which may have been previously adjusted. | Comments noted. No action needed. |

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| | | ***Would sodium zirconium cyclosilicate be a candidate for managed access?***<br>SZC would not be a candidate for managed access.<br>***Do you consider that the use of sodium zirconium cyclosilicate can result in any potential substantial health-related benefits that are unlikely to be included in the QALY calculation?***<br>The health-related benefits of SZC are expected to be captured in the QALY calculation. | |
| | UK Renal Pharmacy Group | Where do you consider sodium zirconium cyclosilicate will fit into the existing care pathway for hyperkalaemia?<br>A. Prescribed in primary care with routine follow-up in primary care<br>I think the only population missing where the drug is licensed is the dialysis population | Comments noted. The population has been amended to “People with persistent hyperkalaemia and a serum potassium level between 5.5 to 6.0 mmol/L” and “People with persistent hyperkalaemia who need dialysis”. No action needed. |
| Additional comments on the draft scope | AstraZeneca | N/A | Comment noted. No action needed. |