NICE National Institute for Health and Care Excellence

Projector, committee, public

# Sodium zirconium cyclosilicate (SZC) for treating hyperkalaemia

3rd appraisal committee meeting

30 May 2019

Committee B

Chair: Amanda Adler

Lead team: Mona Johnson, Chris O'Regan and Nigel Westwood

ERG: ScHARR

NICE technical team: Mary Hughes, Alan Lamb, Ross Dent

Company: AstraZeneca

# Hyperkalaemia - high blood levels of potassium

- Serum potassium ($K^+$) normal range 3.5 to 5.0 mmol/L
  definitions of normal to high vary; many have upper range of normal at 5.5 mmol/L
  - company defines hyperkalaemia (in clinical trials) as >5.1 mmol/L
- **Severe hyperkalaemia** can cause irregular heart beat, cardiac arrest and death
- **Risk factors for hyperkalaemia include**:
  - Diseases: chronic kidney disease, heart failure
  - Medicines for high blood pressure and heart failure:
    - renin-angiotensin aldosterone system inhibitors (**RAASi**) including:
      - angiotensin-converting enzyme (**ACE**) inhibitors
      - angiotensin II receptor blockers (**ARB**)
      - direct renin inhibitors (e.g. aliskerin)
      - aldosterone-receptor antagonists (e.g. spironolactone)
    - other potassium-sparing diuretics
    - beta-blockers

[redacted]

# History of appraisal

**Appraisal committee meeting 1:** not recommended

**Appraisal committee meeting 2:**

- Revised company base case for emergency and outpatient settings
- Significant uncertainties remain in outpatient setting:
  - Modelled relationship between serum $K^+$ and outcomes
  - Proportion of people reducing the dose of or stopping RAASi
  - Most plausible ICER above £30,000 per QALY gained
- Decision:
  - **Recommended in emergency setting**
  - **Not recommended in outpatient setting**

**Today:** revised company base case for outpatient setting

Abbreviations: $K^+$, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor

# Preview of key issues

1. Serum potassium treatment threshold for people with heart failure
2. Epidemiological relationship between serum potassium and outcomes
3. Updated company base case
   - includes **new** (not yet approved) patient access scheme
   - new company scenario analyses

# Sodium zirconium cyclosilicate (SZC), Lokelma

*marketing authorisation does not define hyperkalaemia; population is broad*

| | |
|---|---|
| **Marketing authorisation** | "For the treatment of hyperkalaemia" |
| **Administration & dose** | 5 g or 10 g sachet - powder for oral suspension<br>**Correction phase**: 10 g, 3 times daily, max duration 72 hours<br>**Maintenance phase**: 5 g once daily can be up titrated to 10 g once daily or down titrated to 5 g once every other day to maintain normal potassium levels |
| **Special warnings and precautions for use** | • Monitor serum potassium ($K^+$) when clinically indicated, and after changes to medicines that affect serum $K^+$ (e.g. RAASi or diuretics) and after titrating SZC dose<br>• Hypokalaemia – may require dose titration/discontinuation<br>• May be opaque to X-rays<br>• Risk of intestinal perforation currently unknown (no events reported with SZC) but has been reported with polymers that act in the gastrointestinal tract |

# Treatment pathway

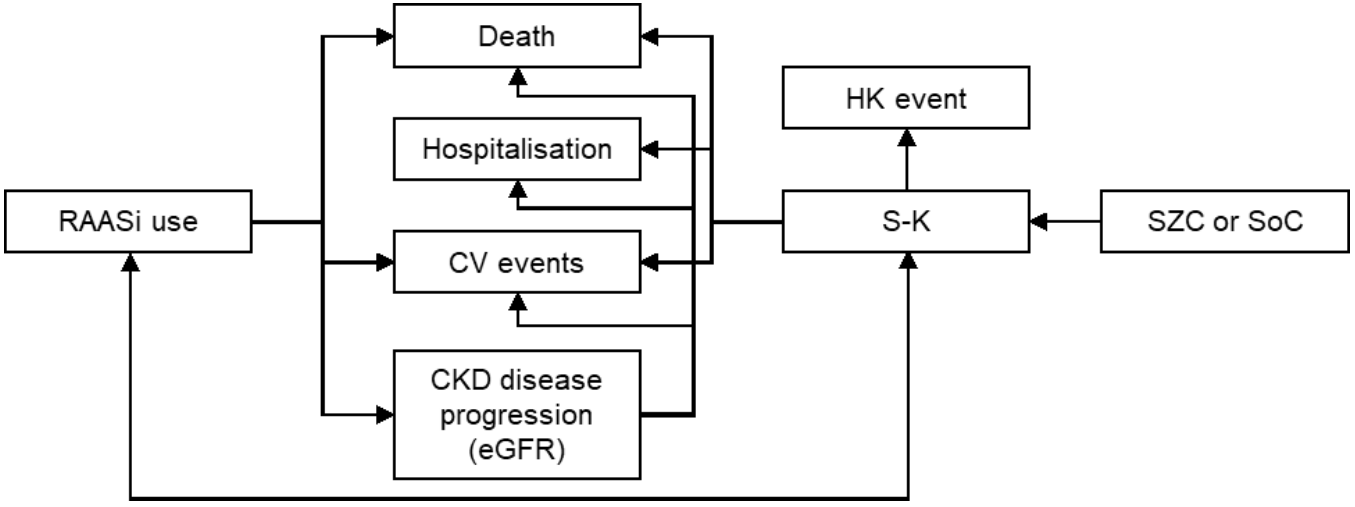
*Company: SZC will be used in emergency + outpatient setting*

| | Setting and $K^+$ levels | Correction phase (recommended in ACD2) | Maintenance phase (not recommended in ACD2) |
|---|---|---|---|
| Current | Emergency ≥ 6.0 mmol/L | **Shift $K^+$ into cells**<br>Insulin-glucose 2x doses then<br>**Bind $K^+$ and excrete**<br>Calcium resonium | **Low $K^+$ diet**<br><br>**Manage drugs that raise $K^+$** |
| Current | Outpatient ≥ 5.5 mmol/L | **Stop or down-titrate drugs that raise $K^+$**<br>**Low $K^+$ diet** | |
| Proposed | SZC | **Bind $K^+$ and excrete**<br><br>SZC 10 g 3x daily for up to 72 hours after insulin-glucose | SZC 5 to 10 g once daily or 5 g every other day<br>Company's suggested duration of treatment:<br>Emergency setting: 28 days<br>Outpatient setting: **lifetime**<br>(revised from **52 weeks**) |

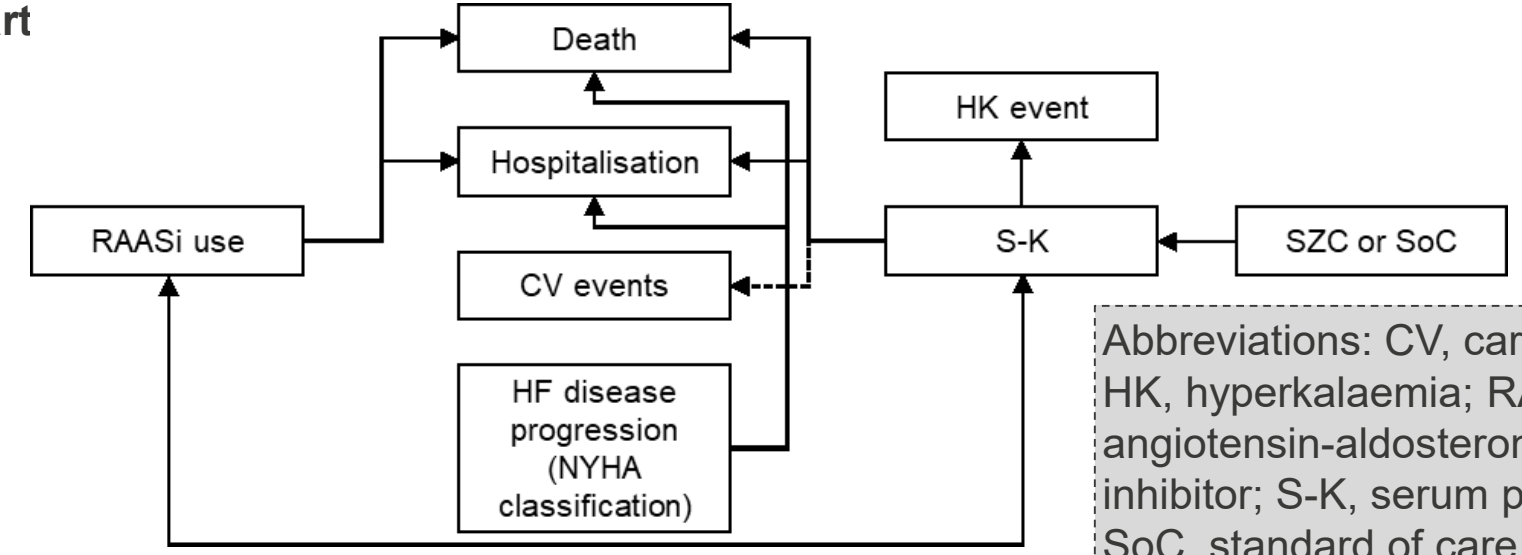
Abbreviations: $K^+$, potassium.

# Company links changes in $K^+$ from trial to observational data to model:
# a) association between $K^+$ and outcomes
# b) association between changes in RAASi and outcomes

**People with Chronic Kidney Disease (CKD)**




**People with Heart**




Abbreviations: CV, cardiovascular; HK, hyperkalaemia; RAASi, renin-angiotensin-aldosterone system inhibitor; S-K, serum potassium; SoC, standard of care

# Appraisal consultation document (ACD) conclusions and key uncertainties

| | |
|---|---|
| **Trial outcome** | • In maintenance phase SZC maintains $K^+$<br>• **No evidence that SZC prolongs survival** |
| **Observational data - relationship between $K^+$ and death** | • Residual confounding likely – 'unmeasured or unknown'<br>• Studies may have been affected by time-dependent confounding<br>• Observational association between $K^+$ and death does not necessarily mean that lowering $K^+$ prolongs life<br>• No evidence that other potassium-lowering drug within this non-urgent range has prolonged life |
| **Number of people who stop, down-titrate or restart RAASi** | • Company assumed RAAS inhibitor use would differ between SZC and standard of care → no evidence<br>• Company based number of people who stop or down-titrate RAASi on clinical expert opinion rather than UK studies |

Abbreviations: $K^+$, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor

# Responses to appraisal consultation document

**Responses received from:**

- Company (AstraZeneca)
- Renal Association (endorsed by Royal College of Physicians)
- Pumping Marvellous Foundation
- Web comments from NHS professionals

**Selected comments from consultees:**

- Long-term maintenance therapy with SZC may ensure people are not 'on sub-optimal [RAASi] treatment and at an increased risk of both progression of kidney disease and death from heart failure'
- 'A well conducted study showing that SZC does allow more patients to receive optimum RAAS would be of great value [and] go a long way to convince clinicians of the value of SZC. A larger study looking at patient outcomes directly […] should also be completed.'

[redacted] Abbreviations: $K^+$, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor

# Treatment threshold for heart failure

**ACD:**

- Company proposed that SZC would be started at serum $K^+$ levels of ≥5.5 mmol/L for people with heart failure
- Clinical expert at committee meeting agreed with this
- Committee accepted that the threshold proposed by the company was intended to align with clinical expert opinion, but noted that some clinicians may wish to treat hyperkalaemia at different thresholds

**Company consultation comments:**

- 'Some clinicians may treat heart failure patients at higher thresholds than previously modelled' → new company base case analysis ↑ serum $K^+$ treatment threshold to ≥6.0 mmol/L

⊙ Is the company's new treatment threshold appropriate?

[redacted] Abbreviations: $K^+$, potassium

# Relationship: serum $K^+$ and long term outcomes

**ACD:** trial results show SZC may lower serum $K^+$ but benefit to patients unclear

- Company provided evidence from a single observational study showing an association between serum $K^+$ levels and death
- Causal relationships cannot be guaranteed by observational data
- No evidence that any other potassium lowering drug prolongs life
- Extent to which the company considered time-dependent confounding unclear
- Committee wished to see SZC cost effective without this assumption

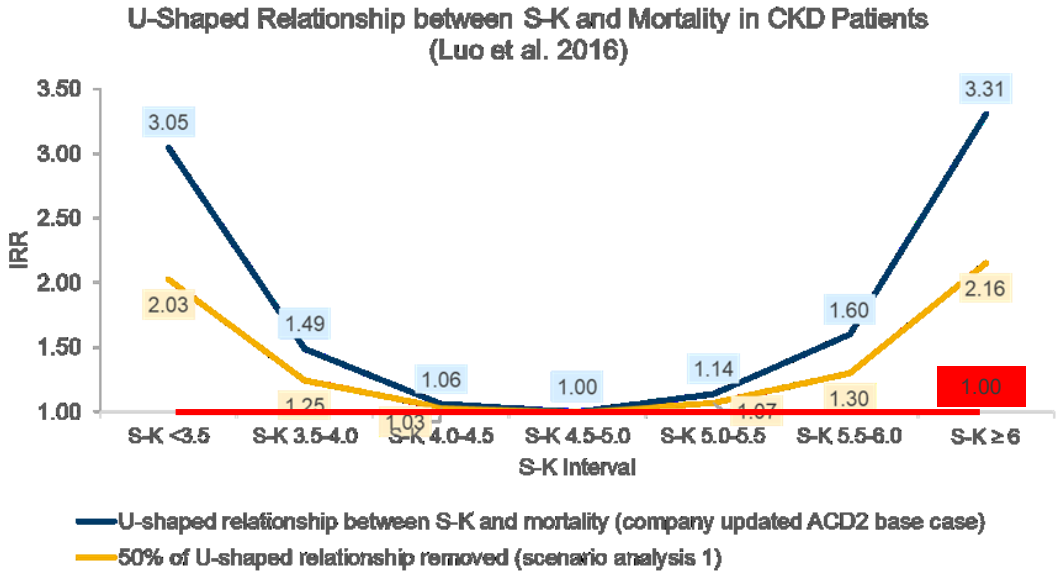
**Company consultation comments:**

- **New:** scenario analyses changing relationship between serum $K^+$ and outcomes in the model (see next slide)
- 'Statistical models used to estimate the relationships between serum $K^+$ and adverse clinical outcomes were carefully selected to ensure all known covariates were appropriately accounted for'
  - n.b. possibility of confounding acknowledged by study authors

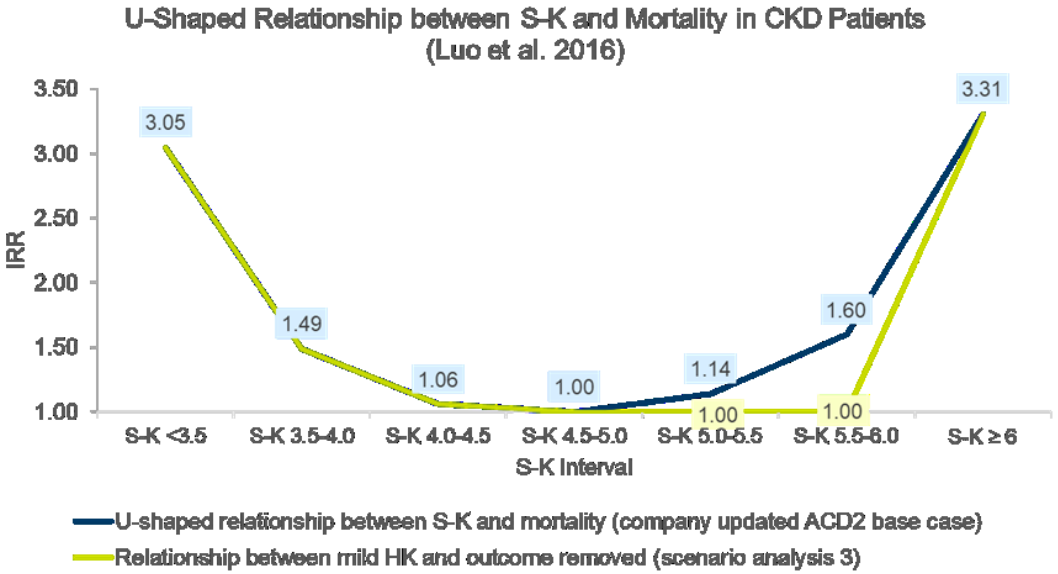
[redacted] Abbreviations: $K^+$, potassium

# Relationship: serum $K^+$ and long term outcomes – new company scenario analyses

## Full effect, 50% effect and no effect




## No relationship: mild hyperkalaemia




- **Base case** (blue line) based on **full effect** observed in epidemiological study
- Explored scenarios with 50% effect (yellow line) and no effect (red line)
- Explored scenario where effect was removed for people with mild hyperkalaemia, between 5.0 mmol/L and 6.0 mmol/L (green line)
  - retain increased risk for hyperkalaemia in emergency setting and hypokalaemia

[redacted]

# ERG comments on company scenarios

- 'Key papers [… ] identify associations between serum $K^+$ levels and adverse events rather than proving that the adverse events are caused by serum $K^+$ levels' → acknowledged by authors
  - base case assuming full association is favourable to SZC
- No association highly unlikely: clinical intervention in patients with ↑ serum $K^+$ levels in emergency setting and modifications to RAASi use in people with ↑ serum $K^+$
  - removing association likely unfavourable to SZC
- 'No clear rationale' for scenario analysis removing the relationship between serum $K^+$ levels and adverse events for people with mild hyperkalaemia (between 5.0 mmol/L and 6.0 mmol/L)

⊙ Do company's scenario analyses address the uncertainty around the relationship between serum potassium and outcomes?

[redacted] Abbreviations: $K^+$, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor

# Company revised base case assumptions

| Assumption | Base case (2nd meeting) | Revised base case | Company's rationale for change |
|---|---|---|---|
| **Threshold $K^+$ for treatment – outpatients** | • ≥6.0 mmol/L for CKD<br>• ≥5.5 mmol/L for heart failure | • ≥6.0 mmol/L for both CKD and heart failure | ACD states clinicians may wish to treat people with heart failure at higher threshold |
| **Association $K^+$ with long-term outcomes** | Based on epidemiological evidence | Based on epidemiological evidence | Evidence supports a strong relationship between hyperkalaemia and long-term outcomes |
| **Proportion of patients who down-titrate, discontinue and re-start RAASi** | Depends on treatment arm | Equal for SZC and standard of care | As ERG assumption |
| **Treatment duration of SZC** | 52 weeks | Lifetime | ACD requests scenario analysis modelling costs and benefits of SZC beyond 52 weeks – treatment expected to continue indefinitely in clinical practice if there is clinical benefit |

# Company: revised base case results

| | Heart failure | Chronic kidney disease |
|---|---|---|
| | List price ICER | List price ICER |
| **Revised base case** | £13,100 | £20,674 |
| **Key scenario analyses around company revised base case** | | |
| **1) 50% of benefit from lower serum $K^+$** | £16,110 | £24,211 |
| **2) 0% of benefit from lower serum $K^+$** | £43,781 | £35,962 |
| **3) No relationship mild $K^+$ (5.0 mmol/L to 6.0mmol/L) and outcomes** | £18,508 | £22,522 |
| **4) Heart failure serum $K^+$ treatment threshold of ≥5.5 mmol/L** | £26,127 | - |
| **Combine 1 and 4 (ERG analysis)** | £38,137 | - |
| **Combine 2 and 4 (ERG analysis)** | £87,170 | - |

ICERs including the proposed patient access scheme for SZC are confidential and are reported in part 2 of meeting

# Summary of ERG conclusions

- ICERs increase considerably when:
  - no relationship between serum $K^+$ levels and outcomes assumed
  - threshold for treatment for heart failure is ≥5.5 mmol/L
- Remaining uncertainties:
  - no trial comparing SZC and **current standard care** in NHS (but approach to populating model reasonable)
  - no trial to demonstrate the impact of SZC on hard clinical endpoints
  - no evidence that SZC enables patients to initiate, re-initiate or increase RAASi therapy and maintain optimum serum $K^+$ levels
- Uncertainties could be resolved by appropriate clinical trial

[redacted] Abbreviations: $K^+$, potassium; RAASi, renin-angiotensin-aldosterone system inhibitor