Technology Guidance

Sodium zirconium cyclosilicate

for treating hyperkalaemia

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has not recommended listing sodium zirconium cyclosilicate on the MOH List of Subsidised Drugs for treating hyperkalaemia due to the uncertain extent of clinical benefit and uncertain cost effectiveness compared with current standard of care.

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Factors considered to inform the recommendations for funding

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of sodium zirconium cyclosilicate (SZC) for treating hyperkalaemia in adults. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical and patient experts from the public healthcare institutions and local patient and voluntary organisations. Published clinical and economic evidence for SZC was considered in line with its registered indication.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's funding considerations.

Clinical need

2.1. Hyperkalaemia is a medical condition of elevated potassium levels in the blood. In severe cases, it may lead to cardiac arrest and death. The current standard of care for hyperkalaemia includes a low potassium diet and treatment with sodium polystyrene sulfonate (SPS). Sodium polystyrene sulfonate is included on the Standard Drug List.

2.2. There is an increased risk of developing hyperkalaemia in people with chronic kidney disease (CKD) and heart failure (HF) and in those who take cardio-renal medicines, such as renin-angiotensin aldosterone system inhibitors (RAASi) including angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers, compared to the general population. Locally, down-titration or discontinuation of RAASi is commonly practised to manage the chronic hyperkalaemia. Sodium polystyrene sulfonate is also used off-label for this condition, however, its long-term use is limited by tolerability and the risk of gastrointestinal adverse events.

2.3. The Committee acknowledged the clinical need to consider SZC, a potassium binder, in selected patients with chronic hyperkalaemia to optimise the use of RAASi, ensure appropriate patient care and improve treatment affordability.

2.4. The Committee considered testimonials from local patient experts about their experience with hyperkalaemia and the treatments they had received. The Committee noted that most patients were able to manage their condition with their current treatment and strict dietary restrictions. However, patients considered that if they needed an alternative treatment for hyperkalaemia, the side effect profile and clinical effectiveness of any new treatment would be the most important factors considered.

Clinical effectiveness and safety

3.1. The Committee reviewed the available clinical evidence for SZC from five phase III, placebo-controlled randomised clinical trials (ZS-003, ZS-004, ZS-D9480, ZS-D9482 and DIALIZE). Results showed that SZC demonstrated statistically superior efficacy versus placebo in the acute correction of hyperkalaemia and maintenance of potassium levels in the normal range for up to eight weeks.

3.2. The Committee also reviewed the clinical evidence from three single-arm extended-dosing studies (ZS-004E, ZS-005 and Kashihara et al.), which demonstrated maintenance of normokalaemia up to 52 weeks.

3.3. The Committee noted that although SZC appeared to lower serum potassium levels, a surrogate outcome, the clinical relevance of the observed changes was unknown. No patient-relevant, clinically meaningful outcomes such as survival, hospitalisation, cardiovascular and renal outcomes were studied.

3.4. In terms of safety, the identified adverse events included oedema-related events, which were clinically important events in the patient population most likely to receive SZC (people with CKD and HF). The Committee agreed that the long-term safety of SZC remained unknown, given that the data were limited in duration with relatively high discontinuation rates (up to 37.5%) observed in the extended-dosing studies.

3.5. Given the absence of an active comparator arm in the trials, evidence of comparative efficacy and safety for SZC versus current standard of care (down-titration or discontinuation of RAASi or treatment with SPS) was lacking. The Committee heard that indirect comparisons were not feasible, given heterogeneity between the studies and small sample sizes of SPS studies.

3.6. Due to limitations of the evidence, the Committee concluded the comparative clinical benefit of SZC remained uncertain. The ongoing trials (expecting completion in the next three years) may provide more evidence on its effect on dose optimisation of RAASi in people with CKD and HF and long-term clinical outcomes.

Cost effectiveness

4.1. No local published cost-effectiveness studies of SZC were identified. The Committee

reviewed the economic evaluations published by overseas HTA agencies. However, the Committee noted the uncertainties in the clinical evidence and agreed that the cost-effectiveness of SZC could not be reliably determined.

4.2. The company of SZC was invited to submit a value-based pricing (VBP) proposal for their product for funding consideration. The Committee noted that at the proposed price, the cost of treatment for SZC was considerably higher than standard of care treatments, including SPS.

4.3. In view of the uncertain comparative clinical benefit, the Committee considered that SZC was unlikely to represent a cost-effective use of healthcare resources in Singapore at the price proposed by the company.

Estimated annual technology cost

5.1. The Committee noted that the annual cost impact to the public healthcare system was estimated to be between SG$1 million to less than SG$3 million in the first year of listing SZC on the Medication Assistance Fund (MAF). The Committee acknowledged that this estimate was uncertain and could potentially be much higher.

Recommendations

6.1. Based on available evidence, the Committee recommended not listing SZC on the MOH List of Subsidised Drugs for treating hyperkalaemia in view of the uncertain extent of clinical benefit and uncertain cost effectiveness compared with current standard of care.

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government funding decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 25 August 2022. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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