Technology Guidance

SGLT2 inhibitors

for treating heart failure and chronic kidney disease

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

✓ Empagliflozin 10 mg and 25 mg tablets

in line with its registered indications for treating heart failure and chronic kidney disease, in view of favourable clinical and cost-effectiveness.

Funding status

Empagliflozin 10 mg and 25 mg tablets are recommended for inclusion on the Standard Drug List (SDL) from 1 November 2023.

Of note, dapagliflozin 5mg and 10 mg tablets will be delisted from the MOH List of Subsidised Drugs with effect from 1 August 2024 due to unfavourable cost-effectiveness compared with empagliflozin.

Updated: 2 January 2024

Factors considered to inform the recommendations for funding

Technology evaluation

1.1. At the May 2022 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of sodium-glucose co-transporter 2 (SGLT2) inhibitors for treating chronic heart failure with reduced ejection fraction (HFrEF) (dapagliflozin and empagliflozin) and chronic kidney disease (CKD) (dapagliflozin only). The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for dapagliflozin and empagliflozin was considered in line with their registered indications.

1.2. Empagliflozin was not evaluated for treating CKD as it was not approved by the Health Sciences Authority (HSA) for this indication at the time of evaluation. Other SGLT2 inhibitors (canagliflozin and ertugliflozin) were also not reviewed as they did not have HSA approval for either indication at the time of evaluation.

1.3. 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.

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

1.5. In 2023, the Committee considered revised proposals for dapagliflozin and empagliflozin, for reclassification onto the SDL and for subsidies to be extended to Healthier SG Clinics. The Committee also reviewed published evidence for the technology evaluation of empagliflozin for treating CKD.

Clinical need

Heart failure with reduced ejection fraction

2.1. In line with international clinical practice guidelines, dapagliflozin and empagliflozin are used in local practice in combination with standard of care (SoC) therapies including a beta blocker, either an angiotensin-converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB) or angiotensin receptor-neprilysin inhibitor (ARNI), and a mineralocorticoid receptor antagonist (MRA), for patients with heart failure (New York Heart Association (NYHA) class II to IV) and left ventricular ejection

fraction (LVEF) ≤ 40%. The Committee heard from local clinical experts that more than 17,000 patients in Singapore are likely to require this treatment regimen for their condition. Therefore, there was a clinical need to consider dapagliflozin and empagliflozin for funding for this indication to improve treatment affordability and ensure appropriate patient care.

Chronic kidney disease

2.2. The Committee heard from local clinical experts that SGLT2 inhibitors are added to maximum tolerated doses of SoC therapy (ACEI or ARB) in local practice for patients with CKD regardless of their T2DM status. Given the large number of patients who are likely to be eligible for treatment the Committee acknowledged the clinical need to consider SGLT2 inhibitors for funding to improve treatment affordability and ensure appropriate patient care.

Clinical effectiveness and safety

Heart failure with reduced ejection fraction

SGLT2 inhibitor versus placebo

3.1. At the 2022 DAC meeting, the Committee reviewed the available clinical evidence from two pivotal phase III randomised controlled trials (RCTs) which compared dapagliflozin (DAPA-HF) and empagliflozin (EMPEROR-Reduced) with placebo, added to SoC, for treating HFrEF. The Committee noted that both SGLT2 inhibitors led to significant improvements in the key composite outcome of time to hospitalisation for heart failure (HF) or cardiovascular (CV) death compared with placebo. Furthermore, in subgroup analyses, the clinical effects of both SGLT2 inhibitors were consistent in patients with and without T2DM.

3.2. Clinically meaningful improvements in health-related quality of life measured by Kansas City Cardiomyopathy Questionnaire – Clinical Summary Score (KCCQ-CSS) (for EMPEROR-Reduced) or KCCQ-Total Summary Score (TSS) (for DAPA-HF) occurred more frequently with the SGLT2 inhibitors compared with placebo in both trials.

3.3. In terms of safety, the Committee noted that both dapagliflozin and empagliflozin were generally well tolerated in the trials. Adverse events leading to treatment discontinuation were similar across arms in both trials (dapagliflozin 4.7% vs placebo 4.9%; empagliflozin 8.5% vs placebo 8.9%).

Dapagliflozin versus empagliflozin

3.4. The Committee noted that there were no head-to-head RCTs that compared dapagliflozin and empagliflozin with each other for treating HFrEF. Thus, the Committee considered results from published indirect treatment comparisons (ITCs) that were reviewed by overseas reference HTA agencies, NICE (UK) and PBAC (Australia). While acknowledging the uncertainty associated with the ITCs due to the

heterogeneity of trial populations, the Committee accepted that empagliflozin was non-inferior to dapagliflozin in terms of clinical effectiveness and safety for treating HFrEF. They further heard that this clinical conclusion was also supported by local clinical experts, who considered that the clinical benefit of the SGLT2 inhibitors in HFrEF was a class effect.

Chronic kidney disease

SGLT2 inhibitor versus placebo

3.5. In 2022 and 2023, the Committee reviewed the available clinical evidence from two phase III RCTs which compared dapagliflozin (DAPA-CKD) or empagliflozin (EMPA-KIDNEY) with placebo as add-on therapy to SoC for treating CKD. The Committee heard that compared with placebo, both SGLT2 inhibitors were associated with statistically significant improvements in the primary composite outcome[a] of time to first occurrence of sustained decline in eGFR or reaching end-stage renal disease (ESRD) or death from renal or CV causes. The Committee noted that results from the subgroup analyses from both trials also suggested that the improvements in the primary composite outcome with both SGLT2 inhibitors were consistent in patients with and without T2DM.

3.6. In terms of safety, both dapagliflozin and empagliflozin were generally well tolerated and there were no new safety signals identified compared with previous trials.

Dapagliflozin versus empagliflozin

3.7. The Committee noted there were no head-to-head RCTs that compared dapagliflozin and empagliflozin with each other for treating CKD. Given the differences in the baseline characteristics and definitions of the primary composite outcomes of the DAPA-CKD and EMPA-KIDNEY trials, the Committee heard that results of an indirect comparison between the DAPA-CKD and EMPA-KIDNEY trials were unlikely to be sufficiently robust. Considering broad expert consensus that the benefits for SGLT2 inhibitors in CKD are a class effect, the Committee agreed that it was reasonable to consider empagliflozin to be non-inferior to dapagliflozin in clinical effectiveness and safety.

Cost effectiveness

4.1. In 2022, the Committee considered that the company's proposal for dapagliflozin provided more certainty in ensuring cost-effective use of healthcare resources compared to that for empagliflozin. The Committee agreed that dapagliflozin was likely to be considered an acceptable use of healthcare resources for treating HFrEF and CKD in the local setting at the proposed price.

4.2. In 2023, the Committee considered revised proposals for dapagliflozin and

[a] The threshold for sustained decline in eGFR was lower in EMPA-KIDNEY (≥40%) compared to DAPA-KIDNEY (≥50%). For the definition of end-stage renal disease, the cut-off for eGFR was lower in EMPA-KIDNEY (<10 mL/min/1.73 m^2) compared to DAPA-CKD (<15 mL/min/1.73 m^2).

empagliflozin and found that the company's proposal for empagliflozin was more favourable and provided more certainty in terms of the overall budget impact. At the proposed price, the Committee also considered that an SDL listing was appropriate to benefit more patients and improve outcomes.

Estimated annual technology cost

5.1. At the 2022 meeting, the Committee noted that the annual cost impact to the public healthcare system was estimated to be more than SG$10 million in the first year of expanding the MAF listing for dapagliflozin to include HFrEF and CKD due to the large number of patients with these conditions in Singapore.

5.2. In 2023, the Committee noted that the annual cost impact to the public healthcare system was estimated to be more than SG$20 million if empagliflozin was listed on the MOH List of Subsidised Drugs for all registered indications.

Recommendations

6.1. In 2022, the Committee recommended that the MAF listing for dapagliflozin 5 and 10 mg tablets should be expanded to also include treatment of HFrEF and CKD in view of clinical need and acceptable clinical and cost-effectiveness based on the company's proposal.

6.2. In 2023, the Committee recommended to reclassify empagliflozin 10 mg and 25 mg tablets from MAF to SDL in view of favourable clinical and cost-effectiveness.

6.3. The Committee also recommended to delist dapagliflozin from the MOH List of Subsidised Drugs on the basis of unfavourable cost-effectiveness compared with empagliflozin based on the company's proposal

VERSION HISTORY

Guidance on SGLT2 inhibitors
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This Version History is provided to track any updates or changes to the guidance following the first publication date. It is not part of the guidance.

1. **Publication of guidance**

Date of Publication	31 Aug 2022

2. **Guidance updated to reflect reclassification of empagliflozin from MAF to SDL and delisting of dapagliflozin**

Date of Publication	2 Jan 2024