Sodium-glucose co-transporter 2 (SGLT2) inhibitors

for treating type 2 diabetes mellitus

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 indication for treating type 2 diabetes mellitus, 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 5 mg 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. Subsidy **does not** apply to any formulations or strengths of canagliflozin.

Updated: 2 January 2024

Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1 At the November 2016 meeting, the MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin and empagliflozin) as part of a dual or triple oral therapy regimen for treating type 2 diabetes mellitus. A subsequent evaluation was presented to the Committee in January 2018, to consider the use of SGLT2 inhibitors as add-on therapy to insulin. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts in the Ministry of Health Diabetes Working Group. Published clinical and economic evidence for SGLT2 inhibitors was considered in line with specific clinical criteria defined by clinical experts to reflect their use in local clinical practice.

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 subsidy considerations.

1.4 Following negative recommendations on the basis of unfavourable cost-effectiveness at the 2016 and January 2018 meetings, the companies of canagliflozin and empagliflozin submitted revised pricing proposals, which the Committee considered in April 2018.

1.5 In 2020, the Committee reviewed local safety data for SGLT2 inhibitors and discussed whether the existing MAF clinical criteria for dapagliflozin and empagliflozin could be revised, to allow use at the same line of therapy as sulfonylureas (SUs) as part of dual therapy with metformin.

1.6 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.

Clinical need

2.1 In 2016, the Committee recognised that:

- Type 2 diabetes mellitus was a substantial and growing public health burden in Singapore;
- SGLT2 inhibitors have a different mechanism of action compared with other commonly used oral agents for diabetes management, such as metformin, sulfonylureas (SU), and dipeptidyl peptidase 4 (DPP-4) inhibitors, and are an important addition to diabetes treatment options; and
- SGLT2 inhibitors are commonly used as add-on therapy to insulin, with or without metformin, in patients whose diabetes is inadequately controlled.

Clinical effectiveness and safety

Dual and triple therapy

3.1 In 2016, the Committee agreed that SU was the appropriate main comparator for SGLT2 dual therapy with metformin given that DPP-4 inhibitors are currently not subsidised.

3.2 The Committee reviewed the clinical evidence for all three SGLT2 inhibitors. It noted that there were no head-to-head randomised controlled trials directly comparing the three SGLT2 inhibitors. Moreover, results from a published network meta-analysis showed no clinically significant difference in HbA1c reduction, and no significant difference in weight reduction, systolic blood pressure reduction, and rates of adverse events among all SGLT2 inhibitors.

3.3 The Committee noted the class safety warnings issued by US FDA for SGLT2 inhibitors in terms of the increased risk of diabetic ketoacidosis (DKA) and serious urinary tract infections (UTIs), as well as the recent cases of DKA reported to Health Sciences Authority (HSA). The Committee noted the recommendations by local and international regulatory agencies that the prevalence of DKA is infrequent and the benefits of SGLT2 inhibitor therapy outweigh the risk.

3.4 The Committee noted that only empagliflozin currently has evidence to show favorable long-term cardiovascular outcomes at three years (EMPA-REG OUTCOME trial). However, these outcomes were restricted to patients with high cardiovascular risk, which the Committee considered was not generalisable to the overall patient population with type 2 diabetes in Singapore. The Committee noted results from outcome studies for canagliflozin (CANVAS) and dapagliflozin (DECLARE) would not be published until 2017 and 2019, respectively.

3.5 The Committee agreed that all SGLT2 inhibitors could be considered as a class given their same mechanism of action and considered that they were clinically comparable in effectiveness and safety.

3.6 The Committee noted that when compared with SU and DPP-4 inhibitors in dual therapy with metformin, SGLT2 inhibitors showed statistically significant reductions in HbA1c (-0.06% and -0.17%). However, SGLT2 inhibitors were not considered clinically superior to SU and DPP-4 inhibitors in terms of HbA1c reduction using a minimal clinically important difference (MCID) of 0.5%.

3.7 The Committee noted that when compared with sulfonylurea in dual therapy, SGLT2 inhibitors were superior in weight loss (-4.75kg), systolic blood pressure reduction (-4.96mmHg), and were associated with lower risk of hypoglycaemia, but higher risk of genital and urinary infections. When compared to DPP-4 inhibitors, the weight loss was less (-2.89kg), but higher risk of genital infections remained.

3.8 The Committee also agreed that in triple oral therapy regimens (combined with metformin and SU), SGLT2 inhibitors showed no clinically meaningful difference in HbA1c reduction but statistically significant reductions in body weight (-2.4kg) and systolic blood pressure compared with DPP-4 inhibitors.

Add-on therapy to insulin

3.9 In January 2018, the Committee reviewed the clinical evidence for the use of SGLT2 inhibitors in combination with insulin. In the absence of head-to-head trials, the Committee considered ACE's indirect comparison showing SGLT-2 inhibitors plus insulin was clinically comparable to DPP-4 inhibitors plus insulin in terms of improvement in HbA1c; however, SGLT-2 inhibitors plus insulin led to statistically better weight reduction (MD -2.05kg, 95%CI: -2.58 to 1.52) but an increased risk of UTI (RR 1.92, 95%CI 1.26 to 2.95) compared to DPP-4 inhibitors plus insulin. The Committee also noted the risk of hypoglycaemia and severe hypoglycaemia was comparable across the treatment groups.

Cost effectiveness

Cost effectiveness of SGLT2 inhibitors versus SU in dual therapy

4.1 In 2016, the Committee considered the cost-effectiveness model compared SGLT2 inhibitors to SU in dual therapy with metformin over a lifetime period. The Committee noted that at a selling price of [redacted], the base-case incremental cost-effectiveness ratio (ICER) would fall in the range of less than $15,000 per quality-adjusted life-year (QALY) gained. The Committee considered that the ICERs were within an acceptable range of cost-effectiveness in sensitivity analyses.

* Information redacted

Cost-effectiveness of SGLT2 inhibitors versus DPP-4 inhibitors in dual and triple therapy

4.2 The Committee was reminded that the ICERs for DPP-4 inhibitors compared with SU in dual therapy, from a previous evaluation considered in April 2016, were considerably higher than the ICERs for SGLT2 inhibitors compared with SU in all modelled scenarios.

The Committee noted that at time of evaluation, SGLT2 inhibitors were generally priced lower than the most commonly used DPP-4 inhibitor (sitagliptin). Therefore, no cost-effectiveness analysis of SGLT2 inhibitors versus DPP-4 inhibitors was conducted because SGLT2 inhibitors would be shown as dominant.

Cost-minimisation among the SGLT2 inhibitors

4.3 Given all three SGLT2 inhibitors were considered as a class, the Committee agreed a cost-minimisation approach was appropriate to select the lowest-priced SGLT2 inhibitor for subsidy consideration. It noted—at the 2016 and January 2018 meetings—that dapagliflozin, which had the lowest cost, was the most cost-effective option.

4.4 In April 2018, following revised price proposals received from the companies for empagliflozin and canagliflozin, the Committee agreed that the cost of empagliflozin was reasonable and could be considered an acceptable use of healthcare resources. Canagliflozin remained at a higher cost compared with dapagliflozin and empagliflozin and was the least cost-effective option.

4.5 In 2023, the Committee considered revised price proposals for dapagliflozin and 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 In April 2018, the Committee estimated up to 8,000 people in Singapore would benefit from government assistance for dapagliflozin and empagliflozin as part of a dual or triple therapy regimen. The cost impact was estimated to fall in the range of SG$1 to SG$3 million per year in the near term. When used as add-on therapy to insulin, the additional annual subvention amount for dapagliflozin and empagliflozin was estimated to be less than SG$1 million. In 2020, the Committee noted that the estimated increase in subvention to revise the MAF clinical criteria (see paragraph 6.3) was around SG$1 million per year.

5.2 The Committee acknowledged that the budget impact would likely increase each year due to the rise in incidence of diabetes, and expected substitution of SGLT2 inhibitors from oral agents—such as SU and DPP-4 inhibitors—once subsidy was available to patients.

5.3 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.

Additional considerations

6.1 In 2016, the Committee expressed concern about the increased risk of DKA associated with SGLT2 inhibitors and advised that as a cautionary measure, the use of SGLT2 inhibitors should be restricted to when SU is contraindicated or not tolerated as a dual therapy with metformin.

6.2 The Committee proposed a phased approach to subsequently remove the restriction if concerns about DKA do not materialise over time, and recommended that the subsidy criteria should be reviewed when more local safety data are available through HSA.

6.3 In 2020, the Committee reviewed the local incidence of DKA and UTIs from 2014 to 2019, and noted that the risk of severe adverse events associated with SGLT2 inhibitors remained low despite an increase in use during that period. The Committee therefore recommended that the existing MAF clinical criteria could be revised to allow SGLT2 inhibitors to be used at the same line of treatment as SU as part of dual therapy with metformin.

Recommendation

7.1 Based on the evidence presented in 2016, the Committee recommended dapagliflozin 5 mg and 10 mg tablets be listed on the MAF as part of dual therapy with metformin or SU, or as triple therapy with metformin and SU in patients with type 2 diabetes who meet certain clinical conditions, given its significant reduction in blood glucose level, weight, and systolic blood pressure, plus acceptable cost effectiveness at the price proposed by the company compared with SU and DPP-4 inhibitors in dual and triple therapy respectively.

7.2 The Committee considered it justifiable to expand the MAF listing to include use in combination with insulin at the January 2018 meeting based on clinical need in local practice, comparable clinical effectiveness to DPP-4 inhibitors, and acceptable cost effectiveness.

7.3 In April 2018, the Committee also recommended empagliflozin 10 mg and 25 mg tablets be listed on the MAF in line with the same clinical criteria as dapagliflozin, following an acceptable price discount offered by the company.

7.4 In 2020, the Committee recommended to revise the existing MAF clinical criteria to allow use of SGLT2 inhibitors at the same line of treatment as SU as part of dual therapy with metformin, in view of local data confirming low risk of serious adverse events associated with use.

7.5 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.

7.6 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 for treating type 2 diabetes mellitus

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	3 May 2017
2.	**Amendment to redact cost information**	
	Date of Publication	5 Feb 2018
3.	**Expansion of MAF listing recommendations to allow combination therapy with insulin**	
	Date of Publication	2 Jul 2018
4.	**Guidance updated to extend MAF listing to empagliflozin**	
	Date of Publication	1 Oct 2018
5.	**Guidance updated to revise MAF clinical criteria for empagliflozin and dapagliflozin**	
	Date of Publication	1 Sep 2020
6.	**Guidance updated to reflect reclassification of empagliflozin from MAF to SDL and delisting of dapagliflozin**	
	Date of Publication	2 Jan 2024

About the Agency

The Agency for Care Effectiveness (ACE) is the national health technology assessment agency in Singapore residing within the Ministry of Health. It conducts evaluations to inform the subsidy of treatments, and produces guidance on the appropriate use of treatments for public hospitals and institutions in Singapore. The guidance 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.

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