# Empagliflozin

Essential medicine status

Section: 18. Medicines for endocrine disorders > 18.5. Medicines for diabetes > 18.5.2. Oral hypoglycaemic agents

ATC codes: A10BK03

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| **Indication** | Type 2 diabetes mellitus ICD11 code: 5A11 |
| **INN** | Empagliflozin |
| **Medicine type** | Chemical agent |
| **List type** | Core |
| **Formulations** | Oral > Solid: 10 mg ; 25 mg |
| **EML status history** | First added in 2021 (TRS 1035) |
| **Sex** | All |
| **Age** | Adolescents and adults |
| **Therapeutic alternatives** | canagliflozin (ATC codes: A10BK02)<br>dapagliflozin (ATC codes: A10BK01) |
| **Patent information** | Main patent is active in several jurisdictions. For more information on specific patents and license status for developing countries visit www.MedsPal.org<br>Read more about patents. |
| **Wikipedia** | Empagliflozin |
| **DrugBank** | Empagliflozin |

## Expert Committee recommendation

Since SGLT2 inhibitors were last reviewed by the Expert Committee in 2017, new evidence has confirmed the positive effect of SGLT2 inhibitors compared with placebo on all-cause mortality, cardiovascular outcomes (cardiovascular mortality, non-fatal myocardial infarction and hospital admission for unstable angina), renal outcomes (kidney failure, end-stage renal disease and renal death), body weight and HbA1c. Based on this new evidence, the Expert Committee had increased confidence in the cumulative estimates and overall evidence for relevant clinical benefits associated with SGLT2 inhibitors as add-on therapy. The Committee noted that the situation is less clear when comparing SGLT2 inhibitors with GLP-1 RAs, although the SGLT2 inhibitors seem to be the preferred option as they are consistently associated with favourable results for most cardiovascular outcomes and are orally administered in contrast to GLP-1 RAs that need to be injected. The Committee considered that SGLT2 inhibitors are associated with some relevant adverse events such as urogenital infections, Fournier gangrene, osmotic diuresis and euglycaemic diabetic ketoacidosis. However, overall, the benefit-to-risk ratio favours SGLT2 inhibitors, particularly in patients with cardiovascular and kidney disease. While prices are substantially higher than for the oral hypoglycaemic agents currently listed on the EML (metformin and sulfonylureas), cost–effectiveness analyses, mainly conducted in high-income countries, suggest favourable incremental cost–effectiveness ratios at usual willingness-to-pay thresholds, given the effect of SGLT2 inhibitors on hard clinical outcomes. The Expert Committee therefore recommended the inclusion of SGLT2 inhibitors on the core list of the EML as a second-line therapy for patients with type 2 diabetes who have not achieved appropriate glycaemic control with metformin or a sulfonylurea. High-quality evidence shows there are clinically beneficial effects in this population, particularly in those at high risk of cardiovascular events and/or diabetic nephropathy, and there is a reasonable safety profile. The Committee recommended listing empagliflozin as the representative of the pharmacological class, with canagliflozin and dapagliflozin as therapeutic alternatives. The Expert Committee also recommended that the Medicines Patent Pool explores how to facilitate affordable access to SGLT2 inhibitors in low- and middle-income countries through public health-oriented licences with the companies holding the patents.

## Background

In 2013, the Expert Committee evaluated evidence comparing alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors (DPP-4), meglitinides and thiazolidinediones with metformin and sulfonylureas (1). The Committee concluded that "there was insufficient evidence to show that any of the medicines in the four groups (alpha-glucosidase inhibitors, dipeptidyl peptidase-4 inhibitors, meglitinides, or thiazolidinediones) offered any efficacy or safety advantages over the existing medicines included in the EML" (i.e. metformin first-line therapy and sulfonylurea second line). SGLT2 inhibitors were not included in the review as they had not entered the market at that time. In 2017, the Committee considered a review of medicines for second-line therapy for type 2 diabetes, including alpha-glucosidase inhibitors, basal, bolus and biphasic human insulins, analogue insulins, DPP-4 inhibitors, glucagon-like peptide 1 receptor agonists (GLP-1 RAs), meglitinides, SGLT2 inhibitors and thiazolidinediones based on an update of the 2013 review by the Canadian Agency for Drugs and Technologies in Health (2,3). The Expert Committee did not recommend the inclusion of second-line medicines for type 2 diabetes on the EML, and confirmed the role of sulfonylureas as one of the most cost-effective treatments for intensification therapy of type 2 diabetes. However, the Committee noted that SGLT2 inhibitors had shown a relevant clinical benefit as second-line therapy in patients at high risk of cardiovascular events, with a reduction in overall mortality. The Committee considered that this finding needed to be confirmed with data from other trials before this class of medicines could be supported for inclusion on the EML (4). These data are now available with several reviews demonstrating cardiovascular and renal benefits of SGLT2 inhibitors. Consequently, these agents are routinely recommended by international guidelines. Empagliflozin was the first of these agents to demonstrate cardiovascular benefits (5).

## Public health relevance

Worldwide, diabetes affected an estimated 463 million people in 2019 (9.3% of the global population), of whom 79% live in low- and middle-income countries (6). The number of people with diabetes has almost tripled in the past 3 decades due to: increase in population size; population ageing; and the increasing prevalence of the main risk factors for diabetes – overweight, obesity and physical inactivity (7). In 2019, diabetes was responsible for over 1.5 million deaths and 2.79% of all global disability-adjusted life years (8). The burden of diabetes is projected to increase to affect 700 million people in 2045 (9). Diabetes is estimated to reduce life expectancy by 6 years when diagnosed at 40 years (10), and is a major cause of peripheral neuropathy, blindness, kidney failure and lower limb amputation. Diabetes complications affect quality of life and often lead to premature deaths, which is experienced by about a half of all people with diabetes. The incidence and prevalence of type 2 diabetes are much higher than type 1 diabetes, with type 2 diabetes responsible for about 90–95% of all diabetes cases (6).The annual global expenditure on health care for people with diabetes is estimated to be US$ 850 billion, 12% of the overall global health care expenditure (9).

## Benefits

Systematic reviews and meta-analyses A systematic review and network meta-analysis of 730 trials (402 030 participants) compared 11 glucose-lowering medicines added to background therapy as part of a guideline development process for the Australian evidence-based clinical guidelines for diabetes (11). For the clinical question, "Should GLP-1 receptor agonist, SGLT2 inhibitors, sulfonylurea or DPP-4 inhibitor be used as an add-on in adults with type 2 diabetes? Will it differ by cardiovascular risk groups?", the following findings were reported. • SGLT2 inhibitors lowered the odds of all-cause mortality compared with placebo, DPP-4 inhibitors, GLP-1 RAs or sulfonylureas as add-on therapy (high-certainty or moderate-certainty in lowest-risk patients because of indirectness). • SGLT2 inhibitors lowered the odds of hospitalization for heart failure compared with placebo, DPP-4 inhibitors, GLP-1 RAs or sulfonylureas when added to background treatment (high-certainty or moderate-certainty in lowest-risk patients because of indirectness). • There was no evidence that SGLT2 inhibitors lowered the odds of a major adverse cardiovascular event (three-item major adverse cardiovascular events – composite of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke) compared with placebo when added to background therapy (moderate-certainty evidence because of imprecision). • SGLT2 inhibitors probably lowered the odds of a major adverse cardiovascular event (four-item major adverse cardiovascular events: three-item plus hospitalization for unstable angina) compared with placebo or a GLP-1 RAs added to background therapy (high-certainty and moderate-certainty evidence in lowest-risk patients because of indirectness). • There was no evidence that an SGLT2 inhibitor added to background therapy increased severe hypoglycaemia more than placebo (high-certainty or moderate-certainty evidence in lowest-risk patients because of indirectness). • SGLT2 inhibitors decreased kidney failure compared with placebo when added to background therapy (high-certainty or moderate-certainty evidence in lowest-risk

patients because of indirectness). • SGLT2 inhibitor therapy decreased HbA1c compared with standard therapy (high-certainty evidence). • The odds of serious adverse events were lower with SGLT2 inhibitors than standard care (high-certainty or moderate-certainty in lowest-risk patients because of indirectness). There was no evidence that other therapies added to background therapy had different odds of serious adverse events (high-certainty evidence). Based on these findings, the guideline group made a strong recommended for the addition of an SGLT2 inhibitor to other glucose-lowering medication(s) in adults with type 2 diabetes who have cardiovascular disease, multiple cardiovascular risk factors and/or kidney disease. A 2021 systematic review and network meta-analysis of 764 trials (421 346 participants) compared SGLT2 inhibitors or GLP-1 RAs with placebo, standard care or other glucose-lowering treatments in adults with type 2 diabetes with varying cardiovascular and renal risks (12). The results are summarized below for the addition of SGLT2 inhibitors to existing diabetes treatment. (Table 8 in WHO Technical Report Series, No. 1035). All-cause mortality Data on all-cause mortality were reported in 238 trials including 290 662 patients. SGLT2 inhibitors lowered all-cause mortality compared with placebo (odds ratio (OR) 0.77, 95% confidence interval (CI) 0.71 to 0.83). In absolute terms, five fewer events per 1000 in 5 years occurred for very-low-risk patients (moderate certainty evidence), 15 fewer events for low-risk patients, 25 fewer events for moderate-risk patients, 34 fewer events for high-risk patients and 48 fewer events for very-high-risk patients (high certainty evidence). SGLT2 inhibitors reduced all-cause mortality compared with GLP-1 RAs (OR 0.88, 95% CI 0.79 to 0.97). In absolute terms, two, seven, 12, 16 and 23 fewer events per 1000 in five years occurred for very low, low, moderate, high, and very high risk patients, respectively (moderate-to-high certainty). Cardiovascular mortality Data on cardiovascular mortality were reported 135 trials including 226 701 patients. SGLT2 inhibitors lowered cardiovascular mortality compared with placebo (OR 0.84, 95% CI 0.76 to 0.92). In absolute terms, two, seven, 12, 16 and 24 fewer events per 1000 in 5 years occurred for very low, low, moderate, high and very high risk patients, respectively (moderate-to-high certainty evidence). There was no difference in effects on cardiovascular mortality between SGLT2 inhibitors and GLP-1 RAs (OR 0.96, 95% CI 0.84 to 1.09; moderate-to-high certainty evidence). Non-fatal myocardial infarction Data on non-fatal myocardial infarction were reported in 208 trials including 265 921 patients. SGLT2 inhibitors lowered the odds of non-fatal myocardial infarction compared with placebo (OR 0.87, 95% CI 0.79 to 0.97). In absolute terms, four, seven, 13, 14 and 21 fewer events per 1000 in 5 years occurred for very low, low, moderate, high and very high risk patients, respectively (moderate-to-high certainty evidence). There was no difference in effects on non-fatal myocardial infarction between SGLT2 inhibitors and GLP-1 RAs (OR 0.95, 95% CI 0.84 to 1.08; moderate-to-high certainty evidence). Non-fatal stroke Data on non-fatal stroke were reported in 176 trials including 261 434 patients. SGLT2 inhibitors had no-to-little effect on non-fatal stroke compared with placebo (OR 1.01, 95% CI 0.89 to 1.14; moderate-to-high certainty evidence). Compared with GLP-1 RAs, SGLT2 inhibitors had higher odds of non-fatal stroke (OR 1.20, 95% CI 1.03 to 1.41; moderate-to-high certainty evidence). Kidney failure Data on kidney failure were reported in 33 trials including 98 284 patients. SGLT2 inhibitors reduced the odds of kidney failure compared with placebo (OR 0.71, 95% CI 0.57 to 0.89). In absolute terms, one, three, six, 25 and 38 fewer events per 1000 in 5 years occurred for very low, low, moderate, high and very high risk patients, respectively (moderate to high certainty evidence). There was no difference in effects on kidney failure between SGLT2 inhibitors and GLP-1 RAs (OR 0.91, 95% CI 0.69 to 1.20; low-to-moderate certainty evidence). Admission to hospital for heart failure Data on admission to hospital for heart failure were reported in 149 trials including 242 361 patients. SGLT2 inhibitors reduced hospital admissions for heart failure compared with placebo (OR 0.70, 95% CI 0.63 to 0.77). In absolute terms, two, nine, 23, 29 and 58 fewer events per 1000 in 5 years occurred for very low, low, moderate, high, and very high risk patients, respectively (moderate-to-high certainty evidence). Compared with GLP-1 RAs, SGLT2 inhibitors reduced hospital admissions for heart failure (OR 0.74, 95% CI 0.65 to 0.85). In absolute terms, one, seven, 18, 24 and 48 fewer events per 1000 in 5 years occurred for very low, low, moderate, high, and very high risk patients respectively (moderate to high certainty evidence). Body weight Data on body weight were reported in 469 trials including 226 361 patients for a median follow-up of 6 months. There was low certainty evidence that SGLT2 inhibitors might reduce body weight compared with placebo (mean difference (MD) −1.92 kg, 95% CI −2.23 to −1.62). There was moderate certainty evidence that SGLT2 inhibitors reduced body weight more than GLP-1 RAs (MD −0.47 kg, 95% CI −0.85 to −0.09). Glycated haemoglobin A1c (HbA1c) Data on HbA1c were reported in 604 trials including 242 745 patients for a median follow-up of 6 months. There was low certainty evidence that SGLT2 inhibitors reduced HbA1c levels more than placebo (MD −0.60%, 95%CI −0.67 to −0.54). There was high certainty evidence that GLP-1 RAs reduced HbA1c more than SGLT2 inhibitors (MD −0.28%, 95% CI –0.37 to −0.19). The 2020 Kidney Disease Improving Global Outcomes (KDIGO) guidelines include a level 1 (strong) recommendation for treating patients with type 2 diabetes who have an estimated glomerular filtration rate greater than 30 mL/min per 1.73m2 with an SGLT2 inhibitor (13). This recommendation was based on the demonstrated cardiovascular benefits reported for SGLT2 inhibitors (empagliflozin, canagliflozin and dapagliflozin) from numerous randomized controlled trials (5,14–18). The benefits of SGLT2 were also reported in a real-world registry study, with reduced risks

of hospitalization for heart failure and cardiovascular mortality (19). Benefits for the kidneys were also demonstrated in studies with prespecified renal outcomes: (i) empagliflozin was associated with a lower risk of incident or worsening nephropathy compared with placebo (–12.7% versus 18.8%, hazard ratio (HR) 0.61, 95% CI 0.53 to 0.70) (20); (ii) canagliflozin was associated with a lower risk of progression of albuminuria (HR 0.73, 95% CI 0.67 to 0.79), and a lower risk of the composite outcome of 40% reduction in estimated glomerular filtration rate, need for kidney replacement therapy or death from renal cause (HR 0.60, 95% CI 0.47 to 0.77) (16); and (iii) dapagliflozin was associated with a lower risk of the composite outcome of 40% reduction in estimated glomerular filtration rate to < 60 mL/min per 1.73m2, end-stage kidney disease and cardiovascular or renal death (HR 0.67, 95% CI 0.67 to 0.87) (15). A systematic review and meta-analysis of four randomized controlled trials of SGLT2 inhibitors examined kidney outcomes in individuals with and without chronic kidney disease (21). For the subgroup of patients with an estimated glomerular filtration rate of 30 to < 60 mL/min per 1.73m2, SGLT2 inhibitors were associated with a reduced risk of adverse kidney outcomes – worsening kidney failure, end-stage kidney disease or renal death – HR 0.76, 95% CI 0.51 to 0.89). Other trials of SGLT2 inhibitors in patients with chronic kidney disease also demonstrated better renal outcomes in the SGLT2 arms (16,22). In addition, real-world data suggest that the renal benefits of SGLT2 inhibitors are generalizable to clinical practice (23).

## Harms

The most common adverse events with SGLT2 inhibitors are genital infections related to glycosuria. The increased risk of genital mycotic infections with SGLT2 inhibitors in both men and women is consistent across all clinical trials. SGLT2 inhibitors increased genital infection compared with placebo with high-certainty, resulting in 143 more genital infections per 1000 patients treated for 5 years (12). Fournier gangrene, an aggressive and life-threatening necrotizing fasciitis of the external genitalia, perineum and perianal region, is a serious but rare adverse event associated with the use of SGLT2 inhibitors. This condition is much more common in men than in women, and diabetes is a predisposing factor. In 2018, the United States Food and Drug Administration required a warning about the risk of Fournier gangrene to be added to the prescribing information of all SGLT2 inhibitors. In a postmarketing review, 55 cases of Fournier gangrene were identified by the Food and Drug Administration in 6 years of SGLT2 inhibitor use compared with 19 cases over 35 years for all other drugs that lower blood glucose (24). High-quality evidence from a systematic review and meta-analysis of 39 randomized controlled trials (60 580 patients) reported an increased risk of diabetic ketoacidosis with SGLT2 inhibitors compared with placebo or other antidiabetic drugs (Peto OR 2.13, 95% CI 1.38 to 3.27), with an absolute rate of three events per 1000 patients over 5 years (25). In May 2015, the Food and Drug Administration issued a drug safety communication warning that treatment with SGLT2 inhibitors may increase the risk of ketoacidosis (26). An increased risk of bone fractures and lower-limb amputations associated with canagliflozin was reported in one randomized controlled trial (14). Subsequent meta-analyses and real-world data, however, did not identify an increased risk of bone fractures in patients treated with SGLT2 inhibitors (27,28). A systematic review of seven randomized controlled trials suggested no statistically significant association between exposure to SGLT2 inhibitors and lower-limb amputations. However, subgroup analysis of canagliflozin versus placebo indicated a statistically significant increased risk (29). The Food and Drug Administration warning on canagliflozin about the increased risk of amputations was removed in 2020 (30). The Australian guideline review found moderate- to high-certainty evidence that SGLT2 inhibitors have lower odds of serious adverse events than standard care, and high-certainty evidence that there was no evidence that other therapies added to background therapy had different odds of serious adverse events. In addition, there was no evidence that an SGLT2 inhibitor added to background therapy increased severe hypoglycaemia more than placebo (11). A 2020 study analysed the safety and tolerability of empagliflozin compared with placebo by pooling data from clinical trials. The frequency of serious adverse events requiring hospitalization was 18.6% for the empagliflozin group and 21.3% for the placebo group. Empagliflozin was not associated with a higher rate of confirmed hypoglycaemia compared with placebo, except in patients also receiving insulin and/or a sulfonylurea. The incidence or urinary tract infections was similar between groups. Genital infections occurred more frequently in patients treated with empagliflozin. Volume depletion events were similar across groups but were more frequent with empagliflozin in patients aged 75–85 years and those on loop diuretics at baseline (31).

## Cost / cost effectiveness

The cost–effectiveness of SGLT2 inhibitors has been studied in recent systematic reviews and a meta-analyses (34–36). Most studies identified found SGLT2 inhibitors to be cost-effective compared with older classes of second-line glucose-lowering medicines, especially for patients at a high risk of developing cardiovascular disease. Beyond glucose-lowering effects, the beneficial effects of SGLT2 inhibitors on renal function, cardiovascular outcomes and obesity are key drivers of cost–effectiveness. Estimates of the cost–effectiveness of SGLT2 inhibitors outside high-income countries are limited. Low- and middle-income

countries are likely to have lower willingness-to-pay thresholds for cost–effectiveness, and SGLT2 inhibitors will have to have significantly lower prices in low- and middle-income countries than the current originator prices in high-income countries in order to be cost-effective. In 2018, the Medicines Patent Pool published a feasibility study examining the SGLT2 inhibitor market in detail, in terms of patient access to SGLT2 inhibitors (at the time), pricing, the intellectual property landscape, and potential clinical benefits and cost savings if access were expanded by voluntary licensing through the Medicines Patent Pool model. The Medicines Patent Pool estimated that SGLT2 inhibitor prices could decrease substantially when and where competitive generic manufacture is established (37).

## WHO guidelines

In 2018, WHO published guidelines on pharmacological agents for managing hyperglycaemia in type 1 and type 2 diabetes for use in primary health care in low-resource settings (32). Several newer oral agents were reviewed, including DPP-4 inhibitors, SGLT2 inhibitors and thiazolidinediones. GLP 1 RAs were outside the scope of these guidelines. The guideline group acknowledged that SGLT2 inhibitors look particularly promising. Empagliflozin, when compared with placebo, had a protective effect on a composite outcome of death from cardiovascular causes, non-fatal myocardial infarction, or non-fatal stroke in one study in people with type 2 diabetes at high cardiovascular risk (5). However, more evidence was needed to determine whether this was a class effect and whether there was a cardioprotective effect in the general population of people with type 2 diabetes. The WHO guideline group considered insulin to be comparable to SGLT2 inhibitors when weighing desirable and undesirable effects. Insulin and thiazolidinediones were most effective at lowering HbA1c, while DPP-4 inhibitors and SGLT2 inhibitors were better than thiazolidinediones in lowering body weight (33). Based on these data, the following recommendations were made for the second- and third-line treatment of type 2 diabetes (32). • Give a sulfonylurea to patients with type 2 diabetes who do not achieve glycaemic control with metformin alone or have contraindications to metformin (strong recommendation, moderate-quality evidence). • Introduce human insulin treatment to patients with type 2 diabetes who do not achieve glycaemic control with metformin and/or sulfonylurea (strong recommendation, very low-quality evidence). • If insulin is unsuitable, a DPP-4 inhibitor, SGLT2 inhibitor or a TZD may be added (weak recommendation, very low-quality evidence).

## Availability

SGLT2 inhibitors have wide global regulatory approval. Empagliflozin (Jardiance®, Boehringer Ingelheim) has primary patent protection until 2025. Canagliflozin (Invokana®, Janssen) has primary patent protection until 2024. Dapagliflozin (Farxiga®, Bristol-Myers Squibb) has primary patent protection until 2020–2023.


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