MTRAC
Midlands Therapeutics Review and Advisory Committee

Commissioning Support
SGLT2 inhibitors:

Dapagliflozin (Forxiga®), canagliflozin (Invokana®), empagliflozin (Jardiance®) and ertugliflozin (Steglatro®▼)

For the treatment of type 2 diabetes

Considerations for Commissioners:

- NICE guidance on the management of type 2 diabetes (NG28; updated 2017) recommends that if diet and lifestyle modification is insufficient to control blood glucose in people with type 2 diabetes, the first-line treatment is metformin, or a DPP-4i (dipeptidyl peptidase-4 inhibitor), pioglitazone or a sulfonylurea if metformin is not tolerated or contraindicated. Sodium-glucose cotransporter- 2 inhibitors (SGLT2i) may be considered instead of a DPP-4i if an SU or pioglitazone is not appropriate. Further 'intensification steps' introduce dual and triple therapy combinations of the antidiabetic drugs; see the NICE treatment algorithm for further details.
- In addition to the management of blood glucose, key therapeutic targets in the NICE treatment pathway on diabetes are the management of blood pressure, management of lipids and cardiovascular (CV) risk, and identifying and managing complications.

Description of the technology

SGLT2i lower glucose levels by reducing renal reabsorption of filtered glucose, lowering the renal threshold for glucose, and thereby increasing urinary glucose excretion. Three SGLT2is are licensed for the treatment of insufficiently controlled type 2 diabetes; these are dapagliflozin (Forxiga®), canagliflozin (Invokana®), and empagliflozin (Jardiance®); the fourth, ertugliflozin (Steglatro®▼) is licensed for the improvement of glycaemic control in type 2 diabetes. All the products are indicated as an adjunct to diet and exercise, or as monotherapy in patients for whom the use of metformin is considered inappropriate due to intolerance or contraindications, or in addition to other medicinal products for the treatment of diabetes. Details of medicinal product combinations tested is in the Summaries of Product Characteristics (SPCs).[1-4]

The SGLT2is are administered as an oral tablet, once daily. For canagliflozin and empagliflozin, doses at the lower end of the range are recommended in people with reduced kidney function (estimated glomerular filtration rate [eGFR] persistently below 60 ml/min/1.73m^2 or CrCl <60 ml/min); no dose adjustment is advised for dapagliflozin or ertugliflozin. SGLT2i treatment should be discontinued where the eGFR is persistently less than 45 ml/min/1.73 m^2 or CrCl is persistently less than 45 ml/min. The box summarises key points from a review of the evidence for the comparative efficacy and safety of SGLT2i, see the main text for more details.

Efficacy (glucose lowering):

- Systematic review analyses showed SGLT2is had significantly improved glucose lowering efficacy (HBA_{1c}) *vs.* placebo treatment (pooled mean difference [MD] 0.69% [7.5 mmol/mol])
- In subgroup analyses of HbA_{1c} reduction, canagliflozin had the largest effect size (MD -0.85% compared with -0.60% for dapagliflozin and -0.69% empagliflozin.
- There was no difference in HbA_{1c} lowering efficacy *vs.* metformin
- Significantly greater HbA_{1c} lowering efficacy with SGLT2is than sulfonylureas and DPP4i.

CV outcome data

- Composite Major Adverse CV Events outcome (MACE: incidence of CV death, myocardial infarction [MI], or ischaemic stroke) was significantly lower with SGLT2i treatment than placebo in people with diabetes and existing atherosclerotic disease.
- A meta-analysis of CV outcome data showed significantly lower hospitalisation for heart failure with SGLT2i treatment *vs.* placebo, regardless of the patient's previous CV history; similar results for dapagliflozin, canagliflozin and empagliflozin from individual trials.
- No CV outcome data available yet for ertugliflozin.

Safety:

Mortality

- Two network meta-analyses found significantly lower all-cause and CV-related mortality for SGLT2i and GLP-1a *vs.* placebo, and for SGLT2i *vs.* DPP4i.

Renal outcomes data

- A meta-analysis found that *vs*. placebo SGLT2is showed significantly:
  - lower risk of dialysis, transplantation, or death due to kidney disease by 33%.
  - lower rates of end-stage renal disease and acute kidney injury.

Other safety outcomes

- **Diabetic ketoacidosis (DKA):** Reported incidences where DKA was present with only moderately elevated glucose levels. If patient unwell during treatment with SGLT2i, check ketone levels and signs of DKA. See overleaf for additional warnings regarding ketone monitoring.

Patient factors:

- Once daily tablet administration
- Genital mycotic infections are one of the common side effects
- Use of these treatments may increase the frequency of need to pass urine
- Potential for weight loss, average losses of 4kg were reported in trials
- Low risk of hypoglycaemia, unless in combination with other agents causing hypoglycaemia.

Annual cost (daily dose range):

• Canagliflozin (100 or 300 mg)	£476.98
• Empagliflozin (10 or 25 mg)	£476.98
• Dapagliflozin (10 mg)	£476.98
• Ertugliflozin (5 or 15 mg)	£383.25

Source: MIMs, January 2020

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Clinical evidence for efficacy and safety

Mortality and CV outcomes

This review focusses on the evidence available for CV and renal outcomes and mortality in patients treated with SGLT2is for type 2 diabetes.

Two network meta-analyses evaluating all newer antidiabetic drugs (DPP-4i, SGLT2i and GLP-1a [glucagon-like peptide agonists]) versus older treatments (sulfonylureas and thiazolidinediones) found that SGLT2is and GLP-1as were associated with significantly lower rates of all-cause mortality and CV mortality than placebo, and SGLT2is showed significantly lower rates than DPP-4is.[5 6]

A large network meta-analysis using indirect comparisons between drug classes (SGLT2is, GLP-1as and DPP-4is) and individual treatments within those classes has also been published[7]. The analyses found that, compared with sulfonylureas, SGLT2is had the highest probability of being more effective for the outcomes of all-cause mortality and lowering CV outcome events (CV death, non-fatal MI, non-fatal stroke, and unstable angina or hospitalization for unstable angina).

A further large systematic review that also incorporated regulatory submission data[8] confirmed some results of the previous reviews, but found no clear benefit for the outcomes of non-fatal MI and hospitalisation for unstable angina for SGLT2is *vs*. comparators.

CV and renal safety RCTs

Three large RCTs were identified that evaluated SGLT2is and focussed on patient-oriented CV and renal outcomes, and mortality[9-11]. All the trials enrolled patients either at increased risk of CV or renal disease, or with established disease. The DECLARE-TIMI 58[11], CANVAS[9] and EMPA-REG OUTCOME[10] trials evaluated dapagliflozin, canagliflozin and empagliflozin, respectively. The proportions of participants with established CV disease was 40.6%, 65.5%, and 100% of participants in the DECLARE-TIMI trial, CANVAS trial and the EMPA-REG OUTCOME trial, respectively.

The main outcome in these trials was the incidence of MACE events. Secondary outcomes included the primary outcome plus hospitalisation for heart failure or angina, and death due to any cause. In the DECLARE-TIMI 58 trial (dapagliflozin), the main secondary outcome was a composite of renal function measures: a sustained decrease of 40% or more in eGFR, incidence of new end-stage renal disease (ESRD), or death from renal or CV causes.

Renal outcomes were also the focus of the CANVAS-R trial, and the CREDENCE trial[12]; both of which evaluated canagliflozin in participants with type 2 diabetes. In the CANVAS-R trial, micro-or macroalbuminuria were amongst the possible risk factors for CVD, and participants had to have an eGFR at entry > 30ml/min/1.73 m^2 of body-surface area. In the CREDENCE trial, participants had established chronic kidney disease (CKD; defined as an eGFR of 30 to <90 ml/min/1.73m^2, and albuminuria (marker of renal function), defined as a urinary albumin-to-creatinine ratio of >300 to 5,000 mg/g (34 to 565 mg/mmol). The specific outcomes of these trials were progression of albuminuria in the CANVAS-R trial, and a composite of ESRD, doubling of the serum creatinine level from baseline, or death from renal or CVD in the CREDENCE trial.

Results

MACE outcome: Participants treated with canagliflozin and empagliflozin had significantly lower rates of MACE events that placebo-treated participants. In the DECLARE-TIMI trial[11], dapagliflozin was only shown to be non-inferior to placebo for this outcome. A meta-analysis of data from the trials found that the risk of MI or death due to CV causes was only reduced in patients with established atherosclerotic CV disease and not in those with multiple risk factors. SGLT2is had no effect on the incidence of stroke[13].

Hospitalisation for heart failure: lower rates of hospitalisation for heart failure were reported with dapagliflozin and canagliflozin treatment. Significantly lower rates of hospitalisation for heart failure, CV death and death due to any cause were reported with empagliflozin treatment. The meta-analysis of trial data found that the risk of hospitalisation for heart failure was significantly lower in SGLT2is versus placebo regardless of the patients' CV history[13].

Renal outcomes: In the CREDENCE trial[12], which included participants with established kidney disease, the rate of the primary composite outcome was 30% lower in the canagliflozin group (43.2 events/1,000 patient-years) *vs*. placebo (61.2 events/1,000 patient-years; HR 0.70, 95% CI 0.59 to 0.82, p = 0.00001). There was also a significantly lower risk of the components of the primary outcome with canagliflozin *vs*. placebo, including the incidence of ESRD, dialysis, kidney transplant or renal death.

In the DECLARE-TIMI trial (dapagliflozin)[11], a secondary outcome was the composite of the occurrences of a sustained decrease of 40% or more in eGFR, new ESRD, or death from renal or CV causes. The study found a significantly lower rate of this outcome (4.3% *vs*. 5.6%) with dapagliflozin *vs*. placebo (HR 0.76; 95% CI, 0.67 to 0.87).

A meta-analysis of renal outcomes data from the EMPA-REG OUTCOME, CANVAS, CREDENCE and DECLARE-TIMI 58 trials[14] evaluated a composite of incidence of dialysis, transplantation, or death due to kidney disease. SGLT2is lowered the risk of dialysis, transplantation, or death due to kidney disease by 33% compared with placebo (RR 0.67, 95% CI 0.52 to 0.86, p = 0.0019). SGLT2is also reduced ESRD (RR 0.65, 95% CI 0.53 to 0.81, p < 0.0001), and acute kidney injury (RR 0.75, 95% CI 0.66 to 0.85, p < 0.0001).[14]

Glucose lowering efficacy

A 2016 systematic review[15] compared canagliflozin 300 mg daily, dapagliflozin 10 mg daily or empagliflozin 25 mg daily with placebo or other active comparator for the treatment of type 2 diabetes. Of the 42 trials included, 12 had an active comparator arm and compared canagliflozin with glimepiride or sitagliptin (4 trials), dapagliflozin with metformin, glipizide or saxagliptin (4 trials), or empagliflozin with linagliptin, glimepiride or sitagliptin (4 trials). The main outcomes assessed were HbA_{1c}, serious adverse

events, death, severe hypoglycaemia, ketoacidosis and CVD.

Compared with placebo, SGLT2is were associated with significantly lower HbA_{1c} levels (MD -0.69%, 95% CI -0.75 to -0.62%). Subgroup analyses showed that canagliflozin had the largest effect size (MD -0.85%, 95% CI -0.99 to -0.71%) compared with -0.60% (95% CI -0.67% to -0.53%) for dapagliflozin and -0.69% (95% CI - 0.78% to -0.59%) for empagliflozin.

Compared with active treatment, there was no difference in HbA_{1c} lowering between SGLT2is and metformin (MD -0.05%, 95% CI 0.21 to 0.12%), but a larger HbA_{1c} lowering effect for SGLT2is compared with SU (MD -0.15%, 95% CI -0.21 to -0.08%) and DPP-4i (MD -0.25%, 95% CI -0.36 to -0.14%).

Ertugliflozin

There is as yet no published CV outcome trial for ertugliflozin. The VERTIS-CV trial[16] is expected to be completed at the end of 2019[17].

A systematic review of the efficacy of ertugliflozin[18] produced by the manufacturer used a network meta-analysis to make indirect comparison between ertugliflozin and other SGLT2is. It reported that ertugliflozin 15 mg was more effective than dapagliflozin 10 mg and empagliflozin 25 mg when added to diet/exercise and to metformin monotherapy. The HbA_{1c} reduction associated with ertugliflozin was no different from that associated with canagliflozin across all populations.

This was also accepted as evidence as part of the NICE technology appraisal of ertugliflozin[19].

Safety and Tolerability

- Data from systematic reviews and individual trials reported increased risks of external genital mycotic infections for all SGLT2is *vs*. placebo (RR 3.37, 95% CI 2.89 to 3.93, I^2 0%), and active comparator (RR 3.89, 95% CI 3.14 to 4.82, I^2 0.3%)[8 20].
- The risk of urinary tract infection (UTI) was not significantly greater than placebo for the SGLT2is as a class, but one systematic review found the risk to be significantly higher with dapagliflozin[20].
- A higher risk of lower limb amputation (mainly toes) was reported with canagliflozin treatment[9] (6.3 *vs*. 3.4 participants with amputation per 1000 patient-years, HR 1.97; 95% CI, 1.41 to 2.75), with 71% of the affected participants having their highest amputation at the level of the toe or metatarsal. This information has been included in an MHRA drug safety update[21]. In the later CREDENCE trial, there was no significant difference in the risk of lower limb amputation between canagliflozin and placebo[12].
- A higher risk of hypoglycaemia was found in the subset of trials in which SGLT2is were given in combination with a sulfonylurea, but not when used as monotherapy or in combination with metformin or insulin[20].
- Other MHRA advice relating to SGLT2is includes reports of Fournier's gangrene[22] (necrotising fasciitis of the genitalia or perineum), and advice on the risk of diabetic ketoacidosis[23].
- The Summaries of Product Characteristics have been updated with additional warnings regarding DKA. "Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. Treatment with the SGLT2i may be restarted when the ketone values are normal and the patient's condition has stabilised." [1-4]

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