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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