NHS
South West London

Sodium-glucose co-transporter-2 (SGLT2) inhibitors

Introduction

There are currently four SGLT2 inhibitors licensed in the UK for the management of type 2 diabetes (T2DM). There are a number of differences between the SGLT2 inhibitors; these include:

- Indications and dose
- Interactions
- Use in hepatic impairment
- Use in renal impairment
- Monitoring requirements

Further detailed information on the above for the prescribing of canagliflozin, dapagliflozin, empagliflozin and ertugliflozin can be found in the BNF.

Mechanism of action

Reversibly inhibits SGLT2 in the renal proximal convoluted tubule to reduce glucose reabsorption and increase urinary glucose excretion.

Before initiating SGLT-2 inhibitors

- **Determine renal function before treatment and refer to BNF for recommended dosing. Please note dose adjustment varies between different SGLT2 inhibitors**
- Check whether the person may be at increased risk of diabetic ketoacidosis (DKA), for example if:
    - They have had a previous episode of DKA
    - They are unwell with intercurrent illness
    - They are following a very low carbohydrate or ketogenic diet
- Address modifiable risks for DKA before starting a SGLT2 inhibitor. E.g., for people who are following a very low carbohydrate or ketogenic diet, they may need to delay treatment until they have changed their diet
- Advise adults with type 2 diabetes who are taking an SGLT2 inhibitor about the need to minimise their risk of DKA by not starting a very low carbohydrate or ketogenic diet without discussing it with their healthcare professional, because they may need to suspend SGLT2 inhibitor treatment

Contraindications

- Diabetic ketoacidosis - serious and potentially life-threatening cases of DKA have been reported in people taking SGLT-2 inhibitors. Advise to stop treatment immediately and seek medical advice if any clinical features of DKA develop
- Severe hepatic impairment: manufacturer advises to avoid canagliflozin, empagliflozin, and ertugliflozin
- Increasing age: avoid empagliflozin if aged over 85 years, as risk of volume depletion

- Active foot disease (such as skin ulceration, osteomyelitis, or gangrene): possible increased risk of lower limb amputation (mainly toes) with canagliflozin. Advise to stop treatment if signs of a foot complication develop, such as skin ulceration, discolouration, infection, or new pain/tenderness, and seek urgent medical assessment

Cautions

- History of foot ulcer, peripheral arterial disease, or lower limb amputation: increased risk of lower limb amputation (mainly toes) with canagliflozin. Advise to stop treatment if signs of a foot complication such as skin ulceration, discolouration, infection, or new pain/tenderness, and seek urgent medical assessment
- Increasing age, hypotension: risk of volume depletion
- Complicated urinary tract infection: consider temporarily stopping empagliflozin and canagliflozin treatment
- Lithium: renal excretion of lithium may be increased by empagliflozin, reducing serum lithium levels. Monitor levels frequently after starting empagliflozin and after dose changes

MHRA/Safety alerts

- SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis (April 2016)
- SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes) (March 2017)
- SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) (February 2019)
- SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness (March 2020)
- Dapagliflozin (Forxiga): no longer authorised for treatment of type 1 diabetes mellitus (December 2021)

Noteworthy Interactions (Individual product license contains full list)

- Cholestyramine: may potentially reduce canagliflozin exposure. Dosing of canagliflozin should occur at least 1 hour before or 4 to 6 hours after administration of a bile acid sequestrant, to minimize possible interference with absorption
- Dabigatran: dabigatran concentrations may be increased with canagliflozin. Monitor for signs of bleeding or anaemia when dabigatran is combined with canagliflozin
- Digoxin: risk of digoxin toxicity, monitor appropriately
- Enzyme-inducers (such as St John's wort, rifampicin, barbiturates, phenytoin, carbamazepine, ritonavir, efavirenz): may decrease the efficacy of canagliflozin
- Insulin and insulin secretagogues (such as sulfonylureas): cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue (such as a sulfonylurea) may be required to reduce the risk of hypoglycaemia

- Thiazide and loop diuretics: additive effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension

Information on adverse effects (Individual product license contains full list)

- Vulvovaginitis, balanoposthitis, urinary tract infection (UTI) or urosepsis
- **Fournier's gangrene**: this is a rare but potentially life-threatening necrotizing fasciitis of the genitalia and perineum (predominantly in men). May present as severe pain or tenderness, erythema, and swelling in the genital or perineal area, with fever or malaise. Advise to stop the SGLT2 inhibitor immediately and seek immediate medical assessment if suspected
- Complicated UTIs including pyelonephritis and urosepsis have been reported in patients treated with canagliflozin: consider temporarily stopping treatment if this occurs. Tubulointerstitial nephritis has been reported in people taking empagliflozin/metformin
- Constipation, nausea, thirst, dyslipidaemia, hypotension, syncope
- Lower limb amputation (canagliflozin)
- Renal impairment

Sick Day rules

If taken during an acute illness that can lead to dehydration, there is an increased risk of developing euglycaemic DKA and therefore SGLT2 inhibitors should be temporarily stopped. Further information can be found in the sick day rules document

Blood Glucose and Ketone Testing Strip Prescribing

For patients prescribed metformin/gliptins/Sodium-glucose Cotransporter-2 Inhibitor (SGLT2i) only or in combination

- Do not prescribe **blood glucose strips** for self monitoring unless short-term use advised by a specialist (e.g. when starting treatment with oral or intravenous corticosteroids or to confirm suspected hypoglycaemia). Advise patients can buy meters and blood glucose strips if they wish to
- Do not prescribe **ketone strips** solely for use by patients prescribed an SGLT2 inhibitor. If a patient on an SGLT2 inhibitor presents unwell, their blood ketone levels should be checked by the healthcare professional, even if blood glucose levels are in the normal range

References

- BNF online (Last accessed 08/09/2022)
- Clinical Knowledge Summaries (Last accessed 08/09/2022)
- Diabetes on the net - How to advise on sick day rules (Last accessed 08/09/2022)
- Drug Safety Updates (Last accessed 08/09/2022)

Document History

Version: V 1.0

Author: **SWL Diabetes Clinical Network**

NHS
South West London

Approved by: Integrated medicines committee (IMOC)

Approval date: **15th February 2023**

Review Date: 15th February 2025