NAPP DIABETES

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For Healthcare professionals:

APPROPRIATE USE OF SGLT2 INHIBITORS IN TYPE 2 DIABETES:

RIGHT PERSON, RIGHT MEDICATION, RIGHT TIME

INTRODUCTION:

Sodium-glucose co-transporter 2 (SGLT2) inhibitors are the latest class of blood glucose-lowering agents available for people with type 2 diabetes. They are taken once - daily and have the added benefits of enabling weight loss and reducing blood pressure as well as reducing HbA1c. They have a low risk of hypoglycaemia, and cardiovascular outcome trials for two of the agents demonstrate a reduced risk in cardiovascular events. Excess weight and an increased risk of cardiovascular disease are key features in type 2 diabetes, SGLT2 inhibitors can therefore be a useful treatment for many with this condition. However, like all medications, there are certain groups of people in whom the risks of taking an SGLT2 inhibitor may outweigh the benefits. This booklet describes best practice when considering the use of this class of medication.

SGLT2 INHIBITORS – HOW DO THEY WORK?

- Canagliflozin (Invokana▼) + Metformin 850mgs or 1g (Vokanamet▼)
- Dapagliflozin (Forxiga) + Metformin 850mgs or 1g (Xigduo)
- Empagliflozin (Jardiance▼) + Metfomin 850mgs or 1g (Synjardy▼)

Brief description of action: SGLT2 is a high capacity cotransporter located in the proximal convoluted tubule of the nephron, responsible for re-absorbing about 90% of the glucose in the glomerular filtrate back into the blood. SGLT2 inhibitors reduce this capacity, thereby promoting loss of glucose in the urine, up to 60 to 80g per day. This action reduces circulating blood glucose levels, encourages a reduction in weight through loss of calories and a reduction in blood pressure. (DeFronzo et al, 2012)

The current licence is for people with type 2 diabetes **NOT** type 1 diabetes

HbA1c efficacy as well as Cardiovascular Outcome Trials such as the CANVAS Program, EMPA-REG and CVD-REAL suggest a reduction in cardiovascular disease and heart failure risk (Zinman B et al, 2015, Neal B et al, 2017). These trials have been necessary, recommended by the Federal Drugs Administration in America, pre-licence since 2012 for all new drugs to show there are no increase in cardiovascular events.

Please check each manufacturer's separate SmPC for specific licence indications. SGLT2 inhibitors should **not** be co-prescribed with loop diuretics or Spironolactone, but are safe to be used with thiazide diuretics. SGLT2 inhibitors should not be initiated with an eGFR lower than 60mL/min/1.73m²

⚠ Always check full prescribing data for individual preparations

To gain optimum benefit from an SGLT2 inhibitor, always advise the person with type 2 diabetes to follow these instructions:

- **to drink at least two litres of fluid (ideally water) throughout the day to maintain good hydration.**
- **that they may void a slightly increased amount of urine at each visit to the toilet**
- **to pay attention to good personal hygiene**
- **that due to its mechanism of action, taking an SGLT2 inhibitor means their urine will test positive for glucose.**
- **to check their feet regularly for any problems with circulation, wounds or sore areas. Seek medical help if any present.**
- **to stop taking temporarily if vomiting**

Potential side effects:

- Urinary tract infection (UTI)
- Candida infections
- Diabetic Ketoacidosis (DKA)
- Increased risk of minor foot amputations
- Osmotic diuresis induced postural hypotension

Only a very small percentage of participants in clinical studies experienced the above side effects. Genital infections are common but can be treated with over the counter medicines. This is often a reason individuals discontinue treatment as they don't expect it

DIABETIC KETOACIDOSIS

Diabetic ketoacidosis (DKA) is a serious and life-threatening complication of diabetes caused by absolute or relative insulin deficiency (JBDS 2015), and usually only seen in people with type 1 diabetes. Rare cases of this condition (between 1 in 1000 and 1 in 10,000 patients) have occurred in acutely unwell people with type 2 diabetes taking SGLT2 inhibitors for the treatment of hyperglycaemia. A number of these cases have been atypical and associated with only moderately raised blood glucose levels (less than 14mmol/L) (EMA, 2016).

Signs and symptoms:

Always consider the possibility of DKA in any individual taking SGLT2 inhibitors with the following (EMA 2016):

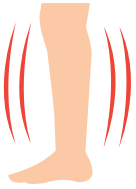
Excessive thirst

Shortness of breath and/or laboured breathing (Kussmauls breathing)

Passing frequent large volumes of urine

Mental confusion and drowsiness.

Abdominal pain



Leg cramps

Nausea and/or vomiting.

Dehydration

The onset of DKA is usually rapid (over hours or days). The diagnosis is confirmed in symptomatic individuals when there is:

- Significant ketonaemia > 3.0mmol/L or significant ketonuria (more than 2+ on standard urine sticks)
- Blood glucose > 11.0mmol/L
- Bicarbonate (HCO_3^-) < 15.0mmol/L and/or venous pH < 7.3

Remember the development of DKA is rare in people with type 2 diabetes on SGLT2 inhibitor treatment. However, always test for ketones and assess for DKA if there are signs of difficulty in breathing, nausea, vomiting, abdominal pain even if the blood glucose is lower than expected.

Who may be at increased risk?

There is an increased risk of developing DKA in those individuals with:

- A low insulin-producing capacity in the pancreas, e g history of pancreatitis, latent autoimmune diabetes in adults (LADA)
- A sudden reduction in insulin dose
- Increased insulin requirement (due to illness, surgery or alcohol abuse)
- In conditions that can restrict food intake or lead to severe dehydration (such as surgery).

Reducing risk:

SGLT2 inhibitors are only licensed for people with type 2 diabetes. Many of the cases of DKA occurred in people with type 1 diabetes prescribed SGLT2 inhibitors off-label. Health care professionals should discuss the risk of DKA along with any other side effects known to occur with individuals taking SGLT2 inhibitors before they are prescribed. They should also be informed of:

- Risk factors which increase the risk of developing DKA
- Common signs and symptoms of DKA
- When to stop or temporarily suspend treatment with SGLT2 inhibitors
- The need to seek urgent medical assistance if they become acutely unwell and/or exhibit any signs associated with DKA

When to stop or temporarily suspend treatment with SGLT2 inhibitor:

Stop treatment with the SGLT2 inhibitor immediately if DKA is suspected. Individuals with DKA will require urgent admission to hospital:

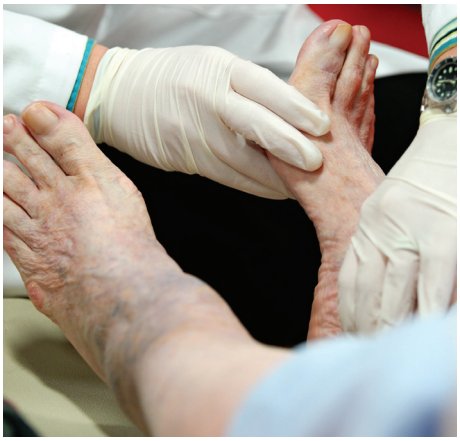
- Do not restart treatment with any SGLT2 inhibitor in individuals who experienced DKA during use, unless another cause for DKA was identified and resolved
- Temporarily suspend treatment with an SGLT2 inhibitor in individuals who are hospitalised; treatment may be restarted once the individual is discharged

INCREASED RISK OF LOWER LIMB AMPUTATION:

CANVAS and CANVAS R (Canagliflozin) demonstrated an increased risk of lower limb amputations (mainly involving toes) affecting between 1 to 10 per 1,000 patient years (Neal et al, 2017). Although not identified in data about the other two agents, the EMA concluded this complication was unlikely to be specifically restricted to the use of canagliflozin and, therefore, issued a warning. The warning is present on the SmPCs for all three agents.

Who may be at increased risk?

All people with diabetes are at increased risk of developing foot ulcers and gangrene requiring amputation, especially if they have poorly controlled diabetes and established renal or cardiovascular disease. SGLT2 inhibitors may not be an appropriate choice of therapy for people with an existing or previous lower extremity skin ulcer, peripheral vascular disease, infection, osteomyelitis or gangrene affecting the foot.



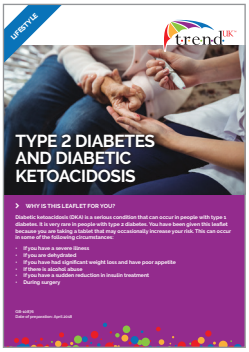
Reducing risk:

All people with diabetes should have their feet and footwear examined as part of their annual diabetes review. They (or their carer) should be taught basic foot care and look after their feet, to wear appropriate shoes and socks/stockings, to keep well-hydrated, and to be able to identify problems with their feet. They should know when and where to access help if they develop pain, discolouration, infection or a wound on their foot.

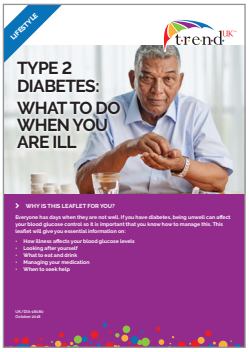
RESOURCES:

TREND-UK website: www.trend-uk.org

TREND-UK leaflets:



Type 2 diabetes and diabetic ketoacidosis



Type 2 diabetes: What to do when you are ill

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TRAINING, RESEARCH AND EDUCATION FOR NURSES IN DIABETES

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