South East London Guide for Prescribing Sodium Glucose Co-transporter 2 (SGLT2) inhibitors in HbA1c Management in Adults with Type 2 Diabetes Mellitus (T2DM)

This guidance was developed by the SEL Diabetes Medicines Working Group on behalf of the SEL IMOC

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South East London Integrated Medicines Optimisation Committee (SEL IMOC). A partnership between NHS organisations in South East London Integrated Care System: NHS South East London (covering the boroughs of Bexley/Bromley/Greenwich/ Lambeth/Lewisham and Southwark) and GSTFT/KCH /SLaM/ Oxleas NHS Foundation Trusts and Lewisham & Greenwich NHS Trust

South East London: Guide for Prescribing Sodium Glucose Co-transporter 2 (SGLT2) inhibitors in HbA1c Management in Adults with Type 2 Diabetes Mellitus (T2DM)

Introduction and scope

- SGLT2 inhibitors are an established class of medication for the treatment of T2DM which act by preventing the absorption of glucose and sodium, mainly from the proximal renal tubule in the kidney. Glucose and sodium are therefore lost in urine. People do not become hyponatraemic (unless on diuretics as well) as most of the sodium is reabsorbed in the distal tubule. This results in decreased blood glucose, weight loss, an osmotic diuresis and a drop in blood pressure (~3-5mmHg systolic and 2mmHg diastolic BP in clinical studies)
- The drugs have been licensed and used widely in T2DM and have shown significant CV and renal benefits in different subsets of this group of patients
- SGLT2 inhibitors also have a growing evidence base for cardio +/- renal protective effects independent of glycaemic effectiveness. Further data is emerging and may be reflected in ongoing licensing changes for individual drugs within the class
- Updated T2DM NICE guidance (NG28, February 2022) recommends a wider group of patients where SGLT-2i are indicated

This document aims to guide safe prescribing of SGLT2 inhibitors within licence for glycaemic control in T2DM and in line with NICE NG28 guideline

Which SGLT2 inhibitors are licensed?

SGLT2 inhibitors have licenses for treatment of insufficiently controlled T2DM, chronic kidney disease (CKD) (with and without T2DM) and symptomatic chronic heart failure (HF) with reduced ejection fraction (with or without T2DM). SGLT2 inhibitors have also been shown to reduce the risk of cardiovascular events in people living with T2DM and atherosclerotic cardiovascular disease (ASCVD).

The table below shows licensed indications (✓) along with SEL formulary RAG rating/status.

SGLT2 inhibitor	Insufficiently controlled T2DM	HF with reduced ejection fraction	CKD/Diabetic kidney disease (DKD)*
Canagliflozin	✓		✓** Please check formulary for current status
Dapagliflozin	✓	✓	✓***
Empagliflozin	✓	✓ Please check formulary for current status	
Ertugliflozin^	✓		

*NICE NG28: Offer SGLT2 inhibitor in T2DM and CKD for those taking an ACEi/ARB titrated to maximum licensed tolerable dose if ACR is >30mg/mmol and SGLT2 inhibitor use is within license (including eGFR thresholds). Consider SGLT2 inhibitor in T2DM and CKD for those taking an ACEi/ARB titrated to maximum licensed tolerable dose if ACR is between 3 and 30mg/mmol and SGLT2 inhibitor is licensed (including eGFR thresholds).

**licensed for DKD

***licensed for treatment of CKD. NICE TA 775: an option for CKD in adults only if it is an add-on to optimised standard care including highest tolerated licensed dose of ACEi/ARB unless contra-indicated and people have eGFR 25 - 75 ml/min/1.73 m^2 at initiation and have T2DM or urine ACR≥ 22.6 mg/mmol.

^ At the time of publication, the SGLT2 inhibitors with proven cardiovascular benefit are canagliflozin, dapagliflozin and empagliflozin.

This information is correct at the time of writing. Licenses and formulary status are changing rapidly. Always check the up to date SEL formulary status and licensing

Who is likely to benefit from SGLT2 inhibitors?

It is important to select the right patient for SGLT2 inhibitor therapy and avoid in others who may be at high risk of DKA (see page 2). The following patients are likely to benefit most:

- Adults above 18 years with T2DM and one or more of the following:
  - established / high risk of cardiovascular disease (NICE guidance NG28 advises SGLT2 use in people with QRISK2 of 10% or higher)
  - chronic kidney disease with albuminuria (please see table above) on standard of care (e.g.ACE inhibitor (ACEi)or angiotensin receptor blocker (ARB))
  - history of heart failure on standard of care – see SEL guidance on management of heart failure
  - inadequate glycaemic control with need to minimise hypoglycaemia if eGFR >45 ml/min (no significant glucose lowering if eGFR<45ml/min)
  - inadequate glycaemic control with need to minimise weight gain / encourage weight loss
- Patients with a clear understanding of the risks associated with SGLT2 inhibitors and how to reduce those risks and follow sick day rules

Looking to start an SGLT2 inhibitor

Discuss individualised benefits of taking SGLT2 inhibitor and document the indication at initiation

Check that this is the right drug for the person (including assessing diabetic ketoacidosis (DKA) risk factors)

Use with CAUTION in the following circumstances

Patient characteristics

- Body mass index <25kg/m^2(<23kg/m^2 in South Asian people)
- Person adhering to a ketogenic/low calorie/low carbohydrate diet/intermittent fasting
- Recent weight loss
- Potential for pregnancy
- People at risk of hypotension/hypovolaemia (e.g. elderly)
- People diagnosed with or at risk of frailty
- Cognitive impairment or use of medicine compliance aids (*may* imply inadequate understanding required to follow sick day rules and take action to prevent and identify DKA)
- On high dose diuretics for heart failure (may need dose adjustment, contact heart failure team for advice)

Other past medical history

- On long term or recurrent courses of steroids (either IV or oral)
- Raised haematocrit
- Severe hepatic impairment
- Recurrent urinary tract or genital tract infections

Diabetes history

- Long duration of diabetes (generally over 10 years since diagnosis)
- Person with very high HbA1c (HbA1c >86mmol/mol)
- Person considered at high risk of acute effects of hyperglycaemia e.g. dehydration due to non-adherence to medication
- Past history of active foot disease/foot ulceration
- Existing diabetes foot ulcers
- Previous lower limb amputation
- History of peripheral arterial disease (PAD)
- Taking sulfonylureas and/or insulin – increased risk of hypoglycaemia if started on SGLT2 inhibitors if eGFR>45 ml/min
- Recurrent problematic hypoglycaemia
- Those with risk factors for DKA e.g. low reserve of insulin secreting cells, conditions that restrict food intake or can lead to severe dehydration, a sudden reduction in insulin or increased requirement for insulin due to illness, surgery.

AVOID in the following circumstances

Patient characteristics

- Age <18 years
- Pregnant, breastfeeding, planning pregnancy, female in their child-bearing years and sexually active without contraception
- Person with excess alcohol consumption or intravenous drug user
- Hypersensitivity to active substance or excipients

Current medical history

- Acutely unwell person (acute medical illness including COVID-19, surgery or planned medical procedure)
- Active foot disease or acute ischaemic limb event
- Inpatient with vascular event who is not stable
- Eating disorder
- eGFR lower than allowed in the up-to date licensing of the medication being considered (see SPC - www.medicines.org.uk)
- Multiple pre-disposing risks for Fournier's gangrene
- Clinical features of significant insulin deficiency e.g. weight loss, symptoms of hyperglycaemia
- Organ transplant (unlicensed - discuss with diabetes team)

Diabetes history

- T1DM or suspected or possible T1DM
- Current/past history of DKA including ketone prone T2DM
- Any diagnosis or suspicion of latent autoimmune diabetes (LADA), other genetic causes of diabetes, known pancreatic disease or injury
- Rapid progression to insulin (within 1 year of diagnosis)
- Recent major surgery

If suitable for starting SGLT2 inhibitor then discuss with the individual the risks and benefits so they are able to make an informed decision about their care. Document the decision made and the discussion regarding risks and benefits. Check eGFR (trend and value), licensing (see page 1& 3) and HbA1c level. Counsel on side effects, sick day rules and when to stop therapy (see page 4)

This guideline is not exhaustive. This guidance does NOT override the individual responsibility of healthcare professionals to make decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. For clinical advice, contact the diabetes team. For further information on use of SGLT2 inhibitors including licensing, restrictions and interactions please see www.medicines.org.uk

Renal and hepatic function summary when used for glycaemic control

SGLT-2 inhibitor	Dose (when using in T2DM for glycaemic control)	Dose adjustments (When using in T2DM for glycaemic control)				
		eGFR≥60	eGFR 45-59	eGFR 30-44	eGFR <30	Hepatic impairment
				Note glycaemic benefit will be limited for all SGLT2 inhibitor below eGFR of 45ml/min as the glucose lowering efficacy of SGLT2 inhibitor therapy is dependent on renal function. Further glycaemic control may be required		
Canagliflozin SPC/PIL	100mg once daily. Increased if tolerated to 300mg once daily if required for glycaemic control	Initiate 100mg, titrate to 300mg if required	Initiate/continue with 100mg once daily only	**Not recommended for glycaemic control in T2DM** Initiate/continue with 100mg once daily only Further glycaemic control may be required	**Not recommended for glycaemic control in T2DM** Continue established treatment with 100mg daily but do not initiate. Can continue until dialysis or transplant if ACR >30mg/mmol when eGFR falls below 30. Stop if dialysis/transplant Further glycaemic control may be required	No dose adjustment in mild/moderate impairment. Not recommended in severe impairment
Dapagliflozin SPC/PIL	10mg once daily	Initiate 10mg daily		**Not recommended for glycaemic control in T2DM** **Do not initiate with an eGFR <15ml/min. Limited experience of initiating with eGFR <25ml/min.** Can continue with 10mg OD if person also has decompensated heart failure with reduced ejection fraction (HFrEF) or CKD down to eGFR of 15ml/min. However, it is worth noting that in the DAPA-HF trial no patients had an GFR <30ml/min Further glycaemic control may be required		No dose adjustment in mild or moderate impairment. Starting dose 5mg in severe impairment – can increase to 10mg if tolerated
Empagliflozin SPC/PIL	10mg once daily. Increased if tolerated to 25mg once daily if required for glycaemic control. Initiation not recommended in adults >85yrs.	Initiate 10mg, titrate to 25mg if required	Initiate with 10mg for those with T2DM and established cardiovascular disease (CVD). For those already taking empagliflozin, continue with 10mg only	**For insufficiently controlled T2DM:** Initiate or continue with 10mg for those with T2DM and established CVD only. Further glycaemic control may be required **For decompensated HFrEF:** Can continue with 10mg daily if person has HFrEF and T2DM down to eGFR of 20ml/min.	**Not recommended for glycaemic control in T2DM** **For decompensated HFrEF:** Can continue with 10mg daily if person has HFrEF and T2DM down to eGFR of 20ml/min. Do not initiate or continue if eGFR <20ml/min	No dose adjustment in mild/moderate impairment. Not recommended in severe impairment
Ertugliflozin SPC/PIL	5mg once daily Increased if tolerated to 15mg once daily if required for glycaemic control Dose to be taken in the morning	Initiate 5mg, titrate to 15mg if needed	Do not initiate. For those already taking ertugliflozin, continue 5mg or 15mg	**Not recommended**		

This document has been adapted with kind permission from Claire Davies, 'Top Tips and Recommendations for use of Sodium Glucose Co-transporter 2 inhibitors (SGLT2i) in people with Type 2 Diabetes (T2DM) For Glycaemic Control', NHS Northern England Clinical Networks (March 2022) and Hannah Beba 'Leeds Citywide Guideline for the Safe and Appropriate Use of Sodium Glucose Co-Transporter 2 inhibitors (SGLT2 inhibitors)' (2022). **Additional references:** GP Notebook, available via: www.gpnotebook.com, ABCD and DUK joint position statement and recommendations for non-diabetes specialists on the use of sodium glucose co-transporter 2 inhibitors in people with type 2 diabetes, January 2021, Clinical Medicine Vol 21, No 3: 204-10 - NICE, NG28, Type 2 diabetes in adults. Available via https://www.nice.org.uk/guidance/ng28 [Accessed 28.3.22], summary of product characteristics for SGLT-2i drugs available at www.medicines.org.uk (accessed 28.3.22 and 16.5.22)

When initiating SGLT-2 inhibitors: Prescribing considerations and monitoring

- **Minimise risk of hypoglycaemia:** Review glucose lowering medication that may cause hypoglycaemia e.g. insulin, sulfonylureas. Consider dose reductions when SGLT2 inhibitors initiated, especially if HbA1c is already at target. If insulin requirements fall significantly, be aware of a potential higher risk of DKA, especially in those with lower BMI and/or insulin sensitive. Contact diabetes team for advice where necessary
- **Minimise risk of diabetic ketoacidosis (DKA)**: review DKA risk factors and address modifiable risk factors (see page 2 and 4 for more information). Only start SGLT2 inhibitors if clinically appropriate. NB DKA can occur with normal glucose levels with SGLT2 inhibitors (euglycaemic ketoacidosis)
- **Minimise risk of hypotension** review diuretic and anti-hypertensive therapy periodically if hypertension improves or if there is postural hypotension.
- **Minimise risk of acute kidney injury**: review eGFR value and trend. Use in line with eGFR licensing and ensure counsel on sick day rules (see below)
- **Monitoring:** Measure HbA1c at baseline (recent HbA1c (up to 3 months prior to baseline) can be used if clinically stable/no changes), 3 months after initiation and then according to clinical need – see T2DM guideline. Blood pressure at baseline and then at least annually. Renal profile at baseline (recent renal profile (up to 3 months prior to baseline) can be used if clinically stable/no changes), and then as clinically indicated - If patient has CKD, see NICE guidance. Counsel on sick day rules and side effects at baseline (see below). Review side effects, adherence and sick day rule understanding at each review. Routine prescribing of urine or blood ketone test strips is **not recommended** for people with T2DM using SGLT2 inhibitors

When initiating SGLT-2 inhibitors: Information for the Patient

Only initiate after ensuring adequate understanding of the person in the following:

- Discuss individualised benefits of taking SGLT-2i
- Side effects and sick day rules (see overleaf)
- Foot care
- Importance of keeping hydrated and drinking plenty of sugar free fluids. If restricting fluid due to other conditions e.g. heart failure, please contact heart failure team for advice and guidance (unless advised to restrict fluids by healthcare professional due to kidney or heart problems or some other reason)
- Management and prevention of hypoglycaemia
- Minimising risk of DKA by not starting a very low carbohydrate diet or ketogenic diet without discussing with healthcare professional first

Patient education – sick day rules for SGLT2 inhibitors:

Sick day rules are essential when a person with diabetes is not well and is unable to eat and drink as normal, some simple rules can prevent further deterioration or DKA.

- If ill with diarrhoea, vomiting, fever, dehydration or unusual drowsiness, **STOP SGLT2** inhibitors. Only restart **AFTER** eating and drinking normally for **AT LEAST 24 HOURS AND** no longer acutely unwell (and as long as no new contra-indications exist)
- Drink plenty of water/sugar-free fluid to avoid dehydration
- Seek medical advice if particularly unwell with infection or illness or if symptoms are not resolved within 24 hours
- Stop SGLT2 inhibitors prior to surgery–as advised by pre-op team (see MHRA alert below for more information including advice on stopping if hospitalised)
- Ensure patients monitor symptoms and glucose levels more frequently during illness

Please ensure individual is aware of sick day rules for other medication they are taking

For further information on sick day rules for T2DM and coronavirus, please see NHS London Clinical Network guidance

Patient education - class side effects. Discuss signs, symptoms and management:

Common:

- Increased risk of UTI and genital infections
- Polydipsia, polyuria
- Volume depletion effects (thirst, postural dizziness, hypotension, dehydration)
- Very common - hypoglycaemia when used with insulin or sulfonylurea

Uncommon but serious (see MHRA info below for more detail):

- DKA (can also occur when glucose levels are normal and not raised)
- Lower limb amputation
- Fournier's gangrene
- Fracture risk

For full side effect profile see drug monograph (BNF/Summary of Product Characteristics (SPC)

Additional important safety information – see hyperlinks for more detailed advice:

- MHRA/CHM advice (updated April 2016): SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis (DKA)
  - People should be informed on the signs and symptoms of DKA, discontinue treatment with the SGLT2 inhibitor immediately if DKA is suspected or diagnosed
- MHRA/CHM advice (MHRA/CHM advice March 2017): SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes)
  - SGLT2 inhibitors may increase the risk of lower-limb amputation (mainly toes). All people taking an SGLT2 inhibitor should be counselled on good preventive foot care. Review if lower limb complications develop (e.g. skin ulcer, osteomyelitis, or gangrene). Monitor people with risk factors for amputation, signs and symptoms of water or salt loss.
- MHRA/CHM advice: SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) (February 2019)
  - If Fournier's gangrene is suspected, stop the SGLT2 inhibitor and urgently start treatment (including antibiotics and surgical debridement as required
- MHRA/CHM advice: SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness (March 2020)
  - SGLT2 inhibitor treatment should be interrupted in people who are hospitalised for major surgical procedures or acute serious medical illnesses & ketone levels measured, preferably in blood rather than urine. Treatment may be restarted when ketone values are normal & the person's condition has stabilised