Hertfordshire and West Essex adult (age ≥18 years) treatment pathway Dapagliflozin, Empagliflozin & Canagliflozin for treating Chronic Kidney Disease (CKD) with or without Type 2 Diabetes based on NICE TA775, NICE TA 942, NICE NG28 and NG203

For **type 2 diabetic patients** on a treatment regimen **without insulin** – **GREEN**

- See section on 'Patients with type 2 diabetic mellitus (T2DM)' for additional considerations.

For **type 2 diabetic patients** on a regimen **with insulin** - **AMBER INITIATION**

- Initiation by community or secondary care diabetes specialist teams.
- Primary care health professionals with specialist diabetes interests or who have undertaken the relevant training may initiate.

For **non-diabetic CKD patients with proteinuria** -

- **GREEN –** Recommended for initiation in primary care for patients in line with NICE TA775 and TA942 except those cases mentioned below under amber initiation.
- **AMBER INITIATION** - Nephrology specialists to initiate dapagliflozin or empagliflozin in patients who fall into the following categories (as there is no data from large randomised controlled trials for these cohorts) – Primary care to continue after specialist initiation:
    - Kidney transplant recipients
    - Polycystic kidney disease
    - Lupus nephritis
    - ANCA associated vasculitis
    - Patients receiving immunological therapy for kidney disease in the previous 6 months.

Initiation criteria in line with NICE TA775, TA 942 and NICE NG28

SGLT2 inhibitors, dapagliflozin, empagliflozin and canagliflozin, are recommended as an option for treating CKD in adults only if it is used as an **add-on to optimised standard care** with the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), unless these are contraindicated.

AND

For dapagliflozin

- CKD in non-diabetics - people have an estimated glomerular filtration rate (eGFR) of 25 to 75 ml/min/1.73 m^2 at the start of treatment **and** have a urine albumin-to-creatinine ratio (uACR) of 22.6 mg/mmol or more (in line with NICE TA775).
- CKD in patients with type 2 diabetes - people have an estimated glomerular filtration rate (eGFR) of 25 to 75 ml/min/1.73 m^2 at the start of treatment (in line with NICE TA775).

For empagliflozin

- CKD in non-diabetics - people have an eGFR of 20 to 45 ml/min/1.73 m2 at the start of treatment OR have an eGFR of 45 to 90 ml/min/1.73 m2 at the start of treatment and have a uACR of 22.6 mg/mmol or more (in line with NICE TA942).
- CKD in patients with type 2 diabetes - people have an eGFR of 45 to 90 ml/min/1.73 m2 at the start of treatment (in line with NICE TA942).

For canagliflozin (alternative option – existing patients may remain on canagliflozin)

- CKD in patients with type 2 diabetes: Recommended if urine albumin-to-creatinine ratio (uACR) of 30 mg/mmol or more and eGFR 30-90 ml/min/1.73m^2(in line with offer recommendation NICE CG28)**.**

Inclusion criteria

- Patients with CKD and meet criteria for treatment in line with NICE TA775, NICE TA 942 or NICE NG28 criteria (see above)
- No risk factors for developing diabetic ketoacidosis (DKA) (only applicable to diabetic CKD patients)

Exclusion criteria

- Age under 18 years
- Type 1 diabetic mellitus
- Hospital admission with DKA
- Ketosis prone diabetes (patients with pancreatic cancer/pancreatitis and patients who rapidly progressed to insulin treatment within 1 year of diagnosis)
- A very low carbohydrate or Ketogenic diet or eating disorder
- Conditions that lead to restricted food intake or severe dehydration
- Symptomatic hypotension
- Acute diabetic foot ulceration/acute foot ischaemia
- Hypersensitivity to SGLT2 inhibitor/excipient
- Pregnancy & breastfeeding
- Severe hepatic impairment (canagliflozin and empagliflozin only)

Cautions for initiation

- Severe hepatic impairment (dapagliflozin only). Dose adjustment may be required.
- Patients at increased risk of volume depletion (dehydration, hypovolaemia and hypotension):
  - Frailty/cognitive impairment. Elderly patients are more likely to have impaired renal function and/or to be treated with anti-hypertensive medicinal products that may cause changes in renal function.
  - Diabetes with HbA1c> 86mmol/mol: increased risk due to osmotic symptoms; refer to diabetologist.
  - Patients on diuretics: increased diuresis; diuretic dose adjustments may be required
  - Caution should be exercised in patients for whom a SGLT2i-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients

Obtain **baseline assessment** including:

- U&Es, eGFR, uACR and LFTs (all patients) and
- HbA1c (in diabetic patients)

Patients with type 2 diabetic mellitus (T2DM)

Prior to initiating a SGLT2 inhibitor for CKD in patients with type 2 diabetes, the anti-diabetic effect of the SGLT2 inhibitor must be considered amongst other concurrent anti-diabetes medications. Patients may need to increase their frequency of blood glucose testing initially when the SGLT2 inhibitor is started to identify any resulting hypoglycaemia.

- ❖ Patients on metformin, GLP-1 receptor agonists and DPP-4 inhibitors (gliptins): low hypoglycaemia risk.
- ❖ Patients on sulphonylureas, a history of hypoglycaemia or with uncontrolled HbA1c may require doses of existing glucose lowering therapies to be reduced prior to initiation of SGLT-2 to reduce the risk of hypoglycaemia: if required discuss with specialist in diabetes care (in community or secondary care).
- ❖ Where patients are on triple therapy consider replacing a glucose lowering therapy with dapagliflozin, empagliflozin or canagliflozin or consider referral for insulin initiation: if required discuss with specialist in diabetes care (in community or secondary care).
- ❖ Patients on insulin refer to/discuss with specialist in diabetes care (in community or secondary care).

Initiation of therapy

Inclusion criteria are met, cautions have been addressed, necessary adjustments to concurrent diabetic medication have been made (applicable to diabetic patients only)

The **recommended dose** of dapagliflozin for CKD is **10 mg once daily** (dose reduction to 5mg in severe liver impairment, increased if tolerated to 10 mg daily).
The **recommended dose** of empagliflozin for CKD is **10 mg once daily** (not recommended in severe liver impairment)

The **recommended dose** of canagliflozin for CKD is **100 mg once daily**, with eGFR ≥30 ml/min/1.73 m^2 (avoid in severe liver impairment). Dose can be increased to 300mg in patients with eGFR ≥ 60 mL/min/1.73m^2 tolerating 100mg and require additional glycaemic control.

At initiation, discuss adverse effects and cautions for use including providing the following information to the patient:

- urine volume increase and risk of dehydration
- sick days, suspend SGLT2 inhibitor if vomiting, severe sepsis and peri-operatively (inform prescriber)
- fungal genital infection, counsel on genital hygiene and advise to stop SGLT2 inhibitor and seek urgent medical help if get symptoms of Fournier's gangrene
- avoidance of foot complications - suspend SGLT2 inhibitor if acute foot ulceration/ischaemia
- Counsel patients on symptoms of DKA and T2DM sick-day rules (temporarily stop if they are unable to eat and drink or are fasting)
- Advise patients to not start a very low carbohydrate diet or ketogenic diet without discussing it with their health professional, because they may need to suspend the SGLT-2 inhibitor treatment.

Patient information leaflet: available from Cardiology, Renal and Metabolic (CaReMe) group (an organisation of the following societies: Association of British Clinical Diabetologists, British Cardiovascular Society, The Renal Association, Primary Care Cardiovascular Society and Primary Care Diabetes Society). This is available on
https://abcd.care/sites/abcd.care/files/site_uploads/Images/ABCD_A4_Leaflet_Final%20%28002%29.jpg
For complete list of adverse drug reactions; see Dapagliflozin SPC, Empagliflozin SPC or Canagliflozin SPC
See NHS website for Overview - Chronic Kidney Disease – [Symptoms, diagnosis, treatment, living with and Prevention]
See NHS East and North Hertfordshire Trust website for patient information leaflets

Specialists transferring prescribing to primary care: Communicate to the GP clearly noting the indication for SGLT2 inhibitor as CKD and request addition to repeat prescription. Transfer information to include initial treatment and monitoring plan.

Monitoring

Primary care

- Monitor renal function (eGFR creatinine and uACR) as per the recommended frequency in **NICE NG203** (tailored to individual needs) – see table below showing the minimum number of monitoring checks per year for people with or at risk of CKD.

	ACR category **A1**: normal to mildly increased (less than 3 mg/mmol)	ACR category **A2**: moderately increased (3 to 30 mg/mmol)	ACR category **A3**: severely increased (over 30 mg/mmol)
GFR category **G1**: normal and high (90 ml/min/1.73 m^2 or over)	0 to 1	1	1 or more
GFR category **G2**: mild reduction related to normal range for a young adult (60 to 89 ml/min/1.73 m^2)	0 to 1	1	1 or more
GFR category **G3a**: mild to moderate reduction (45 to 59 ml/min/1.73 m^2)	1	1	2
GFR category **G3b**: moderate to severe reduction (30 to 44 ml/min/1.73 m^2)	1 to 2	2	2 or more
GFR category **G4**: severe reduction (15 to 29 ml/min/1.73 m^2)	2	2	3
GFR category **G5**: kidney failure (under 15 ml/min/1.73 m^2)	4	4 or more	4 or more

- Monitoring of renal function earlier than 3-6 months after initiation is not required unless titrating ACE inhibitors/ARBs or the patient is at high risk of diuresis.
- A modest initial decline in eGFR that is hemodynamic in nature and reversible is characteristic of SGLT2 inhibitors and would generally not be an indication to discontinue therapy.
- Seek specialist advice on treatment continuation if eGFR falls below 15 mL/min/1.73 m^2 for dapagliflozin, 20 mL/min/1.73 m^2 for empagliflozin or 30 mL/min/1.73 m^2 for canagliflozin whilst on treatment.
- Refer patients (who are not already known to the renal clinic) as per **NICE NG203 referral criteria**

Usual diabetic care provider

- Monitor HbA1c in T2DM patients every 3 to 6 months (tailored to individual needs) until HbA1c is stable on unchanging therapy, then every 6 months as per **NICE NG28**.

Stopping criteria

- Any of the exclusion criteria develop.
- Patient experiences any serious adverse reaction e.g. ketoacidosis, angioedema, Fournier's Gangrene. (Yellow card to be submitted to the MHRA & record in patients notes).
- In patients with intercurrent illness if not eating or at risk of dehydration. Only restart once better and back on normal diet.
- In patients admitted to hospital acutely unwell for any reason. Restart only once fully recovered and eating and drinking normally.
- In patient having elective surgery who is missing more than one meal. Restart only once recovered and eating and drinking normally.

GP to contact renal or diabetes specialist if concerns arise on contra-indications, stopping criteria, cautions and monitoring results.

References

1. NICE NG 203 'Chronic kidney disease: assessment and management', published August 2021, accessed May 2022
2. NICE TA 775 'Dapagliflozin for treating chronic kidney disease', published March 2022, accessed May 2022
3. NICE NG 28 'Type 2 diabetes in adults: management', published December 2015, accessed May 2022
4. UK Kidney Association – SGLT2 Inhibition in Adults with Kidney Disease, published October 2021, accessed May 2022
5. Scottish Medicines Consortium (SMC) – SMC2428 - dapagliflozin 10mg film-coated tablets (Forxiga®), published April 2022, accessed May 2022
6. Forxiga 10 mg film-coated tablets, accessed via https://www.medicines.org.uk/emc/product/7607, May 2022
7. Invokana 100 mg and 300 mg film-coated tablets, accessed via https://www.medicines.org.uk/emc/medicine/28400, May 2022
8. NICE Clinical Knowledge Summaries SGLT-2 inhibitors | Prescribing information | Diabetes - type 2 | CKS | NICE May 2022

9. NICE TA 942 'Empagliflozin for treating chronic kidney disease', published December 2023, accessed January 2024

Further information - Relevant MHRA alerts on SGLT2 inhibitors

1. SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis published 18th April 2016
2. SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes) published 22nd March 2017
3. SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) published 18th Feb 2019
4. SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness published 18th March 2020

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Local Superseded Legacy Pathway Decisions	
Approved by	**Date approved / updated**
Hertfordshire Medicines Management Committee	No previous pathway.
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