NHS
Cheshire and Merseyside

DAPAGLIFLOZIN and EMPAGLIFLOZIN for treating chronic kidney disease: a multiple prescribing statement

The Cheshire and Merseyside Area Prescribing Group recommends DAPAGLIFLOZIN and EMPAGLIFLOZIN as options for treating chronic kidney disease, in accordance with NICE TA775 and NICE TA942.

GREEN

Dapagliflozin and empagliflozin are selective sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

NICE recommends dapagliflozin (TA775)[1] and empagliflozin (TA942)[2] as options for treating chronic kidney disease (CKD) in adults, only if they are an add-on to optimised standard care including the highest tolerated licensed dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs), unless these are contraindicated, **and**[1,2]

For dapagliflozin:

- people have an estimated glomerular filtration rate (eGFR) of 25 mL/min/1.73 m^2 to 75 mL/min/1.73 m^2 at the start of treatment **and**:
  - have type 2 diabetes mellitus (DM) **or**
  - have a urine albumin-to-creatinine ratio (uACR) of 22.6 mg/mmol or more[1]

For empagliflozin:

- people have an estimated glomerular filtration rate of:
  - 20 ml/min/1.73 m^2 to less than 45 ml/min/1.73 m^2 **or**:
  - 45 ml/min/1.73 m^2 to 90 ml/min/1.73 m^2 **and either**:
    - a urine albumin-to-creatinine ratio of 22.6 mg/mmol or more, **or**
    - type 2 diabetes[2]

Dapagliflozin and empagliflozin are not licensed for use in patients with type 1 diabetes and should not be used for treating CKD in patients with type 1 diabetes.

Dapagliflozin and empagliflozin are also licensed for the treatment of type 2 diabetes, for heart failure with reduced ejection fraction and for heart failure with preserved or slightly reduced ejection fraction. Refer to local guidance for further information.

People taking SGLT2-inhibitors for CKD who also have diabetes might need adjustments in their diabetes medication for safety reasons. People taking SGLT-2 inhibitors for CKD who also have heart failure may need adjustments in their heart failure medication due to their modest effect on diuresis and blood pressure.

The indication for the SGLT-2 inhibitor must be clearly documented on the patient's medical record.

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

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Effectiveness

Dapagliflozin[3]

DAPA-CKD Study was a placebo controlled trial which included 2152 patients and had a 2.4 year follow up period. Inclusion criteria were as follows: eGFR 25-75 mL/min/1.73 m^2, uACR 22.6-565 mg/mmol, stable maximally tolerated RAS blockade (unless documented intolerance). The primary outcome was sustained ≥50% decline in eGFR, sustained eGFR <15 mL/min/1.73 m^2, ESKD, death from renal or cardiovascular (CV) cause. A primary outcome event occurred in 197 of 2152 participants (9.2%) in the dapagliflozin group and 312 of 2152 participants (14.5%) in the placebo group. Number needed to treat to prevent one primary outcome event was 19 [95% CI, 15 to 27]). The hazard ratio for the composite of a sustained decline in the estimated GFR of at least 50%, end-stage kidney disease, or death from renal causes was 0.56 (95% CI, 0.45 to 0.68; P<0.001), and the hazard ratio for the composite of death from CV causes or hospitalization for heart failure was 0.71 (95% CI, 0.55 to 0.92; P=0.009). The effects of dapagliflozin were similar in participants with type 2 diabetes and in those without type 2 diabetes.

Empagliflozin[4]

EMPA-KIDNEY was the pivotal, Phase III, randomised, parallel-group, double-blind, placebo controlled trial which included 6609 patients and had a median follow-up of 2years. The primary outcome was a composite of progression of kidney disease (defined as end-stage kidney disease, a sustained decrease in eGFR to <10 ml per minute per 1.73 m^2, a sustained decrease in eGFR of ≥40% from baseline, or death from renal causes) or death from CV causes. Progression of kidney disease or death from CV causes occurred in 432 of 3304 patients (13.1%) in the empagliflozin group and in 558 of 3305 patients (16.9%) in the placebo group (hazard ratio, 0.72; 95% confidence interval [CI], 0.64 to 0.82; P<0.001). The rate of hospitalization from any cause was lower in the empagliflozin group than in the placebo group (hazard ratio, 0.86; 95% CI, 0.78 to 0.95; P=0.003), but there were no significant between-group differences with respect to the composite outcome of hospitalization for heart failure or death from cardiovascular causes (which occurred in 4.0% in the empagliflozin group and 4.6% in the placebo group) or death from any cause (in 4.5% and 5.1%, respectively). The rates of serious adverse events were similar in the two groups.

Safety

Contraindications: Hypersensitivity to the active substance or to any of the excipients.[5][6]

Dapagliflozin and empagliflozin should not be used in patients with type 1 diabetes.[5][6]

Cautions:

- Intermittent fasting (e.g. Ramadan) or following ketogenic diets particularly if elderly or on diuretics; consider withholding or monitoring ketones if unwell.[7]
- In patients also being treated with sulphonylureas/meglitinides/insulin for type 2 diabetes with HbA1c <58mmol/mol and eGFR >45mL/min: dose adjustments of these drugs may be necessary to avoid hypoglycaemia.[6] See **implementation notes**.
- Active foot disease before or during therapy. Patients should be counselled on routine preventative foot care measures, especially if they are at high risk of complications.[7]
- There is no evidence to support the use of dapagliflozin or empagliflozin for CKD in patients with a functioning kidney transplant (patients with an organ transplant were not included in DAPA-CKD or EMPA-KIDNEY trials).
- SGLT-2 inhibitors should not be used in patients with decompensated heart failure.[7]
- Temporary interruption of SGLT-2 inhibitors should be considered when treating pyelonephritis or urosepsis.[7]
- History of mycotic genital infections. Patients should be counselled on good genital hygiene and the symptoms of mycotic genital infections and on how to seek help, including self-management. Consider offering prophylactic antifungals.[7]
- If Fournier's gangrene is suspected, the SGLT2 inhibitor should be discontinued and treatment started.

<u>Ketoacidosis</u>

- Cases of ketoacidosis, including life-threatening and fatal cases, have been reported in patients with diabetes treated with SGLT-2 inhibitors.[5][6] Ketoacidosis is less likely to occur in patients without diabetes, but cases have been reported.[6]
- Before initiating an SGLT-2 inhibitor, factors in the patient history that may predispose to ketoacidosis should be considered.[5][6]
- SGLT-2 inhibitors should not be used in patients with a history of diabetic ketoacidosis (DKA) and should not be used in patients with type 2 diabetes at a higher risk of DKA unless the diabetes team are involved.
- Patients at higher risk of DKA include those with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA) or patients with a history of pancreatitis), patients with conditions that lead to restricted food intake or severe dehydration, patients for whom insulin doses are reduced and patients with increased insulin requirements due to acute medical illness, surgery or alcohol abuse.[5][6]
- Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses. Monitoring of ketones is recommended in these patients. Measurement of blood ketone levels is preferred to urine. SGLT-2 inhibitor treatment may be restarted when the ketone values are normal and the patient's condition has stabilised.[5][6]

See SPCs for dapagliflozin and empagliflozin for full safety details.

See also MHRA alerts:

- SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis
- SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness
- SGLT2 inhibitors: Updated advice on increased risk of lower-limb amputation
- SGLT2 inhibitors: reports of Fournier's gangrene

Cost

The NHS list price for both dapagliflozin and empagliflozin is £36.59 per 28-tablet pack (excluding VAT).[8]
The annual treatment cost per patient is £476.98.
NICE estimates that the cost (net resource impact) of implementing NICE TA942 is 0 in 2023/24, rising to £5,000 per 100,000 population in 2024/25, £22,000 per 100,000 population in 2025/26, £25,000 per 100,000 population in 2026/27 and then £27,000 per 100,000 population in 2026/27 when steady state is assumed to have been reached. These costs take into account the potential resources released from delayed disease progression and includes both dapagliflozin and empagliflozin.[9]

Patient factors

Renal impairment:

Glycaemic control is dependent on renal function. **In patients treated with dapagliflozin or empagliflozin for both CKD and type 2 diabetes, additional glucose-lowering treatment should be considered if eGFR falls persistently below 45 mL/min**.[5][6]

Dapagliflozin

- Dapagliflozin should only be initiated in patients with eGFR of 25mL/min at the start of treatment.[1]
- In patients treated with dapagliflozin for CKD, treatment can be continued if eGFR declines below 25mL/minute. Continue to follow existing NICE CKD guideline recommendations (NG203) in relation to renal function decline.

Empagliflozin

- It is not recommended to initiate treatment with empagliflozin in patients with an eGFR <20 mL/min.[6]
- In patients with an eGFR <60 mL/min the daily dose of empagliflozin is 10 mg.[6]
- In patients treated with empagliflozin for CKD, treatment can be continued if eGFR declines below 20mL/minute. Continue to follow existing NICE CKD guideline recommendations (NG203) in relation to renal function decline.

Hepatic impairment:

Dapagliflozin: No dose adjustment is necessary in mild or moderate hepatic impairment. In severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg.[5]

Empagliflozin: No dose adjustment is required for patients with hepatic impairment. Empagliflozin is not recommended in patients with severe hepatic impairment.[6]

Volume depletion / Hypotension

SGLT-2 inhibitors increase diuresis which may lead to the modest decrease in blood pressure observed. Caution should be exercised in patients for whom an SGLT-2 inhibitor-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.[5][6]

In case of intercurrent conditions that may lead to volume depletion (e.g. gastrointestinal illness), careful monitoring of volume status (e.g. physical examination, blood pressure measurements, laboratory tests including haematocrit and electrolytes) is recommended. Temporary interruption of SGLT-2 inhibitor treatment is recommended for patients who develop volume depletion until the depletion is corrected.[5][6]

Pregnancy / breastfeeding:

- Dapagliflozin is not recommended during pregnancy. When pregnancy is detected, treatment with dapagliflozin should be discontinued. Dapagliflozin should not be used while breastfeeding.[5]
- Empagliflozin is not recommended during pregnancy and should not be used during breastfeeding.[6]

Prescribing information

- The recommended dose of dapagliflozin for CKD is 10 mg once daily. A starting dose of 5mg daily is recommended in severe hepatic impairment.[5]
- The recommended dose of empagliflozin for CKD is 10 mg once daily.[6]
- ACE inhibitor (ACEi) or Angiotensin II Receptor Blocker (ARB) monotherapy dose should be optimised, if indicated and tolerated.[1][2]

Implementation notes

- For diabetic patients the team responsible for their diabetes care should be consulted. Initiating an SGLT-2 inhibitor may require adjustment to diabetes regimens.
- Assessment of renal function is recommended prior to initiation and periodically during treatment (i.e. at least yearly) and prior to initiation of any concomitant medicinal product that may have a negative impact on renal function.[6]
- Prescribers should continue to follow NICE CKD guideline recommendations (NG203) in relation to monitoring and for which individuals require referral to a specialist.
- It is the responsibility of the clinician making the decision or recommendation to prescribe an SGLT2-inhibitor, to assess the patient's suitability for treatment **(see pre-prescribing / recommendation checklist below)** and to clearly document the outcome of the shared decision making conversation and informed patient consent. This should be clearly communicated to the patient's primary care prescriber, using the **GP communication letter** and should include confirmation that appropriate counselling has been provided, to enable them to safely initiate or continue prescribing.
- The initiating prescriber is responsible for ensuring patients have been counselled appropriately before prescribing. This should form part of the shared decision making conversation with the patient, at the point the decision or recommendation is made to initiate SGLT-2 inhibitor treatment.
- The following information should be discussed with the patient before commencing or recommending SGLT-2 inhibitor treatment:
    - For patients with diabetes - risk of DKA (especially if on glucose monitoring therapy), signs and symptoms of DKA, and action to take.
    - Sick day rules - action to take during acute illness when unable to eat or drink including when to stop, duration and when to restart.
    - Action to take if being admitted for operations / procedures or acute severe illness requiring hospitalisation.
    - Risk of mycotic genital infections– counsel on hygiene and consider prophylactic antifungals if existing history of recurrent mycotic genital infections.[7]

- Fournier's gangrene – advise patients to seek urgent medical attention if they experience severe pain, tenderness, erythema, or swelling in the genital or perineal area, accompanied by fever or malaise.[10]
- Acute kidney injury (AKI) (especially if on diuretics/ACEi/ARB) – withhold diuretic/ACEi/ARB if unwell, (see sick-day rules above), avoid hypovolaemia.
- Dehydration – Maintain fluids, withhold SGLT-2 inhibitor if unwell.
- Urinary Tract Infection (UTI) – withhold SGLT-2 inhibitor if UTI occurs.
- Peripheral vascular disease – counsel on foot care and withhold SGLT-2 inhibitor if concerned.
- Fracture risk – patient will require usual CKD-MBD monitoring.
- Hypoglycaemia – relevant if on sulphonylureas/meglitinides/insulin, may need dose adjustment of these drugs.
- Patient consent to treatment should be obtained and documented.

> The following UKKA sodium glucose co-transporter-2 inhibitors (SGLT-2i) patient information leaflets should be supplied on treatment initiation:
  - For patients with diabetes
  - For patients without diabetes

Please refer to the pre-prescribing / recommendation checklist below:

Pre-prescribing / recommendation checklist	Check
Patient does not have Type 1 diabetes	☐
eGFR is ≥25 mL/min for dapagliflozin or ≥20mL/min for empagliflozin at the start of treatment	☐
No critical limb ischaemia (discuss with specialist)	☐
No prior allergy or intolerance to SGLT-2 inhibitors	☐
No previous pancreatitis (discuss with specialist)	☐
No evidence of acute volume depletion	☐
Blood pressure within acceptable limits (SBP >95mmHg)	☐
Baseline blood tests available:	
U&Es (don't start if eGFR is <25mL/min for dapagliflozin or <20mL/min for empagliflozin)	☐
FBC (haematocrit not raised)	☐
LFTs (dapagliflozin starting dose 5mg in severe hepatic impairment, empagliflozin not recommended in severe liver impairment)	☐
HbA1c (If patient has diabetes, the team responsible for diabetes care should be consulted. Initiating an SGLT-2 inhibitor may require adjustment to diabetes regimens).	☐
Patient education	☐
Urinary and genital infections	☐
DKA (patients with type 2 diabetes only)	☐
Sick day rules	☐
Patient information leaflet issued	☐

For patients requiring SGLT-2 inhibitors to be suspended due to acute illness or surgery there should be a clear plan in place for safely restarting including any ketone monitoring required. For patients who cannot restart therapy during their inpatient stay the plan should be clearly communicated to the primary care physician on the discharge summary. Prompt follow up by heart failure teams and diabetes teams, where required, should be ensured to action any further adjustment of treatment.

References

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