

DAPAGLIFLOZIN tablets (Forxiga[®]) for treating chronic kidney disease

The Pan Mersey Area Prescribing Committee recommends the prescribing of DAPAGLIFLOZIN tablets (Forxiga[®]) treating chronic kidney disease in accordance with NICE TA775.

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[NICE technology appraisal \(TA\) 775](#)¹ recommends dapagliflozin as an option for treating chronic kidney disease (CKD) in adults, only if:

- > it is 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**
- > people have an estimated glomerular filtration rate (eGFR) of 25 mL/min/1.73 m² to 75 mL/min/1.73 m² 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 more¹

People taking dapagliflozin for CKD who also have diabetes might need adjustments in their diabetes medication for safety reasons.

Dapagliflozin is not authorised for use in patients with type 1 diabetes and should not be used for treating CKD in patients with type 1 diabetes.

NICE estimates that the cost (net resource impact) of implementing NICE TA775 is £4,000 per 100,000 population in 2022/23 rising to £12,000 per 100,000 population in 2023/24, £16,000 per 100,000 population in 2024/25, £19,000 per 100,000 population in 2025/26 and then £23,000 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.²

Dapagliflozin is also licensed for the treatment of type 2 DM and for heart failure with reduced ejection fraction. See separate Pan Mersey statements:

[CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN and ERTUGLIFLOZIN as MONOTHERAPIES in type 2 diabetes: a multiple prescribing statement](#)

[ERTUGLIFLOZIN, CANAGLIFLOZIN, DAPAGLIFLOZIN, and EMPAGLIFLOZIN as COMBINATION THERAPIES in type 2 diabetes: a multiple prescribing statement](#)

[DAPAGLIFLOZIN tablets \(Forxiga[®]\) for symptomatic chronic heart failure with reduced ejection fraction](#)

The indication for dapagliflozin 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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Effectiveness³

DAPA-CKD Study³ 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 m², uACR 22.6-565 mg/mmol, stable maximally tolerated RAS blockade (unless documented intolerance). The primary outcome was sustained \geq 50% decline in eGFR, sustained eGFR <15 mL/min/1.73 m², ESKD, death from renal or cardiovascular 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 cardiovascular 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 DM.

Safety

Contraindications: Type 1 DM. Dapagliflozin is not licensed for type 1 DM and should not be used.

Cautions:

- Dapagliflozin should only be initiated in patients with eGFR of 25mL/min at the start of treatment.¹
- Intermittent fasting (e.g. Ramadan) or following ketogenic diets particularly if elderly or on diuretics; consider withholding or monitoring ketones if unwell.⁵
- In patients also being treated with sulphonylureas/meglitinides/insulin for type 2 DM with HbA1c <58mmol/mol and eGFR >45mL/min: dose adjustments of these drugs may be necessary to avoid hypoglycaemia. See 'implementation notes'.⁵
- 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.
- There is no evidence to support the use of dapagliflozin for CKD in patients with a functioning kidney transplant (patients with an organ transplant were not included in DAPA-CKD trial).
- Dapagliflozin should not be used in patients with decompensated heart failure.⁵
- Temporary interruption of dapagliflozin should be considered when treating pyelonephritis or urosepsis.⁵
- 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. ⁵ If Fournier's gangrene is suspected, dapagliflozin should be discontinued and treatment started.

Diabetic ketoacidosis (DKA):

Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. ⁴ Dapagliflozin should not be used in patients with a history of DKA, and should not be used in patients with type 2 DM 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 DM 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.⁴

The risk of DKA must be considered in the event of non-specific symptoms such as nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level. Rare cases of DKA, including life-threatening and fatal cases, have been reported in patients treated with SGLT2 inhibitors, including dapagliflozin. In a number of cases, the presentation of the condition was atypical with only moderately increased blood glucose values, below 14 mmol/L (250 mg/dL). In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately. Restarting SGLT2 inhibitor treatment in patients experiencing a DKA while on SGLT2 inhibitor treatment is not recommended, unless another clear precipitating factor is identified and resolved.⁴

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. Treatment with dapagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.⁴

See [SPC](#) 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 of dapagliflozin is £36.59 per 28-tablet pack (excluding VAT; [dm+d Browser](#), accessed 25 Feb 2022). The annual treatment cost per patient is £476.98.

Patient factors

Renal function: No dose adjustment is required based on renal function. Glycaemic control is dependent on renal function. In patients treated with dapagliflozin for both CKD and type 2 DM, additional glucose-lowering treatment should be considered if GFR falls persistently below 45 mL/min.⁴ In patients treated with dapagliflozin for CKD without type 2 DM, 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.

Hepatic impairment: 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 mg⁴

Volume depletion / Hypotension: Dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed. Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients. 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 treatment with dapagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.⁴

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.⁴

Prescribing information

- > The recommended dose for CKD is 10 mg dapagliflozin once daily. A starting dose of 5mg daily is recommended in severe hepatic impairment.⁴
- > ACE inhibitor (ACEi) or Angiotensin II Receptor Blocker (ARB) monotherapy dose should be optimised, if indicated and tolerated.¹

Implementation notes

- > For diabetic patients the team responsible for their diabetes care should be consulted. Initiating dapagliflozin may require adjustment to diabetes regimens.
- > Prescribers should continue to follow NICE CKD guideline recommendations ([NG203](#)) in relation to which individuals require referral to a specialist.

- > The following information about adverse effects should be discussed with the patient at the time of treatment initiation:
 - Risk of DKA (especially if on glucose lowering therapy) - see below for further details.
 - Fournier’s gangrene – counsel on hygiene and consider prophylactic antifungals if existing history
 - Acute kidney injury (AKI) (especially if on diuretics/ACEi/ARB) - hold diuretic/ACEi/ARB if unwell, (sick-day rules), avoid hypovolaemia.
 - Dehydration - Maintain fluids, hold dapagliflozin if unwell.
 - Urinary Tract Infection (UTI) - hold dapagliflozin if UTI occurs and contact prescriber.
 - Peripheral vascular disease – counsel on foot care, report and hold dapagliflozin 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.
- > The initiating prescriber is responsible for ensuring patients are aware of the risk of DKA with dapagliflozin in patients with diabetes. Patients should be provided with specific information including:
 - For patients with diabetes: signs and symptoms of DKA.
 - Actions 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.
- > The following UKKA sodium glucose co-transporter-2 inhibitors (SGLT-2i) patient information leaflets should be supplied on treatment initiation⁵:
 - [For patients with diabetes](#)
 - [For patients without diabetes](#)

For patients requiring dapagliflozin 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

1. National Institute for Health and Care Excellence. Technology Appraisal 775; [Dapagliflozin for treating chronic kidney disease](#), 09 March 2022. Accessed 10 March 2022.
2. National Institute for Health and Care Excellence. Technology Appraisal 775; Resource impact report: [Dapagliflozin for treating chronic kidney disease \(TA775\)](#), 09 March 2022. Accessed 10 March 2022.
3. Heerspink et al. Dapagliflozin in Patients with Chronic Kidney Disease. *NEJM*. 2020. 83:1436-1446 doi: 10.1056/NEJMoa2024816

4. Astra Zeneca UK Ltd. Summary of Product Characteristics; [Forxiga 10mg film-coated tablets](#), 25 October 2021. Accessed 10 March 2022.
5. UK Kidney Association Clinical Practice Guideline: [Sodium-Glucose Co-transporter-2 \(SGLT-2\) Inhibition in Adults with Kidney Disease](#), 18 October 2021. Accessed 10 March 2022.