

## Dapagliflozin for Chronic Kidney Disease in Adults: Prescribing Support Document

### What is it?

Dapagliflozin is a sodium-glucose cotransporter 2 inhibitor (SGLT2i). It works by blocking the action of SGLT-2 in the kidneys. This reduces glucose reabsorption and increases glucose excretion in the urine. It is already an approved drug for the management of type 2 diabetes mellitus (T2DM) and heart failure with reduced ejection fraction, preserved ejection fraction and mildly reduced ejection fraction.

Two randomised control trials (DAPA-CKD and CREDENCE) have shown SGLT2 inhibition reduced the risk of kidney disease progression in patients with T2DM and albuminuric diabetic kidney disease. Subgroup analyses from DAPA-CKD also showed benefit in patients with albuminuric kidney disease without T2DM. The proposed mechanisms for the beneficial effect of SGLT2 inhibition in chronic kidney disease (CKD) are generation of natriuresis and changes in tubuloglomerular feedback related to increased sodium delivery to the macula densa.

### NICE Guidance

[NICE Technology Appraisal Guidance \(TA775; published 9<sup>th</sup> March 2022\)](#) states:

Dapagliflozin is recommended as an option for treating chronic kidney disease (CKD) in adults. It is recommended 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 25ml/min/1.73 m<sup>2</sup> to 75 ml/min/1.73m<sup>2</sup> at the start of treatment and:
  - have type 2 diabetes **or**
  - have a urine albumin-to-creatinine ratio (uACR) of 22.6 mg/mmol or more.

This recommendation is not intended to affect treatment with dapagliflozin that was started in the NHS before this guidance was published. People having treatment outside this recommendation may continue without change to the funding arrangements in place for them before this guidance was published, until they and their NHS clinician consider it appropriate to stop. For prescribing advice related to dapagliflozin for the management of heart failure, please refer to the [Dapagliflozin and Empagliflozin for Heart Failure in Adults Prescribing Support Document](#).

**Please refer to the [Cambridgeshire and Peterborough system-wide formulary](#) for links to local and national guidance.**

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*Suitable for prescribing in Primary Care in line with NICE TA775.*

## Licensed indications and prescribing good practice

### Which health professionals will prescribe?

Dapagliflozin will be prescribed in the community by primary care clinicians for CKD patients who meet the criteria set out in NICE TA775. Many patients will be identified through nephrology clinics but treatment can also be initiated by primary care clinicians. A [local pathway](#) is available to support prescribers in primary care and when to initiate dapagliflozin in patients who fulfil the NICE TA775 criteria. If further advice is needed, this can be requested through Advice and Guidance to the Nephrology Department.

The NICE treatment authorisation suggests that in patients with an eGFR between 15 and 25ml/min/1.73 m<sup>2</sup> there is likely to be benefit from starting dapagliflozin but there is limited evidence from clinical trials in this group. Dapagliflozin should only be started in these patients on the advice of a nephrologist. This can be requested through Advice and Guidance to the Nephrology Department.

There is no data from large randomised control trials regarding the use of dapagliflozin in:

- Kidney transplant recipients.
- Polycystic kidney disease.
- Lupus nephritis.
- ANCA associated vasculitis.
- Patients receiving immunological therapy for kidney disease in the previous 6 months.

This is because these patients were excluded from the trials. It is likely that dapagliflozin would still be beneficial in these groups of patients if they fulfil the other criteria for initiating this medication. For these patients, dapagliflozin should be initiated on the advice of a nephrologist.

## Preparations and Dosage

### Preparation

Dapagliflozin 10 mg and 5 mg tablets.

### Dosage and Administration

10mg once daily. This can be taken with or without food. There is no fixed time, but it should be taken at the same time each day.

## Contraindications and cautions

### Contraindications

- Type 1 diabetes mellitus (unless initiated under the strict direction of the diabetes team).
- History of diabetic ketoacidosis (DKA).
- Pregnancy or breastfeeding.
- Hypersensitivity to dapagliflozin or excipients.

### Cautions

- Patients with type 2 diabetes mellitus at higher risk of DKA.

- Frail elderly patients where there is a risk of volume depletion.
- Hypotension (systolic blood pressure < 95mmHg at 2 out of 3 measurements).
- Hepatic impairment (start at dose of 5mg daily).

## Drug interactions

Below are some general drug interactions but prescribers must consult the Summary of Product characteristics for more detailed information on each specific drug. This is not an exhaustive list.

Drug/ Therapeutic group	Interaction
Insulin and insulin secretagogues	Insulin and insulin secretagogues, such as sulphonylureas and meglitinides, cause hypoglycaemia. A lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin in patients with type 2 diabetes mellitus.
Diuretics	Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension.

There are no significant interactions with ACE inhibitors, angiotensin receptor blockers or mineralocorticoid receptor antagonists.

## Adverse effects

Type	Adverse effect
Common side-effects at 'therapeutic' levels	Most common adverse effects are thrush, back pain, feeling dizzy, skin rash and increased urinary frequency
Other side-effects	Very common: hypoglycaemia (when used in patients with T2DM) Common: urogenital infections, rash and back pain Uncommon: volume depletion Rare: diabetic ketoacidosis (when used in patients with T2DM) Very rare: necrotising fasciitis of perineum (Fournier's gangrene)
Toxicity	No toxicity in healthy subjects at single oral doses up to 500 mg. These subjects had detectable glucose in the urine for a dose-related period of time (at least 5 days for the 500mg dose), with no reports of dehydration, hypotension or electrolyte imbalance, and with no clinically meaningful effect on QTc interval. The incidence of hypoglycaemia was similar to placebo. In clinical studies where once-daily doses of up to 100mg were administered for 2 weeks, the incidence of hypoglycaemia was slightly higher than placebo. Rates of adverse events including dehydration or hypotension were similar to placebo.

Frequency categories: very common ( $\geq 1/10$ ), common ( $\geq 1/100$  to  $< 1/10$ ), uncommon ( $\geq 1/1,000$  to  $< 1/100$ ), rare ( $\geq 1/10,000$  to  $< 1/1,000$ ), very rare ( $< 1/10,000$ ).

**For full details on cautions, contraindications, drug interactions and adverse effects, please consult the latest edition of the [British National Formulary \(BNF\)](#) or [Summary of Product Characteristics \(SPC\)](#).**

## Pregnancy and breastfeeding

### Pregnancy

There is no human data regarding the use of SGLT-2 inhibitors in pregnancy. Animal studies have shown toxic effects relating to ossification delays, renal maturation and tubular dilatations. Dapagliflozin should be stopped in patients who are planning pregnancy and when pregnancy is suspected or confirmed.

### Breastfeeding

There is no human data regarding the use of SGLT-2 inhibitors in breastfeeding. Animal studies have shown toxic effects from SGLT2 inhibitors through exposure to breast milk. Dapagliflozin should not be used while breast-feeding.

### Fertility

The effect of dapagliflozin on fertility in humans has not been studied. In male and female rats, dapagliflozin showed no effects on fertility at any dose tested.

## Monitoring: Specialist responsibility

No additional monitoring is required. Routine monitoring of renal function appropriate for CKD stage should continue.

If renal function is checked for another reason after starting dapagliflozin, an initial reduction in eGFR of up to 20% is common. This should not usually be considered an adverse effect and is not an indication alone to stop treatment.

## Monitoring: Primary care responsibility

No additional monitoring is required. Routine monitoring of renal function appropriate for CKD stage should continue.

If renal function is checked for another reason after starting dapagliflozin, an initial reduction in eGFR of up to 20% is common. This should not usually be considered an adverse effect and is not an indication alone to stop treatment.

## Stopping treatment

Dapagliflozin should be stopped in the following situations:

- Development of diabetic ketoacidosis.
- Development of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum).
- Frequent/severe urinary tract infections.

There are no criteria for stopping dapagliflozin based on eGFR. Dapagliflozin can be continued until dialysis is started or patients have a kidney transplant.

## Advice and support for specific issues

<b>Issue</b>	<b>Concomitant Diabetes</b>	<b>No Concomitant Diabetes</b>
Glycaemic control	<p>If using insulin with HbA1c &lt;58mmol/mol and eGFR &gt;45ml/min/1.73m<sup>2</sup>, ensure close monitoring of serum glucose and reduce dose by 20% if there is a significant risk of hypoglycaemia.</p> <p>If using sulfonylurea or meglitinide with HbA1c &lt;58mmol/mol and eGFR &gt;45ml/min/1.73m<sup>2</sup>, ensure close monitoring of serum glucose and reduce dose by 50% if there is a significant risk of hypoglycaemia.</p> <p>If eGFR &lt;45ml/min/1.73m<sup>2</sup>, additional glucose lowering treatment may be required as the efficacy of SGLT2 inhibition for lowering glucose is reduced. Renal benefits in patients with CKD continue to be seen at eGFR &lt;45ml/min/1.73m<sup>2</sup> and treatment should be continued for this indication.</p> <p>NB. Dose reductions are not needed for metformin, glitazones, DPP-4 inhibitors/gliptins or GLP-1 receptor agonist therapy.</p>	No concerns
Diabetic/euglycaemic ketoacidosis	<p>Sick day rules should be followed – dapagliflozin should be held if unwell, restricted food/fluid intake, dehydration, or hospitalised for surgical procedure or serious medical illness.</p> <p>All patients should be educated on the signs/symptoms of DKA and sick day guidance before starting dapagliflozin.</p> <p>In patients who are unwell, blood ketones should be checked even if blood sugar is in normal range.</p> <p>Dapagliflozin should be stopped if a patient develops DKA.</p> <p>Patients should be advised not to fast whilst taking dapagliflozin.</p>	Not recognised as a risk in non-diabetics.
Diabetic foot care	<p>Increased risk of lower limb amputation seen with canagliflozin (another SGLT2i), but not observed in dapagliflozin studies.</p> <p>People with diabetes should check their feet regularly and adhere to usual foot care advice.</p> <p>Avoid if active foot disease (infection/ulcers/ischaemia) and hold if develop foot complications.</p> <p>Undertake shared decision-making if</p> <ul style="list-style-type: none"> <li>• there is a high risk of amputation or</li> <li>• restarting after treatment of foot complications.</li> </ul>	No concerns
Renal function	Early eGFR reduction up to 20% is common and acceptable. This alone should not be a reason to stop treatment.	Same as diabetes
Volume depletion	<p>Temporarily hold dapagliflozin during acute illness until recovered and oral intake adequate.</p> <p>Consider reduction in dose of diuretics/antihypertensives in patients at high risk of hypovolaemia.</p>	Same as diabetes

<b>Issue</b>	<b>Concomitant Diabetes</b>	<b>No Concomitant Diabetes</b>
Mycotic genital infection	Counsel all patients on the risks and symptoms of mycotic genital infections before starting dapagliflozin and advise good perineal hygiene.	Same as diabetes
Fournier's gangrene	Inform patients of the signs and symptoms of Fournier's gangrene and to seek urgent medical advice if these symptoms develop. Stop dapagliflozin on suspicion of Fournier's gangrene.	Same as diabetes
Urinary tract infection	There is a theoretical increased risk of urinary tract infection in patients taking SGLT2 inhibitors. All patients should be counselled on the risks and symptoms of urinary tract infections before starting dapagliflozin. Dapagliflozin should be temporarily held if patients develop pyelonephritis or urosepsis.	Same as diabetes

Contact the Nephrology Department if further support is required regarding use of dapagliflozin in CKD, particularly if this drug is stopped due to adverse effects.

## References

1. UK Kidney Association. [UK Kidney Association Clinical Practice Guideline: Sodium-Glucose Co-transporter-2 \(SGLT-2\) Inhibition in Adults with Kidney Disease](#). Published: 18<sup>th</sup> October 2021. Available online (accessed 16/04/2022).
2. National Institute for Health and Care Excellence. Dapagliflozin for treating chronic kidney disease. [Technology appraisal guidance \[TA775\]](#). Published: 09 March 2022. Available online (accessed 16/04/2022).
3. Perkovic V, Jardine MJ, Neal B, Bompast S, Heerspink HJL, Charytan DM, et al. Canagliiflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy. *N Engl J Med.* 2019;380(24):2295-306.
4. Heerspink HJL, Stefansson BV, Correa-Rotter R, Chertow GM, Greene T, Hou FF, et al. Dapagliflozin in Patients with Chronic Kidney Disease. *N Engl J Med.* 2020;383(15):1436- 46.

## Document ratification details

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