

Guideline for the use of dapagliflozin for treating patients with chronic heart failure with preserved ejection fraction (HFpEF) or heart failure with mildly reduced ejection fraction (HFmrEF) without diabetes

NICE approved SGLT2 inhibitor dapagliflozin may be prescribed in patients with symptomatic chronic heart failure with preserved or mildly reduced ejection fraction with or without type 2 diabetes mellitus. This guideline focuses on patients without diabetes. For further information see NICE [TA902](#). This guidance is for patients without diabetes: For patients with diabetes please discuss with the diabetes team- *SEL guidance for use of SGLT2i in heart failure and diabetes is in development*

Heart Failure Definitions ^{6 (ESC)}:

Type of HF	HF _r EF	HF _{mr} EF	HF _p EF
CRITERIA	1 Symptoms +/- signs	Symptoms +/- signs	Symptoms +/- signs
	2 LVEF ≤ 40%	LVEF 41 – 49%	LVEF ≥ 50%
	3 N/A	The presence of other evidence of structural heart disease (e.g. increased left atrial size, LV hypertrophy or echocardiographic measures of impaired LV filling) makes the diagnosis of HF _{mr} EF more likely	Objective evidence of cardiac structural and/or functional abnormalities consistent with the presence of LV diastolic dysfunction/raised LV filling pressures including raised natriuretic peptides. For the diagnosis of HF _p EF, the greater the number of abnormalities present the higher the likelihood of HF _p EF

LVEF= left ventricular ejection fraction, HF_rEF = heart failure with reduced ejection fraction (*not covered by this guidance*)

Initiation Guidance

Follow the flowchart below when initiating dapagliflozin for patients with HF_pEF or HF_{mr}EF. Please see [SEL guidance on the pharmacological management of chronic heart failure in adults](#) and [SGLT2i in HF_rEF guidance](#) for more information on the management of all types of heart failure (HF_rEF, HF_{mr}EF and HF_pEF).

Dapagliflozin 10mg OD may be initiated for patients with symptomatic HF_pEF or HF_{mr}EF by a specialist in secondary care or community setting or in primary care (**amber 1** on [RAGG](#) list) on the advice of an appropriate specialist e.g. nurse, doctor or pharmacist (NICE [TA902](#)). Refer to initiation guidance and patient information (*see pages 3 & 4*)



Check this is a suitable choice for the patient based on the relative **cautions** and **contraindications** (*see table on page 2*) and ensure a documented shared decision with the patient (*think overprescribing*)



If dapagliflozin is initiated by a specialist in secondary care or community settings, each patient must have a clear management plan to allow primary care to take over prescribing. **Communication to primary care must include:** 1. Clear indication for dapagliflozin therapy 2. Documentation of baseline checks (*see page 3*)
3. Confirmation that the patient has been counselled on this therapy (*see page 4*)

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Use with CAUTION in the following circumstances

Full list: [Dapagliflozin SPC](#)

Patient Characteristics

- Body mass index <25kg/m² (<23kg/m² in South Asian people)
- Person adhering to a ketogenic/low calorie/low carbohydrate diet/intermittent fasting
- Recent weight loss
- Potential for pregnancy- dapagliflozin is to be avoided in pregnancy
- People at risk of hypotension/volume depletion (e.g. frail, elderly)
- Cognitive impairment or use of medicine compliance aids (may imply inadequate understanding or ability to follow sick day rules and act to prevent and identify DKA)
- On high dose diuretics/metolazone – contact heart failure team for advice as may need dose adjustment

Other past medical history

- On long term or recurrent courses of steroids (IV or oral) e.g.3 or more per year
- Raised haematocrit
- Severe hepatic impairment (dose reduction required at initiation)
- Recurrent urinary tract or genital tract infections
- Pancreatitis (these patients may be at higher risk of DKA)

Diabetes history

- Long duration of diabetes (generally over 10 years since diagnosis)
- Person with very high HbA1c i.e. HbA1c ≥ 86 mmol/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 or foot ulceration
- Existing diabetic foot ulcers/infection
- Previous lower limb amputation
- History of peripheral arterial disease (PAD)
- Taking sulfonylureas and/or insulin – increased risk of hypoglycaemia if started on SGLT2-inhibitor and eGFR >45ml/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 or surgery

AVOID in the following circumstances

Full list: [Dapagliflozin SPC](#)

Patient Characteristics

- Age <18 years
- Pregnancy, 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. The tablets contain lactose therefore do not give in galactose intolerance or total lactase deficiency

Current medical history

- Acutely unwell (acute 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 - [Dapagliflozin SPC](#))
- Multiple pre-disposing risks for Fournier's gangrene e.g. weight loss, symptoms of hyperglycaemia
- Organ transplant (contact transplant team for advice)

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

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Initiation Guidance

Check baseline renal function

- Dapagliflozin is not recommended in eGFR <15 ml/min
- Please note that: Dapa-CKD study showed a benefit in eGFR ≥15ml/min in patients with CKD co-morbidity (eGFR <60ml/min) and is licensed for use in CKD (chronic kidney disease)
- If patients have a diabetes co-morbidity then glycaemic control may be reduced with eGFR <45ml/min (seek advice from diabetes specialists as these patients are excluded from this guidance)
- **Monitor at baseline, within 3 months and as clinically indicated thereafter, at least annually**

Note:

- eGFR can fall approx. 4 to 6 ml/min after starting therapy. Seek renal specialist advice if eGFR drop >10ml/min within a 6-month period or >15ml/min within a 12-month period
- If eGFR becomes <30ml/min during treatment, refer to specialist (HF/renal team). Continue therapy unless an urgent clinical need to stop. NICE approved SGLT2i have been shown to slow progression of CKD alongside CV risk reduction benefits and should only be stopped following a discussion with a specialist.



Check baseline blood pressure

- Caution when initiating if SBP <95mmHg for patients ≥65 years and if symptomatic hypotension
- **Monitor at baseline, within 3 months and as clinically indicated thereafter, at least annually**

Note:

- Dapagliflozin increases diuresis which may lead to a modest decrease in blood pressure (approximately 3 to 5mmHg SBP and 2mmHg DPB observed in clinical studies)
- Monitor for any signs of dizziness or hypotension. A review of existing antihypertensives or diuretics may be required. Refer to heart failure specialist for advice if required.



Assess fluid balance/volume status

- Dapagliflozin has a diuretic effect which may lead to dehydration
- Review of existing diuretic or antihypertensive therapy may be required when starting dapagliflozin. Refer to heart failure specialist for advice if required.
- **Monitor fluid balance, BP and laboratory tests (e.g. haematocrit, urea & electrolytes) at baseline, within 3 months and as clinically indicated thereafter**
- General assessment of patient – check for volume depletion/dehydration alongside a review of diuretic therapy
- Recommend caution in patients with intercurrent conditions which may lead to volume depletion (e.g. gastrointestinal illness)



Check baseline liver function

- No dose adjustment is required in mild hepatic impairment
- In severe hepatic impairment (Childs-Pugh score C, AST/ALT >3 x ULN or Bilirubin 2 x ULN), initiate at lower dose of 5mg daily. Dose may then be increased to 10mg if well tolerated.
- **Monitor liver function at baseline and as clinically indicated thereafter**



Check HbA1c

- Check baseline HbA1c
- It is good practice to check for diabetes prior to starting a NICE approved SGLT2i to exclude undiagnosed type 2 diabetes mellitus (T2DM). Refer to DM team/guidance if HbA1c is above 48mmol/mol (6.5%). See NICE guidance for [T2DM](#)



Check Interactions

- See manufacturers summary of product characteristics for full details: [Dapagliflozin SPC: Interactions](#)

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Information for the patient

- Ensure patient understands the indication for treatment and provide them with an appropriate patient information leaflet ([PIL](#)) clarifying that they do not have diabetes but this treatment is for their heart
- Ensure the patient is counselled on the individualised benefits of taking dapagliflozin i.e. reduced mortality, improved HF symptoms and reduced risk of hospitalisation for heart failure)
- Ensure the patient is counselled on **side effects** and **sick day rules** (see detailed below)-
- Ensure the patient is counselled on appropriate foot care and management
- Advise the patient to not start a very low carbohydrate or ketogenic diet without discussing with an appropriate healthcare professional first
- Documented drug interactions are related to the potential effects of synergistic hypotension, hypovolaemia or hypoglycaemia with medications that lower BP and blood glucose. These parameters should therefore be monitored in these patients.
- **Loop and thiazide diuretics:** Dapagliflozin can potentiate the diuretic effect and increase the risk of hypotension or dehydration. Consider discussing with the patient's HF team to amend doses of co-prescribed diuretics.

Patient Education:

SICK DAY RULES

There are certain circumstances in which dapagliflozin should be **temporarily withheld** to reduce the likelihood of further deterioration or developing diabetic ketoacidosis (DKA). These include:

- If you are unwell with diarrhoea, vomiting, fever, dehydration or unusual drowsiness
- If you are unable to eat and drink normally
- If you are unwell with infection or illness or if symptoms have not resolved within 24 hours
- Prior to surgery – as advised by pre-op team (see [MHRA alert](#) for more information including advice on stopping if hospitalised)
- Consider in any other hospital admission until patient is well/stable. If you are unsure, withhold, and seek advice from senior team member

Ensure monitoring of blood glucose levels more frequently during period of acute illness (where applicable).

Patients can restart dapagliflozin once they are no longer acutely unwell and are eating and drinking normally for at least 24 hours (providing no new contraindications exist)

Patient Education: ADVERSE EFFECTS

For full side effect profile see drug monograph: [Dapagliflozin SPC](#)

Common:

- **Increased risk of UTI and mycotic genital infections:** Reinforce adequate genital hygiene, can be managed with antimicrobial treatment but may require cessation if recurrent or problematic infections. Stop therapy if significant UTIs such as pyelonephritis, urosepsis.
- **Increased urinary frequency:** Due to excretion of glucose in the urine. Consider stopping if problematic.
- **Volume depletion effects (thirst, postural dizziness, hypotension):** Monitor fluid balance. Counsel patients on the risk of dehydration and importance of adequate hydration.
- **Hypoglycaemia:** Most likely to occur in combination with insulin/sulfonylurea. Counsel on prevention, identification and management of hypoglycaemia and follow initiation flowchart on page 3 to reduce risk. Advise to report all episodes of hypoglycaemia to GP practice or specialist diabetes team.

Uncommon, serious

- **Diabetic ketoacidosis (DKA):** *this has not yet been reported in patients without diabetes, but it is important to be aware of and to inform patients of the signs and symptoms of metabolic acidosis, as this may be an issue for undiagnosed T2DM* DKA can also occur when glucose levels are normal (see [MHRA](#) recommendations). The risk of diabetic ketoacidosis 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. In patients where DKA is suspected or diagnosed, dapagliflozin treatment should be stopped immediately.
- **Fournier's Gangrene:** Necrotising fasciitis of the perineum is rare and treatment should be stopped immediately. 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. Report all suspected cases via Yellow Card Scheme. See [MHRA alert](#) for more information.
- **Lower limb amputation risk ([MHRA](#) footcare advice):** Advise on importance of routine preventative footcare and reporting issues in a timely manner.
- **Rash:** Eliminate other possible causes first, if persists, consider stopping
- **Angioedema:** Treatment should be discontinued immediately

Always discuss stopping therapy with a HF or diabetes specialist, unless there is an urgent clinical need to stop immediately

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Roles and Responsibilities

Specialist team – information to be communicated via clinic or discharge letter and to be recorded in primary care:

- Indication for therapy, including an updated HF management/medicines optimisation plan
- Details of the shared decision-making process/counselling with the patient (*Think Overprescribing*)
- Baseline renal function and BP reading (include baseline HbA1c if checked and liver function test if severe hepatic impairment requiring dose adjustment at initiation- *see page 3*)
- Details of upcoming specialist and/or community HF team follow up/support

Refer to the patient's local community pharmacy (via email) for the Discharge medicines service (NHS DMS) if possible, which will assist understanding of and adherence to therapy and ensure accurate medicines reconciliation. All new initiations for **medicines compliance aid** patients must be discussed with their community pharmacy to safeguard the patient and reduce risk of medication errors.

Primary care:

- Initiate on the advice of secondary care (these patients may be seen by specialists in medicine, renal, diabetes, respiratory and cardiology for example), heart failure community team or continue ongoing prescribing of dapagliflozin once initiated by relevant team
- Ensure the indication for therapy is clearly linked to the patient record (SNOMED codes)
- Monitor as indicated and review the patient every 6 to 12 months in line with [NICE HF guidance](#) (see monitoring and side effects on pages 2-3)
 - o *The frequency of monitoring should depend on the clinical status and stability of the person. The monitoring interval may be shortened to within days if the clinical condition has changed or within 2 weeks for medication changes (HF teams or specialist teams may support this), but monitoring is recommended at least 6-monthly for stable people with proven HF*
- Support patient adherence unless adverse effects necessitate cessation of therapy (discuss with HF team before stopping any prognostic medications for heart failure unless there is a clear clinical reason to stop immediately)
- Report any adverse effects via the [MHRA](#) yellow card system

When to refer from primary to secondary care?

Seek advice and guidance from the initiating team or appropriate specialist team in any of the following circumstances:

- Patient tolerability issues and frailty concerns which may lead to cessation of therapy
- If eGFR drops >10ml/min within a 6-month period or >15ml/min within a 12-month period
- If eGFR becomes <30ml/min during therapy or is <15ml/min at initiation
- If concerns re hypoglycaemia in patients with diabetes- refer to diabetes specialists (*this guidance focuses on patients without diabetes*)

Contact details for South East London Community HF teams: see [SEL guidance on the pharmacological management of heart failure in adults](#): page 25. Please note that not all patients with HFpEF and HFmrEF will be under HF teams

Borough	Heart Failure Community Team
Bexley	Email: oxl-tr.cardiac@nhs.net Tel: 0207 188 8952 or 0208 319 7060
Bromley	Email: kch-tr.PRUHheartfailurenurses@nhs.net Tel: 01689866097 (bleep #739) Email: kch-tr.br-bromleyintegratedheartfailurenurses@nhs.net Tel: 07971484508
Greenwich	Email: oxl-tr.cardiac@nhs.net Tel: 0208 319 7060
Lambeth & Southwark	Email: Gst-tr.KHPcommunityHF@nhs.net Tel: 0203 049 4652
Lewisham	Email: LH.commuhreferrals@nhs.net Tel: 0203 049 3473

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DISCLAIMER: This guidance does not override the individual responsibility of healthcare professionals to make appropriate decisions based on the circumstances of the individual patient, in consultation with the patient and/or guardian or carer. If dapagliflozin is prescribed for non-approved/unlicensed indications, prescribing responsibility will remain with the initiating clinician/organisation.

References:

1. Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction TA902 June 2023: <https://www.nice.org.uk/guidance/ta902/chapter/1-Recommendations>
2. [SGLT2i-in-HFrEF-non-DM-Guidance-FINAL-June-2022.pdf \(selondonccg.nhs.uk\)](#)
3. [Forxiga 10 mg film-coated tablets - Summary of Product Characteristics \(SmPC\) - \(emc\) \(medicines.org.uk\)](#)
4. [Recommendations | Chronic heart failure in adults: diagnosis and management | Guidance | NICE](#)
5. [Heart-Failure-adult-treatment-GL-SEL-FINAL-July-2020.pdf \(selondonccg.nhs.uk\)](#)
6. [2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure | European Heart Journal | Oxford Academic \(oup.com\)](#) [accessed 30/05/23]

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