

NICE recommendation for use ([NICE TA679](#) [NICE TA773](#)):

Dapagliflozin & Empagliflozin are recommended as options for treating symptomatic chronic heart failure with reduced ejection fraction in adults, only if it is used as an add-on to optimise standard care with:

- angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs), with beta blockers (BB), and, if tolerated, mineralocorticoid receptor antagonists (MRAs), or
- sacubitril valsartan, with beta blockers, and, if tolerated, an MRA.

Start treatment of symptomatic heart failure with reduced ejection fraction with dapagliflozin or empagliflozin on **the advice of a heart failure specialist**. Monitoring should be done by the most appropriate healthcare professional.

Dapagliflozin & Empagliflozin for the treatment of heart failure have an **AMBER** traffic light status on the BSW formulary; **AMBER**: *These medicines are considered suitable for GP prescribing following specialist initiation or recommendation*. (See <http://www.bswformulary.nhs.uk/> for further information).

General points for use:

- The recommended dose of dapagliflozin or empagliflozin for heart failure is **10 mg once daily**.
- The specialist team (consultant or nurse) should check the patient's HbA1c before initiating dapagliflozin or empagliflozin (if there are no recent results for this) to ensure the patient does not have undiagnosed diabetes.
- Medical notes need to be very clear as to the **indication for use** when this is initiated, as there is a risk that someone reviewing the medication might stop the dapagliflozin or empagliflozin if the patient has type 2 diabetes with renal function deteriorating. This will also help local acute trusts in terms of knowing what to do with respect to the medication when a patient is acutely unwell.
- Although it is recognised that the beneficial effects of sodium-glucose cotransporter 2 inhibitors (SGLT2s) in heart failure is probably a class effect, all **NEW** pts requiring a SGLT2 inhibitor for heart failure should receive dapagliflozin or empagliflozin so that the GP is prescribing a licensed medicine.
- Where possible, the first one-month prescription supply will be provided by the specialist. It is recognised that this might not always be possible due to practicalities. If so, the GP might be asked to initiate dapagliflozin or empagliflozin via written advice from the specialist.

Sequencing of heart failure therapy¹

- Large-scale trials have demonstrated the efficacy of ACE-inhibitors/ARB or sacubitril/valsartan, β -blockers, MRAs, and SGLT2 inhibitors as disease-modifying agents that (when combined) represent foundational therapy for heart failure and a reduced ejection fraction (HFrEF).
- Although the NICE [NG106](#) (Sept 2018) advises that drugs are initiated individually and doses optimised before adding another drug group into treatment, current theory is that any delay in starting the above groups of heart failure drugs is not acceptable because each of the foundational drugs has been shown to reduce morbidity and mortality within 30 days of initiating treatment. With every passing visit, the absence of ≥ 1 therapy results in unnecessary hospitalizations and deaths. Therefore, local specialists are moving towards getting patients onto drugs from each of these 4 drug classes as quickly as possible. Up-titration to target doses would be pursued thereafter.
- The addition of a new drug class yields benefits that are greater in magnitude than up-titration of existing drug classes. Indeed, 3- to 7-fold increments in the dose of an ACE-I or ARB produces none of the mortality reduction seen with the addition of a β -blocker, neprilysin inhibitor, or SGLT2 inhibitors.
- The proper sequencing of drug classes can improve safety and tolerability. Specifically, neprilysin inhibition can reduce the risk of renal insufficiency produced by an ACE-I or ARB, and both neprilysin inhibitors and SGLT2 inhibitors can minimize the risk of hyperkalemia seen with the use of MRAs.

Use of Dapagliflozin & Empagliflozin in renal impairment

Be aware that the renal threshold for reviewing dapagliflozin & empagliflozin differs according to the indication for use. The table below highlights the different thresholds in the licenses (SPC) for the different SGLT2 inhibitors (see individual SPC links in further information section page 4 for full information):

| Drug | Renal threshold to review (type 2 diabetes) | Renal threshold to review (HF) |
|---------------|---|--------------------------------|
| Dapagliflozin | 45ml/min | 15ml/min |
| Canagliflozin | Use lower 100mg dose if eGFR 30-60ml/min | N/A |
| Empagliflozin | 45ml/min | 20ml/min |
| Ertugliflozin | 45ml/min | N/A |

When SGLT2 inhibitors are used to treat type 2 diabetes, it is the anti-diabetic effect that weakens, which leads towards the recommendations to review use at higher renal thresholds, it is not due to concerns about the safety of their use in renal impairment. There is significant clinical trial data regarding the use of SGLT2 inhibitors in low renal function, such as DAPA-CKD² which used dapagliflozin down to a eGFR of 25ml/min, DAPA-HF³ which went down to an eGFR of 30ml/min and canagliflozin (CREDESCENCE⁴) down to a eGFR of 30ml/min. Empagliflozin has positive data from the EMPEROR-Reduced trial.⁵ It should be noted that dapagliflozin has a license for treatment of chronic kidney disease and is NICE approved ([TA775](#)).

Please note that if a patient starts to see a decline their renal function to below 15-20ml/min whilst on Dapagliflozin/Empagliflozin, **do not stop treatment** without a discussion with the heart failure specialist

Use of Dapagliflozin or Empagliflozin for heart failure in T2DM

If a type 2 diabetic patient is seen by a heart failure specialist already on a SGLT2 inhibitor which is not licensed for heart failure (e.g., canagliflozin), and their renal function is comfortably above an eGFR of 60ml/min, there is no rush to switch them to dapagliflozin or empagliflozin. This is due to the class heart failure effect.

If, however, the patient does have an eGFR close to 60ml/min or below, it might be worth reviewing the alternative SGLT2 inhibitor and switching them to dapagliflozin or empagliflozin to allow the GP to prescribe a licensed medicine for that renal function. It would also help to reduce confusion as to what indication the patient is on the SGLT2 inhibitor for. There is a risk that someone reviewing a patient's diabetes medicines could wrongly stop alternative SGLT2 inhibitors if they think they were on it for their type 2 diabetes, when the patient has been left on it because of its effect on their heart failure.

When a cardiologist is considering initiating dapagliflozin or empagliflozin in a type 2 diabetes patient they may need to refer the patient for advice when initiating dapagliflozin or empagliflozin as per the following table to ensure that the anti-diabetic effect of the dapagliflozin or empagliflozin is considered amongst other concurrent anti-diabetes medications. Such patients may need to increase their frequency of blood glucose testing initially when dapagliflozin is started to identify any resulting hypoglycaemia:

| Medication | Refer to |
|--|--------------------------------------|
| Type 2 diabetic patient on insulin | DSN |
| Type 2 diabetic patient on SU/repaglinide | GP |
| Type 2 diabetic patient on metformin alone | Cardiologist can initiate themselves |

Use of Dapagliflozin or empagliflozin for heart failure in T1DM

Use in type 1 diabetic patients is not recommended in the SPCs and neither drug is licensed for this group of patients.

Other considerations when initiating Dapagliflozin/Empagliflozin

Concomitant diuretics: Diuretics are sometimes used in heart failure patients for symptomatic control. SGLT2 inhibitors have a mild diuretic effect and so the specialist will review the use and dose of concurrent diuretics to ensure that the small additive effect of the SGLT2 inhibitor does not cause untoward problems. Many patients will be able to continue their diuretics if they are needed, but care may be needed in the elderly or frail.

Symptomatic hypotension or systolic blood pressure < 95 mmHg: This is more often a problem due to other medications that the patient is taking. Having a systolic BP <95mm Hg is NOT a contra-indication for use. The specialist will carefully review the patients and their medications when initiating dapagliflozin or empagliflozin, but it is not expected that there will be problems initiating dapagliflozin/empagliflozin in most patients with a blood pressure like this. Care will be needed if a patient is experiencing dizziness prior to initiation.

Renal function decline upon initiation of dapagliflozin: After initiation of treatment with dapagliflozin/empagliflozin the eGFR often dips but this usually resolves in 1-3 months. There is no need to monitor U&Es specifically for this.

Dapagliflozin/Empagliflozin should not be used in patients on a very carbohydrate restricted diet (eg Atkins).

Safety considerations for GPs: (See SPCs for full information)

Volume depletion: 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.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses as advised by the specialist.

DKA risk: SGLT2 inhibitors should be used with caution in patients with increased risk of DKA. Patients who may be at higher risk of DKA include those with a low beta-cell function reserve (e.g., type 1 diabetes, type 2 diabetes with low C-peptide or latent autoimmune diabetes in adults (LADA) or those with a history of pancreatitis). Also, 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.

STOP Dapagliflozin/Empagliflozin:

- In patients where DKA is suspected or diagnosed.
- In patients with intercurrent illness if not eating or at risk of dehydration and only restart once better and back on normal diet.
- In patients admitted to hospital acutely unwell for any reason and restart only once fully recovered and eating and drinking normally.
- In any patient having elective surgery who is missing more than one meal and restart only once recovered and eating and drinking normally

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. Specialist advice should be sought.

Urinary tract infections: Urinary glucose excretion may be associated with an increased risk of urinary tract infection; therefore, temporary interruption of dapagliflozin/empagliflozin should be considered when treating pyelonephritis or urosepsis.

Vulvovaginitis, balanitis and related genital infections: Listed as “common” in SPC.

If a patient has a deterioration in their heart failure symptoms (e.g., increasing breathlessness and fluid retention) then the GP will need to seek further advice from the specialist.

Patient advice

This patient information from the manufacturer can be used to counsel patients on what they need to watch out for (Dapagliflozin): [Forxiga-Heart-Failure-Patient-Booklet-Updated.pdf](#) (includes sick day rules).

Empagliflozin: <https://www.medicines.org.uk/emc/product/5441/pil>

Advise patient against having a very carbohydrate restricted diet (e.g., Atkins) –dapagliflozin/empagliflozin should not be started in such patients.

Further information for health care professionals

- [Forxiga \(dapagliflozin\) Information for UK Healthcare Professionals](#)
- [MHRA April 2016 -SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis](#)
- [MHRA Feb 2019 - SGLT2 inhibitors: reports of Fournier’s gangrene \(necrotising fasciitis of the genitalia or perineum\)](#)
- [MHRA March 2017 - SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation \(mainly toes\)](#)
- [MHRA March 2020 -SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness](#)
- SPC for Canagliflozin: <https://www.medicines.org.uk/emc/product/11409/smpc>
- SPC for Dapagliflozin: <https://www.medicines.org.uk/emc/product/7607/smpc>
- SPC for Empagliflozin: <https://www.medicines.org.uk/emc/product/5441/smpc>
- SPC for Ertugliflozin: <https://www.medicines.org.uk/emc/product/10099/smpc>

References

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2. Heerspink HJL et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; 383:1436-1446. <https://www.nejm.org/doi/full/10.1056/NEJMoa2024816>
3. McMurray JJV, Solomon SD, Inzucchi SE, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; 381: 1995-2008. <https://www.nejm.org/doi/full/10.1056/NEJMoa1911303>
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5. Packer M et al. Cardiovascular and renal outcomes with empagliflozin in heart failure. *N Engl J Med* 2020; 383:1413-1424. <https://www.nejm.org/doi/full/10.1056/NEJMoa2022190>

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