NHS
Pan Mersey
Area Prescribing Committee

DAPAGLIFLOZIN tablets (Forxiga ®) for symptomatic chronic heart failure with reduced ejection fraction

The Pan Mersey Area Prescribing Committee recommends the prescribing of DAPAGLIFLOZIN tablets (Forxiga®) for symptomatic chronic heart failure with reduced ejection fraction, following specialist recommendation in accordance with NICE TA679.

AMBER following specialist recommendation

NICE technology appraisal (TA) 679[1] recommends dapagliflozin (Forxiga®) as an option for treating symptomatic chronic heart failure with reduced ejection fraction (HFrEF) in adults, only if it is used as an add-on to optimised standard care with:

- angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs), with beta blockers, and, if tolerated, mineralocorticoid receptor antagonists (MRAs), **or**
- sacubitril valsartan, with beta blockers, and, if tolerated, MRAs.[1]

Treatment should be started on the advice of a heart failure specialist (as defined below in local implementation recommendations) with access to a multidisciplinary heart failure team.[1,2]

People taking dapagliflozin for heart failure who also have diabetes might need adjustments in their diabetes medication for safety reasons. People taking dapagliflozin for diabetes who also have heart failure may need adjustments in their heart failure medication due to its modest effect on diuresis and blood pressure.

Dapagliflozin is also licensed for the treatment of type 2 diabetes mellitus. See separate Pan Mersey statements:

- CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN and ERTUGLIFLOZIN as MONOTHERAPIES in type 2 diabetes: a multiple prescribing statement
- CANAGLIFLOZIN, DAPAGLIFLOZIN, EMPAGLIFLOZIN and ERTUGLIFLOZIN as COMBINATION THERAPIES in type 2 diabetes: a multiple prescribing statement

Dapagliflozin is not recommended for the treatment of heart failure in patients with type 1 diabetes mellitus.[4]

The indication for dapagliflozin must be clearly documented on the patient's medical record.

Please refer to the following supporting documents:

- GP letter: GP communication letter: SGLT2 inhibitors in Heart Failure with Reduced Ejection Fraction
- Treatment Pathway: Pathway for the use of SGLT2 inhibitors in Heart Failure with Reduced Ejection Fraction
- Patient information leaflet: Your guide to Forxiga® (dapagliflozin) in heart failure with reduced ejection fraction (AstaZeneca)

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.

DAPAGLIFLOZIN tablets (Forxiga ®) for symptomatic chronic heart failure with reduced ejection fraction

Effectiveness [1,3]

DAPA-HF[3], the key trial, was a double-blind randomised clinical trial comparing dapagliflozin plus standard care with placebo plus standard care. Standard care was defined as ACE inhibitors, ARBs, or sacubitril valsartan, plus beta blockers, and, if tolerated, MRAs. People in the trial had HFrEF defined by an ejection fraction of 40% or less who despite being 'optimally treated with pharmacological and/or device therapy' remain symptomatic.

The primary efficacy outcome was a composite of cardiovascular death, and hospitalisation for heart failure or an urgent heart failure visit. Intention-to-treat analyses showed that dapagliflozin plus standard care reduced the incidence of the primary endpoint of composite cardiovascular events by 26% compared with placebo plus standard care (hazard ratio 0.74, 95% confidence interval 0.65 to 0.85; p<0.001). It also reduced the incidence of all the individual components of the composite endpoint. Among people randomised to dapagliflozin, 12% of people died compared with 14% of people randomised to placebo. Cox survival modelling estimated a hazard ratio of 0.83 (95% confidence interval 0.71 to 0.97) in favour of dapagliflozin.

NICE concluded that the trial findings were generalisable to NHS clinical practice but highlighted several differences between the population in DAPA-HF and the population in the NHS:

- The average age in the full population was younger than in the NHS
- The proportion of men was higher in the trial than in the NHS
- Not all people in the trial were taking NICE guideline-recommended doses of standard care
- More people were taking diuretics in the trial than in the NHS
- DAPA-HF is a multinational trial whose population may not reflect that of the NHS.

Despite these differences in baseline characteristics, clinical effectiveness results are not expected to change and the committee concluded that data from the overall DAPA-HF population were acceptable for decision making, and it was therefore appropriate to use these for the clinical effectiveness analyses.[1]

Safety [1,3,4]

The frequency and type of most adverse events were broadly similar for people on the dapagliflozin and placebo arms of DAPA-HF. However, in the DAPA-HF trial, more people on dapagliflozin had diabetic ketoacidosis (DKA) and volume depletion, and fewer people had acute kidney injury [1]. All cases of DKA occurred only in patients with diabetes at baseline [3].

Diabetic ketoacidosis (DKA): Before initiating dapagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered. 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. Dapagliflozin should be used with caution in these patients.[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).[4]

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]

Dapagliflozin should not be used in patients with type 1 diabetes.

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 and side effects.

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 (mainly toes)
- SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum)

Cost

The NHS list price of dapagliflozin is £36.59 per 28-tablet pack (excluding VAT).[5] The annual treatment cost is £476.98. Costs may vary in different settings because of negotiated procurement discounts.NICE noted the ICER for this population would be under £10,000 per QALY gained and considered it to be a cost-effective use of NHS resources when compared with optimised standard care based on ACE inhibitors or ARBs, or optimised standard care based on sacubitril valsartan.[1] NICE concluded that dapagliflozin added on to optimised standard care is less costly and at least equally effective as optimised sacubitril valsartan.[1]

Patient factors [4]

Renal function: It is not recommended to initiate dapagliflozin in patients with an eGFR < 15 mL/min and there is limited experience with dapagliflozin in patients with eGFR < 25 mL/min. No dose adjustment is required based on renal function. Glycaemic control is dependent on renal function. In patients treated with dapagliflozin for both heart failure and type 2 diabetes mellitus, additional glucose-lowering treatment should be considered if GFR falls persistently below 45 mL/min.

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. See also MHRA alert.

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 mg.

Prescribing information

- The recommended dose for heart failure is 10 mg dapagliflozin once daily. A starting dose of 5mg daily is recommended in severe hepatic impairment.[4]
- Initiation of dapagliflozin for heart failure in patients who also have diabetes may need adjustments in their diabetes medication. Close collaboration with the clinician responsible for the patient's diabetes management is required.
- Dapagliflozin should not be used in patients with type 1 diabetes mellitus.

Implementation notes

- Within the Pan Mersey health economy, the term 'specialist' for the purposes of this prescribing statement is understood to be a consultant cardiologist, a cardiology GPSi or a prescribing member of the heart failure team with experience of treating chronic heart failure and who has access to the relevant multidisciplinary heart failure team.
- It is the responsibility of the specialist making the recommendation to assess the patient's suitability for treatment (see pre-prescribing checklist below).
- Although initiation of dapagliflozin for heart failure should only be on the advice of a heart failure specialist, for diabetic patients the team responsible for their diabetes care should be consulted. Initiating dapagliflozin may require adjustment to both diabetes and heart failure regimes so clinicians initiating dapagliflozin for diabetes management should also liaise with the team responsible for the patient's heart failure management.
- Advice should be sought from the specialist team if symptoms worsen on optimised therapy to determine the appropriate next treatment.

- Baseline blood tests including U&Es including eGFR, FBC, LFTs and HbA1c should be available prior to prescribing.
- The initiating prescriber is responsible for ensuring patients with diabetes are aware of the risk of DKA with dapagliflozin.
- 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.

Please refer to the pre-prescribing checklist below:

Pre-prescribing checklist	Check
Patient does not have type 1 diabetes	□
eGFR is ≥15 mL/min	□
no critical limb ischaemia (discuss with specialist)	□
no prior allergy or intolerance to SGLT2 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 <15 mL/min)	□
FBC (haematocrit not raised)	□
LFTs (dapagliflozin starting dose 5mg in severe hepatic impairment)	□
HbA1c (refer to pathway)	□
Patient education	
Urinary and genital infections	□
DKA (patients with type 2 diabetes only)	□
Sick day rules	□
Patient information leaflet issued	□

- 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.

Monitoring

- Renal function should be monitored according to current guidelines for heart failure, there is no specific requirement for dapagliflozin.
- People treated with dapagliflozin for heart failure and type 2 diabetes may require a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycaemia.[(1)]

References

1. National Institute for Health and Care Excellence. Technology Appraisal 679; Dapagliflozin for treating chronic heart failure with reduced ejection fraction, 24 February 2021. Accessed 13 July 2021.
2. National Institute for Health and Care Excellence. NICE Guideline 106; Chronic Heart Failure in Adults: Diagnosis and management,12 September 2018. Accessed 13 July 2021.
3. McMurray JJV., Solomon SD., Inzucchi SE., Køber L., Kosiborod MN., Martinez FA,. Ponikowski P., Sabatine MS., Anand IS., Bělohlávek J., Böhm M., Chiang CE. et al., for the DAPA-HF Trial Committees and Investigators. Dapagliflozin in Patients with Heart Failure and Reduced Ejection Fraction. *N Engl J Med* 2019; 381:1995-2008. DOI: 10.1056/NEJMoa1911303
4. Astra Zeneca UK Ltd. Summary of Product Characteristics; Forxiga 10mg film-coated tablets, 25 October 2021. Accessed 16 November 2021
5. NHS Business Services Authority. Dictionary of medicines and devices (dm+d) browser . Accessed online 16 November 2021.