NHS
Cheshire and Merseyside

DAPAGLIFLOZIN and EMPAGLIFLOZIN
for chronic heart failure: a multiple prescribing statement

The Cheshire and Merseyside Area Prescribing Group recommends the prescribing of DAPAGLIFLOZIN and EMPAGLIFLOZIN, following specialist recommendation, as options for treating symptomatic chronic heart failure with reduced ejection fraction in accordance with NICE TA679 and NICE TA773, and symptomatic chronic heart failure with preserved or mildly reduced ejection fraction, in accordance with NICE TA902 and TA929.

AMBER following specialist recommendation

Dapagliflozin and empagliflozin are selective sodium-glucose cotransporter-2 (SGLT-2) inhibitors.

Chronic heart failure with reduced ejection fraction

NICE recommends dapagliflozin (TA679) and empagliflozin (TA773) as options 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] [2]

Chronic heart failure with preserved or mildly reduced ejection fraction

NICE recommends dapagliflozin (TA902) and empagliflozin (TA929) as options for treating symptomatic chronic heart failure with preserved or mildly reduced ejection fraction in adults. [3] [4]

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.

People taking SGLT-2 inhibitors for heart failure who also have diabetes might need adjustments in their diabetes medication for safety reasons. People taking SGLT-2 inhibitors for diabetes who also have heart failure may need adjustments in their heart failure medication due to their modest effect on diuresis and blood pressure.

SGLT-2 inhibitors are also licensed for the treatment of type 2 diabetes mellitus. Refer to local guidance for further information.

SGLT-2 inhibitors should not be used for the treatment of heart failure in patients with type 1 diabetes mellitus.

The indication for the SGLT-2 inhibitor 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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Effectiveness

Dapagliflozin and empagliflozin are selective and reversible inhibitors of SGLT-2. They reduce reabsorption of glucose from the glomerular filtrate in the proximal renal tubule with a concomitant reduction in sodium reabsorption leading to urinary excretion of glucose and osmotic diuresis. The overall effect is a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling and diastolic function and preserve renal function.[5][6] Indirect comparison suggests the treatments have similar clinical effectiveness and a similar effect on quality of life.[4]

Heart failure with reduced ejection fraction

In the two key trials, dapagliflozin and empagliflozin were superior to placebo in reducing the incidence of their respective composite primary endpoints; cardiovascular (CV) death, and hospitalisation for heart failure or an urgent heart failure visit in DAPA-HF [7], and CV death and hospitalisation for heart failure for EMPORER-Reduced.[8] In DAPA-HF, dapagliflozin reduced the incidence 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.[7] In EMPORER-Reduced, empagliflozin reduced the incidence by 25% compared with placebo plus standard care (hazard ratio 0.75, 95% confidence interval 0.65 to 0.86; p<0.0001). At a median follow up of 16 months, results showed that empagliflozin is clinically effective compared with placebo and that it reduces the risk of CV events when added to standard care.[8]

Heart failure with preserved or mildly reduced ejection fraction

In the two key trials, dapagliflozin and empagliflozin were superior to placebo in reducing the incidence of their respective composite primary endpoints of worsening heart failure or CV death in patients with heart failure and preserved ejection fraction (LVEF >40%). In DELIVER, dapagliflozin reduced the incidence by 18% (hazard ratio (HR) 0.82; [95% confidence interval (CI) 0.73 to 0.92]; p<0.001).[9] In EMPEROR-Preserved, empagliflozin reduced the incidence by 21% (HR, 0.79; [95% CI, 0.69 to 0.90]; P<0.001).[10]

Safety

Contraindications: hypersensitivity to the active substance or to any of the excipients.[5][6] Dapagliflozin and empagliflozin should not be used in patients with type 1 diabetes.[5][6]

Cautions:

- Intermittent fasting (e.g. Ramadan) or following ketogenic diets particularly if elderly or on diuretics; consider withholding or monitoring ketones if unwell.[11]
- In patients also being treated with sulphonylureas/meglitinides/insulin for type 2 diabetes dose adjustments of these drugs may be necessary to avoid hypoglycaemia.[5][6] See **implementation notes.**
- 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.[11]
- There is no evidence for use of SGLT-2 inhibitors in patients with decompensated heart failure.[11]
- Temporary interruption of SGLT-2 inhibitors should be considered when treating pyelonephritis or urosepsis.[11]
- 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.[11]
- If Fournier's gangrene is suspected, the SGLT2 inhibitor should be discontinued and treatment started.[12]

Ketoacidosis

- Cases of ketoacidosis, including life-threatening and fatal cases, have been reported in patients with diabetes treated with SGLT-2 inhibitors.[5][6] Ketoacidosis is less likely to occur in patients without diabetes, but cases have been reported. [6] 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).[5][6]
- Before initiating an SGLT-2 inhibitor, factors in the patient history that may predispose to ketoacidosis should be considered.[5][6]
- SGLT-2 inhibitors should not be used in patients with a history of diabetic ketoacidosis (DKA) and should not

be used in patients with type 2 diabetes at a higher risk of DKA unless the diabetes team are involved.

- Patients at higher risk of ketoacidosis 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. SGLT-2 inhibitors should be used with caution in these patients.[5][6]
- 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. SGLT-2 inhibitor treatment may be restarted when the ketone values are normal and the patient's condition has stabilised.[5][6]
- In patients where ketoacidosis is suspected or diagnosed, SGLT-2 inhibitor treatment should be stopped immediately. Restarting is not recommended, unless another clear precipitating factor is identified and resolved.[5][6]

See Summary of Product Characteristics (SPCs) for dapagliflozin and empagliflozin for full safety details and side effects.

See also MHRA alerts:

- SGLT-2 inhibitors: updated advice on the risk of diabetic ketoacidosis
- SGLT-2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness
- SGLT-2 inhibitors: Updated advice on increased risk of lower-limb amputation (mainly toes)
- SGLT-2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum)

Cost

The NHS list price for both dapagliflozin and empagliflozin is £36.59 per 28-tablet pack (excluding VAT).[13] The annual treatment cost per patient is £476.98.

Chronic heart failure with reduced ejection fraction

Overall, NICE anticipates a net resource impact for both dapagliflozin and empagliflozin (when savings from reduced hospitalisations are taken into account) of £1,000 per 100,000 population in 2022-23, rising to £2,000 per 100,000 population by year 2025-26 when steady state is assumed to have been reached.

Chronic heart failure with preserved or mildly reduced ejection fraction

Based on the NICE Resource Impact Template, NICE estimates the cost of implementing NICE TA902 as £15,000 per 100,000 in 2023/24, £31,000 per 100,000 in 2024/25, £46,000 per 100,000 in 2025/26, rising to £47,000 per 100,000 in 27/28 when it is assumed that steady state has been reached. For TA929, the NICE Resource Impact Template assumes an equal split between dapagliflozin and empagliflozin.

Patient factors[5][6]

Renal function:

No dose adjustment is required based on renal function. Glycaemic control is dependent on renalfunction. In patients with both heart failure and type 2 diabetes mellitus, additional glucose-lowering treatment should be considered if glomerular filtration rate (GFR) falls persistently below 45 mL/min. Dapagliflozin should not be initiated in patients with estimated glomerular filtration rate (eGFR) <15mL/min. There is limited experience with dapagliflozin in patients with eGFR <25 mL/min. Empagliflozin is not recommended in patients with eGFR <20 mL/min.

Volume depletion / Hypotension:

SGLT2-inhibitors increases diuresis which may lead to the modest decrease in blood pressure. Caution should be exercised in patients for whom this modest 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 SGLT-2 inhibitors 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, dapagliflozin may be started at a dose of 5mg and increased to 10mg if well tolerated. Empagliflozin is not recommended in severe liver impairment.
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. Empagliflozin is not recommended during pregnancy and should not be used during breastfeeding.

Prescribing information

- The recommended dose for heart failure is 10mg dapagliflozin or 10mg empagliflozin once daily. In severe hepatic impairment a starting dose for dapagliflozin of 5mg daily is recommended, empagliflozin is not recommended.[5][6]
- SGLT-2 inhibitors should not be used in patients with type 1 diabetes mellitus.

Implementation notes

- Within the Cheshire and Merseyside 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.
- Although initiation of SGLT-2 inhibitors 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. Likewise, clinicians initiating SGLT-2 inhibitor for diabetes management should liaise with the team responsible for the patient's heart failure management. Any other changes to medicines, including to oral hypoglycaemic medications, insulin or diuretics must be clearly communicated to the GP.
- It is the responsibility of the specialist clinician making the decision or recommendation to prescribe an SGLT2-inhibitor, to assess the patient's suitability for treatment **(see pre-prescribing / recommendation checklist below)** and to clearly document the outcome of the shared decision making conversation and informed patient consent. This should be clearly communicated to the patient's primary care prescriber, using the GP communication letter and should include confirmation that appropriate counselling has been provided, to enable them to safely initiate or continue prescribing.
- The initiating prescriber is responsible for ensuring patients have been counselled appropriately before prescribing. This should form part of the shared decision making conversation between the specialist clinician and patient, at the point the decision or recommendation is made to initiate SGLT-2 inhibitor treatment. The specialist clinician recommending treatment will usually be the initiating prescriber but, if not, the prescriber must ensure that pre-treatment checks and patient education have been completed and patient consent obtained before prescribing.
- The following information should be discussed with the patient by the specialist clinician before commencing or recommending SGLT-2 inhibitor treatment:
  - Risk of ketoacidosis (especially if on glucose monitoring therapy), signs and symptoms of ketoacidosis, and action to take.
  - Sick day rules - action 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.
  - Risk of mycotic genital infections– counsel on hygiene and consider prophylactic antifungals if existing history of recurrent mycotic genital infections.[11]
  - Fournier's gangrene – 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.[12]
  - Acute kidney injury (AKI) (especially if on diuretics/ACEi/ARB) – withhold diuretic/ACEi/ARB if unwell, (see sick-day rules above), avoid hypovolaemia.
  - Dehydration – maintain fluids, withhold SGLT-2 inhibitor if unwell.
  - Urinary Tract Infection (UTI) – withhold SGLT-2 inhibitor if UTI occurs.

- Peripheral vascular disease – counsel on foot care and withhold SGLT-2 inhibitor 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.
- Patient consent to treatment should be obtained and documented.

> 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.

> Please refer to the pre-prescribing checklist below:

Pre-prescribing *checklist*	Check
Patient does not have Type 1 diabetes	☐
eGFR is ≥15 mL/min for dapagliflozin or ≥20mL/min for empagliflozin	☐
No critical limb ischaemia (discuss with specialist)	☐
No prior allergy or intolerance to SGLT-2 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 <15mL/min for dapagliflozin or <20mL/min for empagliflozin)	☐
FBC (haematocrit not raised)	☐
LFTs (dapagliflozin starting dose 5mg in severe hepatic impairment, empagliflozin contra-indicated in severe liver impairment)	☐
HbA1c (if patient has diabetes, the team responsible for diabetes care should be consulted. Initiating an SGLT-2 inhibitor may require adjustment to diabetes regimens. Refer to pathway)	☐
Patient education	
Urinary and genital infections	☐
Ketoacidosis	☐
Sick day rules	☐
Patient information leaflet issued	☐

> For patients requiring SGLT-2 inhibitors 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.

> The following patient information leaflets should be supplied on treatment initiation:
  - Patient information leaflet: Your guide to Forxiga® (dapagliflozin) in heart failure for patients without type 2 diabetes (AstraZeneca)
  - Patient information leaflet: Your guide to Forxiga® (dapagliflozin) in heart failure for patients with type 2 diabetes (AstraZeneca)
  - Patient information leaflet: Jardiance® (empagliflozin) and heart failure (Boehringer Ingelheim)

Monitoring

- Renal function and U&Es should be checked prior to SGLT-2 inhibitor initiation and then monitored according to the Cheshire and Merseyside heart failure pathway and current guidelines for heart failure, accounting for other medicines the patient is taking including ACE inhibitors or MRA. See NICE Guideline [NG106]: Chronic heart failure in adults: diagnosis and management.
- People treated with SGLT-2 inhibitors for heart failure and type 2 diabetes may require a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycaemia. [5][6]

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