NHS
Cheshire and Merseyside

DAPAGLIFLOZIN and EMPAGLIFLOZIN for symptomatic chronic heart failure with preserved or mildly reduced ejection fraction: a multiple prescribing statement

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

AMBER following specialist recommendation

Dapagliflozin and empagliflozin are selective sodium-glucose cotransporter-2 (SGLT-2) inhibitors. NICE recommends dapagliflozin (TA902) and empagliflozin (TA929) as options for treating symptomatic chronic heart failure with preserved or mildly reduced ejection fraction in adults.[1,2]

If people with the condition and their clinicians consider dapagliflozin or empagliflozin to be suitable after discussing the advantages and disadvantages of all the options, NICE recommends using the least expensive. Take account of administration costs, dosage, price per dose and commercial arrangements.[2]

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.[3, 4]

The indication for the SGLT-2 inhibitor must be clearly documented on the patient's medical record.

Please refer to the following supporting documents:

- 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)

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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DAPAGLIFLOZIN and EMPAGLIFLOZIN for symptomatic chronic heart failure with preserved or mildly reduced ejection fraction

Effectiveness [1-6]

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.[3,4] Indirect comparison suggests the treatments have similar clinical effectiveness and a similar effect on quality of life.[2]

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 cardiovascular 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).[5] In EMPEROR-Preserved, empagliflozin reduced the incidence by 21% (HR, 0.79; [95% CI, 0.69 to 0.90]; P<0.001).[6]

Safety [3-6]

Contraindications: hypersensitivity to the active substance or to any of the excipients. In both DELIVER and EMPEROR-Preserved, the frequency and type of most adverse events were similar for people on the active treatment and placebo arms. In DELIVER, there were 2 cases of diabetic ketoacidosis (DKA) in patients with diabetes. [5] In EMPEROR-Preserved, uncomplicated genital and urinary tract infections and hypotension were more common in patients treated with empagliflozin.[6]

Diabetic ketoacidosis (DKA): Before initiating SGLT-2 inhibitors, 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. SGLT-2 inhibitors should be used with caution in these patients.[3, 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 SGLT-2 inhibitors. 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).[3, 4]

In patients where DKA 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. SGLT-2 inhibitors 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 may be restarted when the ketone values are normal and the patient's condition has stabilised.[3,4]

See Summary of Product Characteristics (SPCs) 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[1,2]

Drug	Dosage	Annual cost per patient
Dapagliflozin	10mg daily	£477
Empagliflozin	10mg daily	£477

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 [3,4]

Renal function: No dose adjustment is required based on renal function. Glycaemic control is dependent on renal function. 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.

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.[3,4]
- SGLT-2 inhibitors should not be used in patients with type 1 diabetes mellitus.
- Both treatments are licensed for treatment of chronic heart failure irrespective of ejection fraction but due to the differing approach to management, separate prescribing statements for dapagliflozin and empagliflozin in heart failure with reduced ejection fraction are available. For information on the use of SGLT-2 inhibitors in symptomatic chronic heart failure with reduced ejection fraction, refer to local guidance.[3,4]

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.
- 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 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 for diabetes management should 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 SGLT-2 inhibitors
- 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 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 (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 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.

Monitoring

- Renal function should be checked prior to SGLT-2 inhibitor initiation and then monitored according to current guidelines for heart failure.[3,4,7]
- 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.[3, 4]

References

1. National Institute for Health and Care Excellence. Technology Appraisal 902; Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction, 21 June 2023. Accessed 27 June 2023.
2. National Institute for Health and Care Excellence. Technology Appraisal 929; Empagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction, 01 November 2023. Accessed 10 November 2023.
3. AstraZeneca UK Ltd. Summary of Product Characteristics; Forxiga 10mg film-coated tablets , 6 December 2022. Accessed 28 October 2023
4. Boehringer Ingelheim Ltd. Summary of Product Characteristics Jardiance 10mg film-coated tablets 09 September 2023. Accessed 28 October 2023
5. Solomon SD, McMurray JJV, Claggett B, de Boer RA, DeMets D, Hernandez AF, Inzucchi SE, Kosiborod MN, Lam CSP, Martinez F, Shah SJ, Desai AS, Jhund PS, Belohlavek J, Chiang CE, Borleffs CJW, Comin-Colet J, Dobreanu D, Drozdz J, Fang JC, Alcocer-Gamba MA, Al Habeeb W, Han Y, Cabrera Honorio JW, Janssens SP, Katova T, Kitakaze M, Merkely B, O'Meara E, Saraiva JFK, Tereshchenko SN, Thierer J, Vaduganathan M, Vardeny O, Verma S, Pham VN, Wilderäng U, Zaozerska N, Bachus E, Lindholm D, Petersson M, Langkilde AM; DELIVER Trial Committees and Investigators. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022 Sep 22;387(12):1089-1098. doi: 10.1056/NEJMoa2206286. Epub 2022 Aug 27. PMID: 36027570.
6. Filippatos G, Butler J, Farmakis D, Zannad F, Ofstad AP, Ferreira JP, Green JB, Rosenstock J, Schnaidt S, Brueckmann M, Pocock SJ, Packer M, Anker SD; EMPEROR-Preserved Trial Committees and Investigators. Empagliflozin for Heart Failure With Preserved Left Ventricular Ejection Fraction With and Without Diabetes. Circulation. 2022 Aug 30;146(9):676-686. doi: 10.1161/CIRCULATIONAHA.122.059785. Epub 2022 Jun 28. PMID: 35762322; PMCID: PMC9422757.
7. National Institute for Health and Care Excellence. NICE Guideline 106; Chronic Heart Failure in Adults: Diagnosis and management, 12 September 2018. Accessed 6 June 2023.