NHS
Pan Mersey
Area Prescribing Committee

# EMPAGLIFLOZIN tablets (Jardiance®) for symptomatic chronic heart failure with reduced ejection fraction

**The Pan Mersey Area Prescribing Committee recommends the prescribing of EMPAGLIFLOZIN tablets (Jardiance®) for symptomatic chronic heart failure with reduced ejection fraction, following specialist recommendation in accordance with NICE TA773.**

## AMBER following specialist recommendation

NICE TA773 [1] recommends empagliflozin (Jardiance®) 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 empagliflozin for heart failure who also have diabetes might need adjustments in their diabetes medication for safety reasons. People taking empagliflozin 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.

Empagliflozin 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

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

**The indication for empagliflozin 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: 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.

# EMPAGLIFLOZIN tablets (Jardiance®) for symptomatic chronic heart failure with reduced ejection fraction

**Effectiveness** [1,3]

EMPORER-Reduced[3], the key trial, was a double-blind randomised clinical trial comparing empagliflozin plus standard care with placebo plus standard care. Standard care could include medical therapy with an ACE inhibitor, an ARB, a beta blocker or an MRA. People in the trial had HFrEF defined by an ejection fraction of 40% or less. The primary efficacy outcome was a composite of cardiovascular death, and hospitalisation for heart failure. Intention-to-treat analyses showed that empagliflozin plus standard care reduced the incidence of the primary outcome 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 cardiovascular events when added to standard care.

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

- The average age in the intention-to-treat population was 67 years, while the average in the NHS at diagnosis is 77 years
- The proportion of women (24%) was smaller than would be expected in the NHS
- The proportion of people using an ACE inhibitor or ARB was lower than would be expected in the NHS

The evidence review group stated that the characteristics of people in EMPORER-Reduced may not reflect that of the population in the NHS. The clinical experts agreed this might be an issue of how people are recruited to take part in clinical trials. People who are older and who might have more comorbidities would be less likely to be involved in a clinical trial so they might be under-represented. NICE noted EMPORER-Reduced was not powered to show any difference in subgroups by age. The clinical experts said there would be no apparent reason why relative treatment effects would be different between subgroups of younger and older ages. NICE concluded that data from the intention-to treat population in EMPORER-Reduced was broadly generalisable to NHS clinical practice.[1]

**Safety** [4]

Approximately half of the patients in the EMPORER-Reduced trial had type 2 diabetes. The most frequent adverse reaction was volume depletion (10.6% versus 9.9% for placebo). Major hypoglycaemic events were observed only in patients with diabetes. The overall safety profile of empagliflozin was generally consistent across the studied indications. No new adverse reactions were identified in the EMPORER-Reduced trial.

Diabetic ketoacidosis (DKA): Before initiating empagliflozin, 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. Empagliflozin 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 empagliflozin. 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, empagliflozin 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]

Empagliflozin 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 empagliflozin 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 empagliflozin 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 concluded that dapagliflozin was the most appropriate comparator based on its comparable mechanism of action and place in the treatment pathway along with the results of the indirect treatment comparison which showed no difference between the 2 treatments.[1] NICE was satisfied that empagliflozin is similarly effective to dapagliflozin and that its costs are identical.[1]

**Patient factors** [4]

Renal function: No dose adjustment is required based on renal function. For the indication of heart failure, empagliflozin is not recommended in patients with eGFR < 20 mL/min. Empagliflozin should not be used in patients with ESRD or on dialysis.

Volume depletion / Hypotension: Caution should be exercised in patients for whom an empagliflozin-induced drop in blood pressure could pose a risk, such as patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older.

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 empagliflozin is recommended for patients who develop volume depletion until the depletion is corrected. See also MHRA alert.

Hepatic impairment: No dose adjustment is required. Empagliflozin exposure is increased in patients with severe hepatic impairment and therapeutic experience is limited. Therefore empagliflozin is not recommended for use in severe hepatic impairment.

**Prescribing information**

- The recommended dose for heart failure is 10 mg empagliflozin once daily. [4]
- Initiation of empagliflozin 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.
- Empagliflozin 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.
- Although initiation of empagliflozin 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 empagliflozin may require adjustment to both diabetes and heart failure regimes so clinicians initiating empagliflozin 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 empagliflozin.
- 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 GP pre-prescribing checklist below:

| **Pre-prescribing *checklist*** | Check |
|---|---|
| eGFR ≥ 20ml/min for empagliflozin | □ |
| 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 <20ml/min for empagliflozin) | □ |
| FBC (haematocrit not raised) | □ |
| LFTs (empagliflozin not recommended 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 empagliflozin 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 prior to empagliflozin initiation and periodically during treatment ie at least yearly.[4]

> People treated with empagliflozin for heart failure and type 2 diabetes may require a lower dose of insulin or insulin secretagogue to reduce the risk of hypoglycaemia.[4]

**References**


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2. National Institute for Health and Care Excellence. NICE Guideline 106; Chronic Heart Failure in Adults: Diagnosis and management,12 September 2018. Accessed 10 March 2022.
3. Packer M., Anker SD., Butler J., Filippatos G., Pocock SJ., Carson P., Januzzi J., Verma S., Tsutsui H., Brueckmann M., Jamal W., Kimura K., et al., for the EMPORER-Reduced Trial Investigators. Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure. *N Engl J Med* 2020; 383:1413-1428. DOI: 0.1056/NEJMoa2022190
4. Boehringer Ingelheim Ltd. Summary of Product Characteristics Jardiance 10mg film-coated tablets 21 December 2021. Accessed 10 March 2022
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