North Central London
Joint Formulary Committee

Factsheet

Dapagliflozin (Forxiga®) and Empagliflozin (Jardiance) for chronic heart failure with reduced ejection fraction

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Disclaimer

Factsheets support GPs in taking ongoing responsibility for continuing a medicine initiated in secondary care. It differs from a shared care agreement where secondary cares retain a proportion of responsibility for ongoing care.

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Factsheet – Dapagliflozin (Forxiga®) and Empagliflozin (Jardiance)

Chronic heart failure with reduced ejection fraction (as per NICE TA679 and NICE TA 773 respectively)

As per formulary agreement:

- Dapagliflozin and Empagliflozin are recommended for chronic heart failure with reduced ejection fraction.
- The initiation of therapy may be in secondary care but initiation may also be in primary care on advice of a heart failure specialist with an established expertise in managing patients with heart failure and access to a multidisciplinary team.
- Before the recommendation of dapagliflozin or empagliflozin, factors in the patient history that may predispose to ketoacidosis should be considered (see section on DKA below including MHRA alert).
- For patients with diabetes with chronic heart failure with reduced ejection fraction on complex anti-diabetic medication regimes (i.e., three of more anti-diabetic medicines and any patient on insulin and/or sulphonylurea), the suitability and safety of dapagliflozin or empagliflozin should be discussed with a consultant endocrinologist.

Specialist recommending or initiating responsibilities:

1. Provide the patient with initial information regarding the treatment and possible adverse effects (including the risk of diabetic ketoacidosis (DKA) in patients who may be at risk).
2. Where initiated in secondary care, transfer to primary care should occur after 1 month.
3. In patients with diabetes who have chronic heart failure with reduced ejection fraction on complex diabetic medication regimes (i.e., three of more anti-diabetic medicines and any patient on insulin and/or sulphonylurea), the suitability and safety of dapagliflozin or empagliflozin should be discussed with a consultant endocrinologist prior to initiation or recommendation. This includes ensuring that patients who are required to undertake regular blood glucose or ketone monitoring have access to this (and the need communicated to the GP)
4. Emphasise to the GP that in patients with:
    a. **Both diabetes and heart failure**, dapagliflozin or empagliflozin has been added PRIMARILY for heart failure prognosis and symptoms, and that the medication should be continued even if HbA1c is not reduced.
    b. **Do not have diabetes but do have heart failure**, dapagliflozin or empagliflozin has been added for heart failure prognosis and symptoms and not for a diabetes indication.
5. Ensure documented communication has been sent to the GP, including the indication for use, the frequency of monitoring required for the patient, and that the specialist has counselled the patient on dapagliflozin or empagliflozin (benefits, side effects/risks).
    a. If it is acknowledged that the patient has an increased risk of DKA, this should be clearly stated in the letter to the GP with appropriate monitoring advice (i.e., regular blood sugar monitoring) and the patient counselled on early warning symptoms of DKA.

Checklist and actions for GP:

- Ensure documented communication has been received from a heart failure specialist with an indication for use and evidence that the specialist has counselled the patient on dapagliflozin or empagliflozin (benefits, side effects/risks), and this must be clearly documented and coded in the patients notes.
- Ensure that the patient meets criteria for continuation of treatment as per NICE TA679 or NICE TA773 (i.e., symptomatic heart failure [NYHA II to IV] with reduced ejection fraction [left ventricular ejection

fraction ≤40%], despite optimal treatment with ACEi/ARB/Sacubitril Valsartan, beta blocker and spironolactone/ eplerenone)

- Conduct necessary blood test monitoring at agreed schedule (see Clinical Monitoring section)
- Monitor the patient's overall physical health and well-being.
- Refer patient back to the heart failure team if the patient:
  - Is intolerant of side effects
  - Is non-compliant with medicines (or this is suspected)
  - Has a change in circumstances affecting dapagliflozin or empagliflozin (e.g. diabetic ketoacidosis)
- Manage adverse effects as indicated
- Contact the relevant heart failure team at any time during therapy for further advice

Dose and Administration of Dapagliflozin
Dapagliflozin should be taken orally at 10mg once-daily. Dapagliflozin can be taken with or without food.

***Dapagliflozin dosing in renal impairment**:*

- eGFR ≥15 mL/min/1.73m^2: no dose adjustment
- eGFR <15ml/min/1.73m^2: no experience, not recommended for initiation. If already established for heart failure with reduced ejection fraction, continue 10mg once-daily.

***Dapagliflozin dosing in hepatic impairment**:*

- Child-Pugh A or B: No dose adjustment is required
- Child-Pugh C: a starting dose of 5 mg once daily is recommended. If well tolerated, the dose may be increased to 10 mg once daily.

Dose and Administration of Empagliflozin
Empagliflozin should be taken at 10mg once daily. Empagliflozin can be taken with or without food.

Empagliflozin dosing in renal impairment

- eGFR ≥20 mL/min/1.73m^2: no dose adjustment
- eGFR -<20ml/min/1.73m^2: Due to limited experience, empagliflozin is not recommended.
- eGFR <15ml/min/1.73m^2: Not recommended; discontinue and refer back to specialist

Empagliflozin dosing in hepatic impairment

- Child-Pugh A or B: No dose adjustment is required
- Child-Pugh C: no experience, not recommended for initiation.

In patients treated with dapagliflozin or empagliflozin for both heart failure and type 2 diabetes mellitus, additional glucose-lowering treatment should be considered if eGFR falls persistently below 45 mL/min.1.73m^2 as there is diminished glycaemic effect, however sustained cardio-renal protection

Sick day rules: Please see adverse effects table for information if the patient experiences signs and symptoms of dehydration (e.g., because of infection or diarrhoea) or DKA.

Discontinuing treatment: Treatment should only be discontinued if severe adverse effects are seen (e.g., DKA); otherwise please discuss with the specialist prior to considering treatment cessation

Adverse Effects

The overall safety profile of **both** dapagliflozin and empagliflozin in patients with heart failure was consistent with the known safety profile of both these medicines.

Adverse effect	Frequency	Suggested management by GP
Hypoglycaemia (in patients with diabetes on insulin and/or sulphonylurea)	Very common	Offer additional education focusing on avoiding and treating hypoglycaemia if the patient has impaired awareness of hypoglycaemia. If on insulin, review regimes and doses and prioritise strategies to avoid hypoglycaemia. If the patient continues to have episodes of hypoglycaemia, liaise with or arrange referral to the diabetes specialist team (and ensure you inform the initiating heart failure specialist), the urgency depending on clinical judgement.
Urinary tract infections	Common	In recent large trials, any increase in risk was small and insignificant and rarely leads to discontinuation of therapy. Treat infection as appropriate and continue dapagliflozin or empagliflozin.
Vulvovaginitis, balanitis and related genital infections	Common	Counsel patients on good genital hygiene. Most cases can be treated with topical antifungals. Treat infection as appropriate and continue dapagliflozin/empagliflozin.
Renal impairment during initial treatment	Common with dapa; uncommon with empa	At 4 weeks there is an expected dip in eGFR of up to 20% for which there is no reason to withdraw dapagliflozin/empagliflozin, therefore it is unnecessary to check renal function at this stage. The recommendation is to check renal function 8 weeks post initiation and if there is a decline of eGFR >20%, refer back to the heart failure specialist.
Volume depletion (risk of dehydration)	Uncommon	See section on volume depletion below. Frail patients or those with cognitive impairment may be at increased risk of dehydration or hypotension. See 'special warnings and precautions for use' below for full details and management strategy.
Diabetic ketoacidosis (DKA): higher risk in some patients, e.g. those with T1DM or T2DM (see MHRA alert) – please note patients with T1DM are not recommended to receive dapagliflozin or empagliflozin for HFrEF in NCL	Rare	See section on DKA below. If DKA is diagnosed, dapagliflozin or empagliflozin should be immediately discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution has occurred. Dapagliflozin or empagliflozin must not be re-administered. See further information in 'special warnings and precautions for use' below.
Necrotising Fasciitis (Fournier's Gangrene) (see MHRA alert)	Very rare	Rare post-marketing incidents have been reported. Recent large trials have not shown any increase in risk. Patients should be advised to seek urgent medical attention if they experience fever/malaise along with pain, tenderness or redness in the genital or perineal area.

This list is not exhaustive; please see the dapagliflozin SPC or empagliflozin SPC for further information. Healthcare professionals are asked to report any suspected adverse reactions using the Yellow Card Scheme.

Contraindications

- For both dapagliflozin or empagliflozin - Hypersensitivity to the active substances or to any of the excipients.
- In NCL, dapagliflozin and empagliflozin are not recommended for the treatment of heart failure in patients with type 1 diabetes mellitus.

Special Warnings and Precautions for Use

- Use in patients at risk for volume depletion and/or hypotension
  - Due to its mechanism of action, dapagliflozin and empagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies. It may be more pronounced in patients with very high blood glucose concentrations.
  - Caution should be exercised in patients for whom a dapagliflozin/empagliflozin-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 urea and electrolytes) is recommended.
  - Temporary discontinuation of dapagliflozin/empagliflozin may need to occur for patients with volume depletion until the depletion is corrected. Consider discussing with a HF specialist.
  - Patients on moderate to high dose loop diuretics (furosemide >40 mg twice-daily or bumetanide >1 mg twice daily) where adjustments may not be easy to navigate, please contact the patient's heart failure team for advice.
- Diabetic Ketoacidosis
  - Sodium-glucose co-transporter 2 (SGLT2) inhibitors should be used with caution in patients with increased risk of diabetic ketoacidosis (DKA) and factors in the patient history that may predispose to ketoacidosis should be considered. Patients who may be at higher risk of DKA include patients with a low beta-cell function reserve (e.g. type 2 diabetes patients with low C-peptide or latent autoimmune diabetes in adults (LADA), patients with a history of pancreatitis or those patients who are prone to ketosis), 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. Moreover, patients on a ketogenic diet, have an eating disorder or a very low calorie diet may also be at risk. Please seek specialist support if considering use in any of these populations (e.g., an endocrinologist for patients with T2DM or LADA). [Note: type 1 diabetes also indicates a higher risk to DKA, but these patients are not recommended to receive dapagliflozin or empagliflozin for HFrEF in NCL]
  - The risk of diabetic ketoacidosis 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. An additional symptom incudes breath that smells fruity (like pear drop sweets). Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.
  - If it is acknowledged they are at a higher risk of DKA, the patient will need to be counselled on early warning symptoms (detailed in paragraph above) by the healthcare professional recommending

dapagliflozin or empagliflozin (as well as the prescriber on initiation of therapy, if different), with advice on when to seek immediate medical attention; advice for patients with hyperglycaemia is available via the NHS website

- 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 or empagliflozin may be restarted when the ketone values are normal and the patient's condition has stabilised.

- Impaired renal function (see 'Dosing and administration' and 'Adverse effects')
- Hepatic impairment (see 'Dosing and administration')

Pregnancy and Breastfeeding: There is no data on from the use of dapagliflozin or empagliflozin in pregnant women. When pregnancy is detected, treatment with dapagliflozin/empagliflozin should be discontinued. Dapagliflozin and empagliflozin is not recommended during breast-feeding.

Drug Interactions

- Diuretics - see 'special warnings and precautions of use'
- Insulin and sulphonyureas - Insulin and sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or sulphonylurea may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin in patients with heart failure with reduced ejection fraction *and* type 2 diabetes mellitus.

Please refer to SPC/BNF for full information on interactions with dapagliflozin and empagliflozin and how to manage these interactions.

Clinical Monitoring

All patients with chronic heart failure require monitoring in line with NICE NG106.

Blood test	Frequency	Action if out of range
Urea and electrolytes post initiation (including urea and creatinine clearance)	Check renal function 8 weeks post initiation.	If there is reduction of creatinine clearance >30% from baseline, refer back to the specialist. If the change is 30% or less from baseline, continue treatment.
Urea and electrolytes for continued treatment (including urea and creatinine clearance)	If baseline renal function normal, review annually; if baseline renal function (eGFR) <60ml/min, review every 3-6 months	If used for diabetes and HF, review blood glucose also and consider whether modification/additional anti-hyperglycaemic medication is required. Consider increase in monitoring frequency. If deterioration in renal function is observed : - For dapagliflozin (eGFR <15ml/min) used for HF only: continue treatment. Consider increase in monitoring frequency. - For empagliflozin (eGFR <20ml/min) used for HF only: discontinue treatment and refer back to specialist. -

Monitoring should also include:

- An annual clinical assessment of functional capacity, fluid status, cardiac rhythm (minimum of examining the pulse), cognitive status and nutritional status, in line with NICE NG106.
- A six-monthly review of medication (ACE inhibitors, angiotensin-receptor blockers, sacubitril/valsartan, as per NICE NG106), including need for changes and possible adverse effects

More detailed monitoring will be required if the patient has significant comorbidity or if their condition has deteriorated since the previous review. The frequency of monitoring should depend on the clinical status and stability of the patient. The monitoring interval should be short (days to 2 weeks) if the clinical condition or medication has changed but is required at least 6-monthly for stable patients with proven heart failure. The specialist will advise on the frequency of monitoring required for each patient; the patient's heart failure team can be contacted for further advice if needed.

At the time of approval, no specific monitoring, over-and-above usual monitoring requirements for patients with heart failure, was required for dapagliflozin or empagliflozin. GPs should review their patients as per NICE guidance.

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References

1) Dapagliflozin Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc/product/7607/smpc#
2) Empagliflozin Summary of Product Characteristics. Available at https://www.medicines.org.uk/emc/product/5441/smpc
3) NICE Clinical Guideline 106 'Chronic heart failure in adults: diagnosis and management'. Available at https://www.nice.org.uk/guidance/ng106
4) NICE TA679 'Dapagliflozin for treating chronic heart failure with reduced ejection fraction'. Available at https://www.nice.org.uk/guidance/TA679
5) NICE TA773 'Empagliflozin for treating chronic heart failure with reduced ejection fraction'. Available at https://www.nice.org.uk/guidance/ta773
6) Dashora U, Patel D, Nagi D, Rowles S, Wilmot E, Macklin A, Winocour P and Dhatariya K on behalf of the Association of British Clinical Diabetologists (ABCD). SGLT-2 inhibitors in people with type 2 diabetes: An educational resource for health professionals. Available on https://abcd.care/sites/abcd.care/files/resources/ABCD%20SGLT-2i%20guide%20for%20non-specialists.docx22.09.2020.docxrevised_0.pdf