NHS
Frimley
Clinical Commissioning Group

Amber without shared care – information sheet	
Name of medicine	Dapagliflozin (Forxiga®)
Indication	Dapagliflozin is licensed for the treatment of adults (with or without type 2 diabetes) with symptomatic chronic heart failure with reduced ejection fraction (≤40%)
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Dapagliflozin for heart failure has been classified as an Amber without Shared Care Medicine; this can be prescribed in primary care, on specialist advice without the need for a formal shared care agreement.

This **AMBER** without shared care information sheet sets out the patient pathway relating to this medicine and any information not available in the British National Formulary and manufacturer's Summary of Product Characteristics. Prescribing must be carried out with reference to those publications whenever appropriate.

Roles and responsibilities

Consultant / specialist team (specialist nurses/pharmacists)

- Diagnosis of condition ensuring patients fit criteria for use and initiation of treatment.
- Prescribe and supply if in-patient, recommend following an outpatient appointment with a cardiologist, recommend following heart failure multidisciplinary team meeting (MDT) at Frimley Park and Wexham Park hospitals.
- Undertake baseline monitoring if in-patient.
- Provide GP with diagnosis, relevant clinical information and baseline results.
- Provide GP with details of outpatient consultation in a timely manner.
- Advise diabetic patients on potential effect on disease management and any additional monitoring required. Refer to diabetes team as appropriate or contact for further information.
- Provide patient with relevant drug information to enable informed consent to therapy and understanding of potential side effects and appropriate action.
- Document when dapagliflozin is being used for HFrEF to ensure it is not stopped when diabetes medication is reviewed.

Primary care prescriber

- Prescribe or continue further prescriptions.
- Monitor the patients overall health and well-being and observe patient for evidence of adverse drug reactions and consult with secondary care clinician if necessary.
- Undertake baseline monitoring of kidney function on initiation and re-check 4 weeks after initiation. Re-check renal function depending on baseline function but as a minimum 6 monthly.
- Undertake more frequent tests if there is evidence of clinical deterioration, abnormal results or other risk factors. Contact consultant team for advice on monitoring in these circumstances.

Patient relatives & carers

- Ask the specialist or GP for information if they do not have a clear understanding of the treatment.
- Attend hospital and GP clinic appointments
- Read the patient information leaflet regarding the medication and report any side effects or concerns they have to the specialist or GP.

Key information on the medicine

Please refer to the current edition of the British National Formulary (BNF), available at https://bnf.nice.org.uk/ and Summary of Product Characteristics (SPC), available at www.medicines.org.uk for detailed product and prescribing information and specific guidance.

Background to disease and use of medicine for the given indication

Dapagliflozin is the first sodium-glucose transport protein 2 (SGLT2) inhibitor licensed for the treatment of adults (with or without type 2 diabetes) with symptomatic heart failure with reduced ejection fraction (≤40%).
SGLT2 inhibition leads to reduced reabsorption of glucose in the kidneys with a resultant increased excretion of glucose and an osmotic diuresis. SGLT2 inhibitors were initially licensed for use in diabetics.
The DAPA –HF trial evaluated dapagliflozin versus placebo in patients with heart failure and reduced ejection fraction (≤40%) in patients with or without type 2 diabetes. The primary end-point of cardiovascular death, worsening heart failure (unplanned hospital admission for heart failure or urgent HF visit requiring IV therapy) was significantly reduced (ARR 4.9%, NNT =21) in the treatment group regardless of diabetic status.

Mechanism of action

Inhibition of SGLT2 by dapagliflozin reduces 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. Dapagliflozin therefore increases the delivery of sodium to the distal tubule which is believed to increase tubuloglomerular feedback and reduce intraglomerular pressure. This combined with osmotic diuresis leads to a reduction in volume overload, reduced blood pressure, and lower preload and afterload, which may have beneficial effects on cardiac remodelling. The cardiac benefits of dapagliflozin are not solely dependent on the blood glucose-lowering effect and not limited to patients with diabetes as demonstrated in the DAPA-HF study. The amount of glucose removed by the kidney through this mechanism is dependent upon the blood glucose concentration and eGFR. Thus, in subjects with normal blood glucose, dapagliflozin has a low propensity to cause hypoglycaemia. Dapagliflozin does not impair normal endogenous glucose production in response to hypoglycaemia. It acts independently of insulin secretion and insulin action. SGLT2 is selectively expressed in the kidney and dapagliflozin does not inhibit other glucose transporters important for glucose transport into peripheral tissues and is >1,400 times more selective for SGLT2 versus SGLT1, the major transporter in the gut responsible for glucose absorption.

Place in therapy

1. Dapagliflozin is recommended as an option for treating symptomatic (NYHA class II to IV) HFrEF in adults, with or without type 2 diabetes and eGFr >30mls/min. It may be prescribed as an add-on to optimised standard care. This is currently:
    - Diuretics (if required for congestion)
    - Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs) or angiotensin Receptor Neprilysin Inhibitor (ARNI)
    - Beta blockers
    - Mineralocorticoid receptor antagonists (MRAs)
2. In patients with HFrEF and type 2 diabetes dapagliflozin may be prescribed as part of the regimen for glycaemic control in line with national and local guidelines for the management of type 2 diabetes. Dapagliflozin is not effective as a glucose lowering agent if eGFR<45mls/min but it still has benefits in HFrEF.

Dose

The recommended dose is 10 mg dapagliflozin once daily. Can be taken with or without food.

Who can prescribe?

Recommendation via secondary care specialist teams eg: heart failure (MDT), cardiology, diabetes, renal.
Recommendation via primary care specialists team eg: heart failure, diabetes
Primary care clinicians on the recommendation of the above teams.

Diabetes and HFrEF (see cautions)

SGLT2 inhibitors have a low risk of hypoglycaemic events. Reducing blood glucose levels via this mechanism could potentially predispose patients taking other anti-glycaemic medication (especially sulponylureas and insulin) to hypoglycaemia. Medications prescribed for glycaemic control must be reviewed in line with the patient's HbA1c target. In patients with type 2 diabetes refer for specialist diabetes team advice prior to initiation/during treatment if for example:

- The patient is taking insulin
- There is a history of hypoglycaemia (previous/frequent)
- Any advice is needed on diabetes

In patients with HFrEF who are already prescribed an alternative SGLT2 inhibitor (e.g. empagliflozin, canagliflozin) for the management of type 2 diabetes this may be continued. It is important to document when dapagliflozin is being used for heart failure (HFrEF) to ensure it is not stopped when diabetes medication is reviewed.

Additional glucose lowering treatment may be needed if eGFR falls persistently below 45ml/min in patients treated with dapagliflozin for both heart failure and type 2 diabetes. SGLT" inhibitors have minimal effect on glycaemic control with reduced renal function.

Contra-indications	**Cautions**
• Hypersensitivity to the active substance or to any of the excipients • Unacceptable side effects associated with, an SGLT2 inhibitor • Type 1 diabetes • History of diabetic ketoacidosis (DKA) • Pregnancy and breastfeeding • Age under 18 years old • Systolic blood pressure of less than 95 mm Hg	• Severe hepatic impairment • HFrEF with NYHA IV symptoms • Patients at risk of Fournier's Gangrene • Patients at increased risk of urinary tract infections or candida • Patients at increased risk of DKA (discuss sick day rules) • Patients with eGFR<30mls/min (limited experience) • Severe peripheral vascular disease • Patients with type 2 diabetes who are already at target HbA1c and currently taking hypoglycaemic agents eg. insulin and suphonylureas (Consider reducing dose of current hypoglycaemic agent) • Patients with type 2 diabetes who are not at target HbA1c level and eGFR 30-45mls/min (Dapagliflozin is still indicated and effective to treat HFrEF and has been shown to be reno-protective, but it may not be effective as a hypoglycaemic agent)

Drug Interactions

Refer to current Summary of Product Characteristics (SPC): www.medicines.org.uk

- Diuretics - Dapagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension. Adjustments should be based on clinical judgement and tailored to the patient
- Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of these agents may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin in patients with type 2 diabetes mellitus

Side effects

Common or very common	Uncommon	Rare or very rare
Back pain Creatinine renal clearance decreased during initial treatment Dizziness Dyslipidaemia Dysuria Genital infections Hypoglycaemia (in combination with insulin or sulfonylurea) Increased risk of infection Polyuria Rash Urinary tract infections	Constipation Dry mouth Fungal infection Genital pruritus or vulvovaginal pruritus (ensure good hygiene) Nocturia Weight decreased Hypovolaemia Thirst	Angioedema Diabetic ketoacidosis (when used in type 2 diabetes) Fournier's gangrene

Counselling/advice

- Risk of diabetic ketoacidosis (DKA)

Inform patients of the signs and symptoms of DKA - nausea or vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat, and advise them to seek immediate medical advice if they develop any of these. Patients should be assessed for ketoacidosis immediately if these symptoms occur, regardless of blood glucose level.

- Encourage good genital hygiene. Counsel on thrush and increase in urination volume and/or frequency. Most cases of thrush can be treated with OTC topical antifungals. Report any pain or redness in genital area with accompanying fever.

With intercurrent illness

Temporarily withhold dapagliflozin (or any other SGLT2 inhibitor) in patients who

- are hospitalised for major surgery or acute serious illnesses: blood ketone levels should be monitored (and be normal before restarting)
- are not eating and drinking
- admitted for elective surgery/procedure requiring starvation
- have vomiting or diarrhoea (or any inter-current conditions that may lead to volume depletion)
- have major infection

Treatment may be restarted once the patient's condition has stabilised and they are eating normally for at least 24 hours and no longer acutely unwell and no new contra-indications exist. Alternative diabetes treatment may be required in the interim.

Monitoring

Monitoring requirements: frequency - as recommended by the specialist	Responsible clinician
Pre-treatment: • Blood Pressure • U&E's	Consultant/specialist/GP
Maintenance: (minimum of six months or as per patients' baseline renal function and clinical status) • Blood Pressure • U&E's • HbA1c (for diabetic patients only)	GP

Further resources for counselling/advice

- **Patient information booklet –** Dapagliflozin in patients with HFrEF (produced by Astra Zeneca)
- **Association of Clinical Diabetologists** – SGLT2 inhibitors in people with Type 2 diabetes: An educational resource for health professionals.
- Diabetes UK advice for patients on **'Diabetes when you are unwell'**

References

1) Nice Technology Appraisal: Dapagliflozin for treating chronic heart failure with reduced ejection fraction. Technology appraisal guidance [TA679] Published 24/2/2021 [Accessed May 2021]
2) Forxiga 10mg tablets. Summary of Product Characteristics. www.medicines.org.uk [Accessed May 2021]
3) Guideline for Dapagliflozin in Heart Failure with Reduced Ejection Fraction (HFrEF) – Brighton and Sussex University Hospital NHS Trust (Approved January 2021)
4) Guidelines for the Initiation of Dapagliflozin in Adults with Left Ventricular Systolic Dysfunction – Frimley Health NHS Foundation Trust (Approved March 2021)