Surrey Heartlands Integrated Care System
Area Prescribing Committee (APC)

Integrated Care Partnership - Surrey Downs, Guildford & Waverley, North-West Surrey, and East Surrey Places & associated partner organisations.

NICE Technology Appraisals (TA) briefing paper for local implementation.

NICE TA Guidance name and number	Dapagliflozin for treating chronic heart failure with preserved or mildly reduced ejection fraction (HFp/mrEF) [TA902]		
Available at	https://www.nice.org.uk/guidance/ta902		
Date of issue	21st June 2023	**Implementation deadline**	4th October 2023

Medicine details[1]	
Name and brand name	Dapagliflozin (Forxiga®)
Manufacturer	AstraZeneca UK Limited
Mode of action	SPC accessed 14th July 2023 Dapagliflozin is a sodium-glucose co-transporter 2 (SGLT2) inhibitor. 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 increases tubuloglomerular feedback and reduces 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 and diastolic function and preserve renal function. The cardiac and renal benefits of dapagliflozin go beyond the blood glucose-lowering effect and are not limited to patients with diabetes as demonstrated in the DAPA-CKD, DAPA-HF and DELIVER studies.
Licensed indication	SPC accessed 12th July 2023 Dapagliflozin is indicated in adults for the treatment of symptomatic chronic heart failure.
Formulation	SPC accessed 12th July 2023 Yellow, biconvex, approximately 1.1 x 0.8 cm diagonally diamond-shaped, film-coated tablets with “10” engraved on one side and “1428” engraved on the other side.
Dosage	SPC accessed 12th July 2023 The recommended dose is 10mg once daily, at any time of day with or

	without food. Tablets are to be swallowed whole. No dose adjustment is required in treatment of treating chronic heart failure with preserved or mildly reduced ejection fraction. It is not recommended to initiate treatment with dapagliflozin in patients with an estimated glomerular filtration rate (eGFR) < 15 mL/min/1.73m^2.
Comparison of NICE TA with Summary of Product Characteristics (SmPC)[2]	SPC accessed 16th July 2023 The recommended dose of 10mg once daily, at any time of day with or without food. This is current dose considered by NICE as part of this NICE evaluation. Subsequent changes in the license following NICE publication will need to be considered by the Area Prescribing Committee and will not be routinely funded by local commissioners, as the incremental cost per QALY would not have been considered.

NICE TA recommendations[2]

Recommendations

Dapagliflozin is recommended, within its marketing authorisation, as an option for treating symptomatic chronic heart failure with preserved or mildly reduced ejection fraction in adults.

Decision making framework (DMF)

National guidance and priorities

The ICS has a legal obligation to commission this medicine in line with the NICE TA 902.

- This NICE TA has been assigned an implementation deadline of 3 months.
- The implementation deadline has been agreed as 4th October 2023 (Note: 90 days from publication = 19th September 2023)

Clinical effectiveness

Heart Failure - background
You have Heart Failure with reduced Ejection Fraction (HFrEF) which happens after cardiac damage, e.g. heart attack, in these cases there are many proven treatments including beta blockers, RAAS inhibitors, and SGLT2 inhibitors etc. which prevent the heart from remodelling and therefore deterioration of the heart failure. Remodelling is when the heart wall becomes thicker to try and compensate for the poor ejection fraction but in fact makes it even less efficient.

In this TA, the treatment is for heart failure with preserved, or mildly reduced ejection fraction (HFp/mrEF). In these cases the heart failure is not usually because of an injury, but the entire heart muscle is diseased and therefore not contracting/ pumping sufficiently. The usual treatments do not usually have enough of an effect to be sufficient to justify treatment. (Ref Carina Joanes, Cardiovascular Clinical Lead, Surrey Heartlands)

Dapagliflozin is a novel agent in the treatment of heart failure with a preserved or mildly reduced ejection fraction (HFp/mrEF). We have previous experience of using dapagliflozin as a treatment option in diabetes, heart failure with reduced ejection fraction and chronic kidney disease.

Current standard care for heart failure with preserved or mildly reduced ejection fraction is loop diuretics and treatment for other conditions the person may have. These manage symptoms, but do not reduce hospitalisations for heart failure.

- Clinical trial evidence shows that dapagliflozin plus standard care reduces the combined risk of dying from cardiovascular causes or likelihood of first hospitalisation for heart failure compared with placebo plus standard care (primary outcome).

- DELIVER TRIAL : The primary outcome occurred in 512 (16.4%) patients in the dapagliflozin group and in 610 (19.5%) patients in the placebo group (HR 0.82, 95% CI 0.73 to 0.92; p<0.001; NNT 32) **which was driven by reduction in heart failure hospitalisations** (329 [10.5%] vs 418 [13.3%]; HR 0.77, 95% CI 0.67 to 0.89).

- Evidence for cardiovascular death with dapagliflozin was lower than placebo **but not statistically significant** (7.4%) and (8.3%) respectively (hazard ratio, 0.88; 95% CI, 0.74 to 1.05).

- The NICE committee concluded that hospitalisation for heart failure impacted patient quality of life for up to 6 months, there are currently no other disease modifying treatments available for HFp/mrEF and that the trial data results were broadly generalisable to NHS clinical practice.

Patient safety

The product should be used within its product license.

SPC accessed 18 July 2023

In type 1 diabetes mellitus studies with dapagliflozin, DKA was reported with common frequency. **Dapagliflozin should not be used for treatment of patients with type 1 diabetes**

In 2016 there was a Drug Safety Update from the MHRA. Serious and life-threatening cases of DKA have been reported in patients taking SGLT2 inhibitors (canagliflozin, dapagliflozin or empagliflozin):

- Clinicians should inform patients of the signs and symptoms of DKA (e.g. nausea, vomiting, anorexia, abdominal pain, excessive thirst, difficulty breathing, confusion, unusual fatigue or sleepiness) and test for raised ketones in patients with these signs and symptoms.
- Discontinue treatment with the SGLT2 inhibitor immediately if DKA is suspected or diagnosed.
- Interrupt treatment with the SGLT2 inhibitor in patients who are hospitalised for major surgery or acute serious illnesses (sick day rules); treatment may be restarted once the patient's condition has stabilised.

In 2019 there was a Drug Safety Update from the MHRA. Post-marketing cases of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum) have been associated with the use of SGLT2 inhibitors:

- Fournier's gangrene is a rare but serious and potentially life-threatening infection.
- If Fournier's gangrene is suspected, the SGLT2 inhibitor should be stopped, and treatment urgently started (including antibiotics and surgical debridement as required).
- Clinicians should 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.

Renal impairment

There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m^2, and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m^2. Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 mL/min/1.73m^2

Hepatic impairment

There is limited experience in clinical studies in patients with hepatic impairment. Dapagliflozin exposure is increased in patients with severe hepatic impairment.

Use in patients at risk for volume depletion and/or hypotension.

Due to its mechanism of action, dapagliflozin increases diuresis which may lead to the modest decrease in blood pressure observed in clinical studies (see section 5.1). It may be more pronounced in patients with very high blood glucose concentrations.

Caution should be exercised in patients for whom a dapagliflozin-induced drop in blood pressure could pose a risk, such as patients on anti-hypertensive therapy with a history of hypotension or elderly patients.

SPC accessed 20 July 2023

Adverse reactions in placebo-controlled clinical studies and post marketing experience:

System organ class	Very common	Common*	Uncommon**	Rare	Very rare
Infections and infestations		Vulvovaginitis, balanitis and related genital infections Urinary tract infection	Fungal infection**		Necrotising fasciitis of the perineum (Fournier's gangrene)
Metabolism and nutrition disorders	Hypoglycaemia (when used with SU or insulin)		Volume depletion Thirst**	Diabetic ketoacidosis (When used in type 2 diabetes mellitus)	
Nervous system disorders		Dizziness			
Gastrointestinal disorders			Constipation Dry mouth		
Skin and subcutaneous tissue disorders		Rash			Angioedema
Musculoskeletal and connective tissue disorders		Back pain			
Renal and urinary disorders		Dysuria Polyuria	Nocturia		Tubulointerstitial nephritis
Reproductive system and breast disorders			Vulvovaginal pruritus Pruritus genital**		
Investigations		Haematocrit increased. Creatinine renal clearance decreased during initial treatment. Dyslipidaemia	Blood creatinine increased during initial treatment. Blood urea increased** Weight decreased		

Summary of Patient Safety

The overall safety profile of dapagliflozin in patients with heart failure was consistent with the known safety profile of dapagliflozin. (SPC accessed 06/09/23)

- **An increased risk of volume depletion should be considered. Special attention should be given to volume intake (especially during intercurrent illness e.g. gastrointestinal illness) and review of concomitant medication that may lead to volume depletion (e.g., diuretics, ACE inhibitors)**

- **For patients with diabetes (& heart failure), primary care prescribers must clearly document the indication for dapagliflozin in the patients notes so that dapagliflozin is not stopped at the patient's routine diabetes review.**

- **Dapagliflozin should not be prescribed in patients with type 1 diabetes due to the increased risks of Diabetic Ketoacidosis.**

- **There is limited experience in initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m2. In this cohort of patients, initiation of dapagliflozin should be carried out by the heart failure specialist.**

Patient factors

Impact on quality of life:

The TA (TA902) © NICE 2023 committee noted the additional treatment option would be valued by patients.

- Symptoms of heart failure with preserved or mildly reduced ejection fraction include difficulty breathing, tiredness and ankle swelling. Whilst treatment options are available or patients with heart failure with reduced ejection fraction (HFrEF), there are no disease modifying treatments for HF with preserved or mildly reduced ejection fraction.
- The TA committee concluded that there is an unmet need for people with heart failure with preserved or mildly reduced ejection fraction and a new treatment option for this group would be welcome.
- In addition, the lack of hope because of the lack of research and available treatments impacts the quality of life and mental health of people with heart failure with preserved or mildly reduced ejection fraction. The patient experts considered both improvement in quality of life and survival to be important for this group.
- Fewer hospital admissions for patients (when added to standard care) are expected.

Patients with swallowing difficulties:

- No current recommendation or guidance to crush or disperse prior to administration. No licensed liquid formulation available. Tablets to be swallowed whole with water. May impact on patients with swallowing difficulties.

Summary of patient factors

Improvement in patients' quality of life and a reduction in hospital admissions are expected when dapagliflozin is added to standard care. Patients with swallowing difficulties may be negatively impacted as tablets are non-crushable and no licensed liquid formulation is available.

Environmental impact

Commissioners and providers have a responsibility to promote an environmentally sustainable health and care system and should assess and reduce the environmental impact of implementing NICE recommendations wherever possible. https://www.nice.org.uk/guidance/ta902

SPC accessed 23 July 2023

Special precautions for storage:

This medicinal product does not require any special storage conditions.

Shelf life: 3 years

Special precautions for disposal and other handling:
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Equality & diversity

The TA (TA902) © NICE 2023 committee noted that previous NICE technology appraisals in chronic heart failure had identified that people from Black or South Asian family backgrounds may have a higher risk of developing heart failure. The committee noted that the results from DELIVER did not suggest dapagliflozin was more effective at treating chronic heart failure with preserved or mildly reduced ejection fraction in people from Black or Asian family backgrounds. But, it noted that trials are not usually powered to detect differences by family background. The committee noted that its recommendation applied to all people, regardless of family background.

NICE's guideline on chronic heart failure in adults recommends that a specialist heart failure multidisciplinary team should work in collaboration with primary care to start new medicines that need specialist supervision. Dapagliflozin is currently prescribed for heart failure with reduced ejection fraction in primary care, according to the advice of a heart failure specialist. It was noted that socioeconomic deprivation is a strong risk factor for developing heart failure and experiencing adverse heart failure outcomes. It was suggested that inequality in access to specialist care across the UK may contribute to these health inequalities. So, broad prescribing of dapagliflozin in primary and secondary care may reduce health inequalities.

https://www.nice.org.uk/guidance/ta902

Place in therapy relative to available treatments

1. **Please see Appendix 1 in the document pack for proposed place in therapy.**
   Appendix 1 Place in therapy for dapagliflozin in HFp/mrEF document. If agreed, this will replace the current heart failure place in therapy document on the PAD.

NICE recommends dapagliflozin as an option for initiated in patients with symptomatic chronic HFp/mrEF on standard care. Note: Patients have a formal diagnosis of HFp/mrEF as per NICE guideline on Chronic Heart Failure in adults. Initiation should be on the recommendation of a heart failure specialist.

Dapagliflozin will be a novel agent in the treatment of heart failure with a preserved or mildly reduced ejection fraction. Dapagliflozin will provide a treatment option for patients where there is little or no evidence for any treatment, other than symptomatic relief with diuretics.

(TA902) © NICE 2023 states treatment options of NICE's guideline on chronic heart failure in adults: diagnosis and management recommend low- to medium-dose loop diuretics (such as furosemide and bumetanide) for people with heart failure with preserved ejection fraction. Specialist treatment advice is recommended for people whose heart failure does not respond to treatment. Symptomatic treatments for comorbidities are also offered to people with heart failure with preserved ejection fraction, including angiotensin-converting enzyme inhibitors, angiotensin 2 receptor blockers, beta blockers or mineralocorticoid receptor antagonists. According to DELIVER, Dapagliflozin had a minimal effect on 1-month systolic blood pressure and there was no treatment-related excess in renal or hypovolaemic serious adverse event.

Stakeholder views

The paper was sent out for consultation and comments are listed on the front sheet.

Cost-effectiveness:

The cost-effectiveness estimates are below what NICE considers acceptable use of NHS resources. Dapagliflozin is recommended.

https://www.nice.org.uk/guidance/ta902/resources/dapagliflozin-for-treating-chronic-heart-failure-with-preserved-or-mildly-reduced-ejection-fraction-pdf-82615423312069

The committee concluded that when its preferred assumptions are incorporated, dapagliflozin is a cost-effective use of NHS resources. Therefore, the committee recommended dapagliflozin for treating symptomatic chronic heart failure with preserved or mildly reduced ejection fraction.

Section 1: Cost of the technology

Drug costs in Primary care

Annual cost per patient:
The list price of 10 mg dapagliflozin is £36.59 per 28-tablet pack (excluding VAT; BNF online accessed April 2023)

The annual drug treatment cost in Primary Care is **£477.30**

This would be in addition to the standard care drug costs of approximately £11 per annum (standard care = diuretic use) ref NICE Resource Impact Report https://www.nice.org.uk/guidance/ta902/resources/resource-impact-report-pdf-13074136093. Accessed 14th August 2023)

Drug costs in secondary care:

The drug cost of dapagliflozin in secondary care is similar to that in Primary Care. Prescribing in Secondary Care would not provide a cheaper option.

Availability of CAP/PAS price: NO

Section 2: NICE resource impact statement and template

Eligibility: Approximately **3,300 adult patients in Surrey Heartlands**. (Adult patients with symptomatic, chronic HF with LVEF > 40% who do not have type-2 diabetes or chronic kidney disease)

The NICE resource impact template assumes an approximate 10% uptake of dapagliflozin year on year to year 3 where it reaches a steady state to year 5.

Drug costs for Surrey Heartlands:

Although NICE states that a significant impact on resources is not expected, there is still a new cost pressure even though this may be below the £9,000 per 100,000 population thresholds for NICE. This TA represents a new line of treatment.

Assuming there are 3,300 eligible patients in Surrey Heartlands with an approximate 10% uptake year on year to year 3, this translates into the following changes in dapagliflozin drug costs for Surrey Heartlands

At Year 1:

There is a projected approximate cost of £160,000 for dapagliflozin across the SH population.

Table 1 - Breakdown of cost at Place at year 1

Table 1	East Surrey	Guildford and Waverley	Surrey Downs	Northwest Surrey	Surrey Heartlands ICB
Population*	193,532	232,784	316,690	388,466	1,131,472
Approximate Cost	£28,000	£31,000	£46,000	£55,000	£160,000

At Year 3:

Uptake across the SH population has risen to approximately 30%

Table 2 – Breakdown of cost at Place at year 3

Table 2	East Surrey	Guildford and Waverley	Surrey Downs	Northwest Surrey	Surrey Heartlands ICB
Population*	193,532	232,784	316,690	388,466	1,131,472
Approximate Cost	£85,000	£94,000	£140,000	£168,000	£487,000

Note: costs are approximate due to changing populations over time.

At year 3, projected costs show that Surrey Downs and Northwest Surrey Place may exceed the £100,000 at Place threshold. *Caveat – we await further clarification from the Surrey Heartlands finance team and will update at Oct APC.*

Note: The drug costs are likely to be partially offset by the projected reduction in hospital admissions for heart failure.

* August 2022 population figures from NHS Prescription Services through ePACT.

The Surrey Heartlands Director of Pharmacy and Medicines Optimisation has delegated authority to enable the Committee to be a decision-making committee providing the impact of any single decision does not exceed £100,000 within an individual Place per annum. Decisions with a cost impact of over £100,000 within an individual Place per annum require authorisation from Surrey Heartlands Health & Care Professionals Committee at their next meeting. Exception to this will be for any decision made in relation to a NICE Technology Appraisal (which are subject to requiring mandatory funding by commissioners) and other urgent items. The exceptions will be taken to the next Executive Meeting (which meets weekly) for authorisation.

Traffic light recommendation to APC

NHS Payment Scheme (NHSPS) excluded high-cost drug: No

- Recommended traffic light status and rationale: BLUE with BLUE information sheet for Dapagliflozin/Empagliflozin in HFrEF adapted to include dapagliflozin in HFp/mrEF (to be brought to APC at a later date).

The TA committee concluded that dapagliflozin would be started on the advice of a heart failure specialist who can determine the most appropriate treatment.
This also ensures the diagnosis has been confirmed by a specialist based on echocardiographic changes and the patient's signs and symptoms.

PAD definitions, available at: Traffic Light Status (res-systems.net)

Implementation

NICE TA implementation must be within 90 days of publication.

Actions to implement:

Initiation by a heart failure specialist or *on the advice of a heart failure specialist* with transfer to primary care for ongoing prescribing and monitoring without the need for a formal shared care agreement.

- It is proposed that dapagliflozin is initiated in patients with symptomatic chronic HFp/mrEF on standard care. Patients should have a formal diagnosis of HFp/mrEF as per NICE guideline on Chronic Heart Failure in adults. Initiation should be on the recommendation of a heart failure specialist.
  Note: **There is limited experience in initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m2. In this cohort of patients, initiation of dapagliflozin should be carried out by the heart failure specialist.**

- The definition of a heart failure specialist as per the current BLUE information sheet for Dapagliflozin/Empagliflozin in HFrEF:
  - Cardiology consultant, specialist, or registrar
  - Heart failure specialist nurse
  - GP with a specialist interest in heart failure or GP cardiologist
  - General physician with heart failure expertise
  - Renal physician

- Initiation, monitoring and onward management as per the BLUE information sheet for Dapagliflozin/Empagliflozin in HFrEF adapted to include dapagliflozin in HFp/mrEF (to be brought to APC at a later date).

- Appendix 1 Place in therapy for dapagliflozin in HFp/mrEF document. If agreed, this will replace the current heart failure place in therapy document on the PAD.

Proposed tick box forms

References:

1 Summary of Product Characteristics (emc)
Available at: https://www.medicines.org.uk/emc/product/7607/smpc.
Accessed 10th August 2023

2 NICE Technology Appraisal Guidance: Dapagliflozin for treating chronic heart failure with preserved or mildly reduced [TA902]. Published date: 21 June 2023. Available at: https://www.nice.org.uk/guidance/ta902. Accessed 10th August 2023

3 NICE Resource Impact Report: Dapagliflozin for treating chronic heart failure with preserved or mildly reduce ejection fraction. Available at https://www.nice.org.uk/guidance/ta902/resources/resource-impact-report-pdf-13074136093. Accessed 14th August 2023

4 NICE Resource British Society of Heart failure position statement on heart failure with preserved ejection fraction: https://bjcardio.co.uk/2022/05/bsh-position-statement-on-heart-failure-with-preserved-ejection-fraction/

5 Heerspink HJL, et al. Dapagliflozin in patients with chronic kidney disease. *N Engl J Med* 2020; 383(15):1436–46.

6 McMurray JJV, et al. Dapagliflozin in patients with heart failure and reduced ejection fraction. *N Engl J Med* 2019; 381(21):1995–2008.

7 Solomon SD, McMurray JJV, Claggett B, et al. Dapagliflozin in Heart Failure with Mildly Reduced or Preserved Ejection Fraction. N Engl J Med. 2022

8 Renal and blood pressure effects of dapagliflozin in recently hospitalized patients with heart failure with mildly reduced or preserved ejection fraction. https://pubmed.ncbi.nlm.nih.gov/37212168/#:~:text=Dapagliflozin%20had%20a%20minimal%20effect,irrespective%20of%20recent%20HF%20hospitalization.

9 NHSBSA Drug Tariff online: NHS Electronic Drug Tariff (nhsbsa.nhs.uk) [Accessed 13TH August 2023.