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Surrey Heartlands Integrated Care System Area Prescribing Committee (APC)

INFORMATION SHEET – Blue Traffic Light Classification		
Name of medicine	**Dapagliflozin and Empagliflozin**	
Indication **(Including whether for adults and/or children)**	**Adult Heart Failure with reduced ejection fraction (HFrEF) as per NICE TA679 and NICE TA773**	
APC policy statement reference **(if applicable)**	N/A	
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The information sheet is intended to facilitate the accessibility and safe prescribing of complex treatments across the secondary/primary care interface for medicines classified by Area Prescribing Committee (APC) as **BLUE**

BLUE drugs are considered suitable for prescribing in primary care, following initiation and stabilisation by a specialist (or for specific drugs, GPs can initiate *on the advice* of a specialist). Ongoing monitoring can be undertaken in primary care without specialist support and WITHOUT the need for a formal shared care guideline.
For each drug classified as **BLUE**, the Area Prescribing Committee will recommend the minimum supply and whether an information sheet is required or not. A minimum of one month supply of medication will be provided by the initiating consultant.
This 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. A GP or Primary Care Prescriber must ensure they are familiar with the prescribing responsibilities. This information sheet is available on the internet **http://pad.res360.net/** forming part of the Prescribing Advisory Database (PAD) giving GPs appropriate advice / guidance and is not required to be sent to the GP with the clinic letter.

RESPONSIBILITIES and ROLES

Consultant / Specialist responsibilities
1. To assess the suitability of patient for treatment
2. To discuss the aims, benefits, and side effects of treatment with the patient and/or carer as well as their role
3. Explain to the patient and/or carer the treatment plan including the dosing schedule and request for transfer of care to GP
4. Baseline monitoring undertaken - see monitoring section below under 'Key Information on the medicines' starting on page 3 Prior to initiation the following should be monitored: a. Blood pressure b. Bloods: renal function, electrolytes, liver function N.B Renal function can decline upon initiation of dapagliflozin or empagliflozin, but this usually resolves in 1-3 months. If renal function falls below 15 mL/min/1.73m2 (Dapagliflozin) or 20 mL/min/1.73m2 (Empagliflozin), GP will refer back to the specialist.
5. Specialist to either: a. provide a minimum of one month supply OR b. provide advice and guidance and recommend to the patient's primary care prescriber to initiate prescribing.

6. Points to consider:
a) Specialist initiating treatment: The specialist should evaluate response to treatment, including any adverse drug reactions. Once the patient is stabilised, the specialist may ask the primary care prescriber to continue prescribing in line with agreed treatment plan. If the specialist considers that the patient requires close monitoring after initiation and is not stabilised, then prescribing should remain with the specialist and transfer of care should not be requested until the patient has stabilised.

b) Specialist ***advises*** the GP to initiate treatment: The specialist should give advice to the GP on the monitoring and evaluation of the response to treatment, including adverse drug reactions, for the specific patient and when to continue / discontinue treatment in line with agreed treatment plan. In this case where initiation is on the ***advice*** of a Specialist, baseline monitoring can be undertaken by the most appropriate healthcare professional (including primary care).
Note: Specialist must be aware of the results of the baseline monitoring as part of their responsibility prior to recommendation to GP to prescribe. If the specialist considers that the patient requires close monitoring after initiation, then the initiation of prescribing should remain with the specialist and transfer of care should not be requested until the patient is stabilised.

7. Supply GP with summary:

a) Within 1 month if *specialist is initiating* OR
b) Immediately if *Specialist is advising* GP to initiate treatment.

The summary should include details of the patient review, anticipated length of treatment and a copy of any information sheet available.

8. Provide primary care prescriber with information on any monitoring and the required frequency

8. Advise GP if treatment is to discontinue at any point

9. Inform GP if patient does not attend planned follow-up

10. No dose titration required (for patients with severe hepatic impairment see 'Key points' box on page 4.

11. Include in the summary letter - The indication ("to treat heart failure") to allow for recording on the primary care prescription.

12. Safety consideration – diabetic ketoacidosis and volume depletion –see page 5

13. Patient Counselling: Ensure the patient has been given a patient information booklet (if appropriate):
Foxiga® patient information booklet (includes sick day rules) – Patient advice – see page 4
Jardiance® medication guide (patient information includes advice on dehydration and ketoacidosis)

General Practitioner (GP) or Primary Care Prescriber responsibilities

1. Initiation (on advice of a heart failure specialist) or on-going prescribing of dapagliflozin or empagliflozin for HFrEF

   a. Specialist to have undertaken baseline monitoring as part of their responsibility prior to recommendation to GP to ***continue*** to prescribe.

   b. If GP initiates on the ***advice*** of a heart failure specialist, baseline monitoring can be undertaken by the most appropriate healthcare professional (including primary care). Note, specialist must be aware of the results of the baseline monitoring as part of their responsibility prior to recommendation to GP to prescribe.

2. Patient monitoring in Primary Care setting - see the monitoring section below under 'Key information on the medicines starting on page 3.
   - Re-check renal function and blood pressure after initiation of dapagliflozin or empagliflozin.
   - Check renal function prior to, and after, initiation of concomitant medicinal products that may reduce renal function.

If renal function falls below 15 mL/min/1.73m2 (Dapagliflozin) or 20 mL/min/1.73m2 (Empagliflozin), refer back to the specialist.

3. The indication ("to treat heart failure") should be recorded on the primary care prescription next to the dosing instructions.

4. Safety considerations – diabetic ketoacidosis and volume depletion –see page 9

5. Patient Counselling: Ensure the patient has been given a patient information booklet (if appropriate):
Foxiga patient information booklet (includes sick day rules) – Patient advice – see page 10
Jardiance® medication guide (patient information includes advice on dehydration and ketoacidosis)

Patient / Carer role
1. Informing the specialist team, primary care prescriber or other healthcare professional if he or she has further questions or wants more information about the treatment
2. Tell the consultant / specialist or GP or Primary Care Prescriber of any other medication being taken, including over-the-counter products.
3. Sharing any concerns about their treatment and problems they are having taking their medicines with the specialist team, primary care prescriber or other healthcare professional involved in their care
4. Supported to know how to report any adverse effects to the specialist team, primary care prescriber or other healthcare professional involved in their care, and how adverse effects can be managed
5. To be available for monitoring as required.
6. Attend follow-up appointments with the consultant / specialist / GP. **Non-attendance of appointments may result in treatment being stopped**
6. Patient Counselling: Ensure you have been given a patient information booklet (if appropriate): Foxiga patient information booklet (includes sick day rules) – Patient advice – see page 10 Jardiance® medication guide (patient information includes advice on dehydration and ketoacidosis)

Key information on the medicines

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

Management of medication in patients with HF and diabetes

Type 2 diabetes

Although SGLT2 inhibitors have a low risk of hypoglycaemic events, reducing blood glucose levels via this mechanism could potentially predispose patients taking other blood glucose lowering medication (**particularly insulin or sulphonylureas)** to hypoglycaemia.
Medication 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 previous / frequent hypoglycaemia
- Any advice is needed on diabetes management or suitability of an SGLT2 inhibitor

Renal Function-minimum levels

Renal function (eGFR) minimum levels for prescribing SGLT2 inhibitors are different depending on indication. Blood glucose lowering effects of SGLT2 inhibitors are diminished below certain eGFRs, but cardiac effects persist. Do not stop SGLT2 inhibitors prescribed for heart failure in diabetics solely because *diabetes* eGFR cut offs have been breached. Continue the SGLT2 inhibitor and add another antidiabetic medication if necessary to reach desired HbA1c
Heart failure eGFR minimum levels = 15 and 20ml/min/1.73m2 dapagliflozin and empagliflozin respectively
Diabetes eGFR minimum levels = 45 and 30ml/min/1.73m2 dapagliflozin and empagliflozin respectively

Type 1 diabetes NOT RECOMMENDED

Dapagliflozin or empagliflozin are NOT recommended for the treatment of Heart Failure in patients with type 1 diabetes mellitus

Key Points for patients with HFrEF (with or without diabetes)

- **Dapagliflozin and empagliflozin are sodium-glucose cotransporter-2 (SGLT2) inhibitors licensed for the treatment of adults (with or without type 2 diabetes) with symptomatic chronic heart failure with reduced ejection fraction (≤40%).**

- **NICE TA679 & NICE TA773 recommend dapagliflozin or empagliflozin as add-on options to optimised standard HFrEF treatment with:**
  - **ACEi (or ARB if ACEi not tolerated) with BB and if tolerated MRA or**
  - **Sacubitril valsartan (ARNI) with BB and if tolerated MRA**

- **It is not a requirement to swap ACEi/ARB to ARNI before commencing an SGLT2 inhibitor. Clinician should weigh benefits and risks in each individual case.**

- **In patients with type 2 diabetes refer for specialist advice where the patient is taking insulin, has a history of previous / frequent hypoglycaemia or if advice needed on diabetes management prior to initiation/during treatment of SGLT2 inhibitor.**

- **The recommended dose of dapagliflozin or empagliflozin for heart failure is 10 mg once daily. Note: in *severe* hepatic impairment (Childs-Pugh score C, AST/ALT > 3x ULN or Bilirubin > 2x ULN)**
  - **Starting dose of dapagliflozin is 5mg daily**
  - **Empagliflozin is NOT recommended in patients with *severe* hepatic impairment. Empagliflozin exposure is significantly increased in patients with severe hepatic impairment and therapeutic experience with this patient cohort is limited.**

- **Dapagliflozin and empagliflozin are NOT recommended for treatment of Heart Failure in patients with type 1 diabetes mellitus.**

- **To prevent inadvertent cessation of dapagliflozin or empagliflozin treatment as part of a diabetes review.**
  - **Write in the dosing instructions, 'for the treatment of Heart Failure'.**
  - **Link the medication to the indication of HFrEF on the clinical system.**

- **Advise the patient of the potential of a modest decrease in blood pressure on initiation of dapagliflozin or empagliflozin and encourage home BP monitoring where appropriate**

- **Do not discontinue dapagliflozin or empagliflozin due to a lack of improvement in symptom control. Long term mortality benefits, reduction in the rate of renal function decline and a reduction in hospitalisation for HFrEF may still be seen.**

- **Renal function (eGFR) minimum levels for prescribing SGLT2 inhibitors are different depending on indication. Do not stop SGLT2 inhibitors prescribed for heart failure in diabetics solely because *diabetes* eGFR cut offs have been breached**

- **Clinical judgement should be used to assess the timing of post initiation (renal function & BP) monitoring and ongoing frequency based on the patient's specific characteristics and as a minimum should be in line with the SPC and NICE clinical guideline (NG106) Chronic heart failure in adults. (See the monitoring section on page 7)**

Indication

Dapagliflozin and empagliflozin are recommended as option (as per NICE TA679 & NICE TA773) for treating symptomatic chronic heart failure with reduced ejection fraction ≤40% in adults, only when they are used as an add-on to optimised standard care with:

- angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers (ARBs), with beta blockers (BB), and, if tolerated, mineralocorticoid receptor antagonists (MRAs), or
- sacubitril valsartan, with beta blockers, and, if tolerated, MRAs.

Place in therapy for management of heart failure (HFrEF) in Surrey Heartlands
See Surrey PAD for APC decisions and place in therapy for these two treatments

APC decision:
The Surrey Heartlands Integrated Care System Area Prescribing Committee have agreed that dapagliflozin or empagliflozin for treating chronic heart failure with reduced ejection fraction should be implemented in line with their NICE technology appraisals (NICE TA679 & NICE TA773 respectively).

Dapagliflozin or Empagliflozin are NOT recommended for the treatment of Heart Failure in patients with type I diabetes mellitus.

All NEW patients requiring a SGLT2 inhibitor for heart failure should receive either dapagliflozin or empagliflozin so that the GP is prescribing a licensed medicine.

Dosage and Administration

For full guidance please refer to current Summary of Product Characteristics (SPC): SPC for Dapagliflozin or SPC for Empagliflozin

The recommended dose is dapagliflozin 10mg or empagliflozin 10mg once a day, swallowed whole with water and can be taken with or without food. *Please see under 'Cautions' on page 9 for patients with severe hepatic impairment.*

Expected outcome

Improvement in symptom control in patients with HFrEF.
Do not discontinue SGLT2 inhibitors due to a lack of improvement in symptom control. Long term mortality benefits, reduction in the rate of renal function decline and a reduction in hospitalisation for HFrEF may still be seen.

Who can recommend dapagliflozin or empagliflozin for heart failure:
NICE TA679 and NICE TA773 suggests that dapagliflozin or empagliflozin should be recommended by a specialist, i.e.

- 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

N.B Dapagliflozin or empagliflozin may still be started in primary care for patients with type 2 diabetes in line with local diabetes guidelines without specialist input – *Green* classification on the PAD.

Renal Function

After initiation of SGLT2i, the eGFR can dip by up to 15-20% this is not usually reflective of nephrotoxicity, but rather a reduction in renal blood flow. If the decline in eGFR is greater than expected, it is important to consider over diuresis. Dapagliflozin and empagliflozin can potentiate the effects of existing diuretic treatment. Clinical review of fluid balance is necessary to differentiate a decline in renal function due to volume depletion and the expected reduction in eGFR.

Dapagliflozin and empagliflozin are also indicated for the treatment of Type 2 diabetes mellitus. The glucose lowering efficacy of dapagliflozin and empagliflozin is dependent on renal function and is reduced in patients with eGFR < 45 ml/min/1.73m2 and < 30ml/min/1.73m2 respectively and is likely absent in patients with severe renal impairment, additional diabetes treatments may be needed.

Dapagliflozin: *For full guidance please refer to current Summary of Product Characteristics (SPC*): SPC for Dapagliflozin

There is limited experience with initiating treatment with dapagliflozin in patients with eGFR < 25 mL/min/1.73m2, and no experience with initiating treatment in patients with eGFR < 15 mL/min/1.73m2.

Therefore, it is not recommended to initiate treatment with dapagliflozin in patients with eGFR < 15 mL/min/1.73m2

For the indication of Heart failure, if renal function falls below 15 mL/min/1.73m2, refer back to the Heart failure specialist.

Empagliflozin: *For full guidance please refer to current Summary of Product Characteristics (SPC):* SPC for Empagliflozin

For treatment of heart failure in patients with or without type 2 diabetes mellitus, empagliflozin 10 mg may be initiated or continued down to an eGFR of 20 ml/min/1.73 m^2 or CrCl of 20 ml/min.

For the indication of heart failure, empagliflozin is not recommended in patients with eGFR <20 ml/min/1.73 m^2.

Empagliflozin should not be used in patients with end stage renal disease (ESRD) or in patients on dialysis. There are insufficient data to support use in these patients.

For the indication of Heart Failure, if renal function falls below 20 mL/min/1.73m2, refer back to the heart failure specialist.

Initiation of dapagliflozin and empagliflozin in Primary care

Surrey Heartlands does not recommend the *initiation* of dapagliflozin or empagliflozin in primary care for patients with eGFR < 25 mL/min/1.73m2 for the following reasons:

- There is limited experience in initiating treatment with dapagliflozin in patients with eGFR <25ml/min/1.73m2
- The potential for a 15-20% reduction in eGFR after initiation of empagliflozin when starting at a baseline eGFR of less than 25ml/min/1.72m2 could result in the eGFR falling to below 20ml/min/1,72m2 and a referral back to the heart failure specialist

For patients with a baseline eGFR of less than 25ml/min/1.73m2, initiation of either dapagliflozin or empagliflozin should be carried out by the heart failure specialist.

Monitoring – Renal function

Post initiation monitoring Renal Function-Pragmatic guide	**Column 1. Patients with renal impairment**	**Column 2. Patients without renal impairment where a drop in renal function would not pose a risk**
Use clinical judgement to assess the timing of post initiation renal function monitoring and the ongoing frequency based on the **patient's specific characteristics** and as a minimum should be in line with the SPC and NICE clinical guideline (NG106) Chronic heart failure in adults.*	Exercise caution in patients for whom a dapagliflozin or empagliflozin-induced drop in renal function could pose a risk. Volume status re-assessment and concomitant diuretic dose review is recommended at follow-up within 4 weeks of SGLT2i initiation, especially in those with renal impairment at baseline.	Please see details in column 1 if further clarification is required
When to carry out post initiation renal function monitoring for dapagliflozin or empagliflozin in HFrEF Renal function can decline *by up to* 15-20% upon initiation, but this usually resolves in 1-3 months. Trial data showed a reduction in eGFR of *up to* 5ml/min/1.73m^2 , and a transient creatinine rise of *up to* 20%, 14-28 days post initiation. This is expected and should not lead to premature discontinuation in the majority of cases.	**Within 4 weeks of initiation** Patients to consider: • Baseline eGFR is within 20% of renal cut off for HFrEF or diabetes (if patient is also diabetic and SGLT2i is being used to manage diabetes) • Patients on drugs that require specific creatinine clearance rates for dosing e.g., DOACs • Patients on other drugs where a decline in renal function can pose a risk e.g., ACEi/ABR, diuretics, NSAIDs, digoxin, methotrexate • Frail, elderly patients where there is a risk of volume depletion • Where over diuresis is a concern. SGLT2i can potentiate the effects of existing diuretic treatment.	**Within 12 weeks of initiation** Note: Over diuresis can still pose a concern even in patients without renal impairment at baseline.

*NICE clinical guideline (106) recommends at least 6 monthly reviews of patients with heart failure which should include monitoring BP and renal function. SPCs for dapagliflozin and empagliflozin recommend periodic renal function testing and as minimum annually, as well as prior to, and after, initiation of concomitant medicinal products that may reduce renal function.

Monitoring – Blood Pressure

Post initiation monitoring Blood Pressure- Pragmatic guide	**Patients in whom a dapagliflozin/ empagliflozin-induced drop in Blood Pressure could pose a risk**	**Patients in whom a dapagliflozin/ empagliflozin-induced drop in Blood Pressure *would not* pose a risk**
Use clinical judgement to consider the **specific patient's characteristics** when making a clinical decision on the timing of post initiation BP monitoring and ongoing frequency. As a minimum ongoing frequency should be in line with the SPC and NICE clinical guideline (NG106) Chronic heart failure in adults*	Volume status re-assessment and concomitant diuretic dose review is recommended at follow-up within 4 weeks of SGLT2i initiation, especially in those with renal impairment at baseline	
When to carry post initiation blood pressure monitoring for dapagliflozin or empagliflozin in HFrEF Trial data for dapagliflozin and empagliflozin showed a modest decrease in blood pressure (approximately 3-5mmHg SBP and 2mmHg DBP) after initiation.	**Within 4 weeks of initiation** Patients to consider: • Baseline systolic BP is within 10% of 95mmHg. Caution if systolic blood is pressure less than 95 mmHg, consider reduction in diuretics to reduce risk of dehydration, particularly in patients with very high blood glucose • Frail, elderly patients where there is a risk of volume depletion • patients with known cardiovascular disease, patients on anti-hypertensive therapy with a history of hypotension or patients aged 75 years and older. • Cases of intercurrent conditions that may lead to volume depletion (e.g., gastrointestinal illness) BP will need to be assessed promptly and remedial action taken.-See 'volume depletion' section on page 9 of blue information sheet for more information	**Within 4 weeks of initiation**

Contraindications - *For full details please refer to current Summary of Product Characteristics (SPC)*: SPC for Dapagliflozin or SPC for Empagliflozin

• Type 1 diabetes (known or suspected)
• Recurrent or particularly problematic hypoglycaemia
• Pregnancy or breast feeding
• Hypersensitivity to dapagliflozin or lactose intolerant (excipient)
• Previous history of diabetic ketoacidosis
• Patients on very low calorie / low carbohydrate diets

Cautions - *For full details please refer to current Summary of Product Characteristics (SPC)*: SPC for Dapagliflozin or SPC for Empagliflozin

- Frail, elderly patients where there is a risk of volume depletion
- Volume depletion or hypotension: Caution if systolic blood pressure less than 95 mmHg, consider reduction in diuretics to reduce risk of dehydration, particularly in patients with very high blood glucose.
- Severe hepatic impairment:
  - Reduce Dapagliflozin to 5 mg starting dose
  - Empagliflozin is not recommended in *severe* hepatic impairment

Safety Considerations - *For full details please refer to current Summary of Product Characteristics (SPC)*: SPC for Dapagliflozin or SPC for Empagliflozin

1. Diabetic ketoacidosis

Diabetic ketoacidosis (DKA) can occur in patients with diabetes on SGLT2 inhibitors but is not seen in people without diabetes.

Patients at higher risk of DKA include those with:
- a low beta-cell function reserve (e.g., type 1 diabetes patients, type 2 diabetes patients with low C-peptide
- or latent autoimmune diabetes in adults (LADA)
- a history of pancreatitis or pancreatectomy),
- conditions that lead to restricted food intake or severe dehydration
- insulin doses reduced too fast at the time of SGLT2 inhibitor initiation
- increased insulin requirements due to acute medical illness, surgery or alcohol abuse.

• Signs and symptoms of DKA are nausea or vomiting, as well as abdominal pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat.
• Inform patients with diabetes of the signs and symptoms of DKA and advise them to seek immediate medical advice if they develop any of these.
• Check blood ketone levels as well as blood sugar if any concern about possible diabetic ketoacidosis; note that DKA can be euglycaemic (i.e., normal blood sugar levels, but raised ketones).
• Ketone meters should be available in GP surgeries.
• Patients on SGLT2 inhibitors should not undertake a “ketogenic” diet (e.g., low carb diets).
• If patients do develop DKA, they should not use SGLT2 inhibitors again in the future.

2. Volume depletion

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 dapagliflozin or empagliflozin is recommended for patients who develop volume depletion until the depletion is corrected.

Treatment should be interrupted in patients who are hospitalised for major surgical procedures or acute serious medical illnesses as advised by the specialist.

Adverse effects - *For full details please refer to current Summary of Product Characteristics (SPC*): SPC for Dapagliflozin or SPC for Empagliflozin

Report Adverse effects via the Yellow Card Scheme https://yellowcard.mhra.gov.uk/

Common or very common	Uncommon	Rare or very rare
Vulvovaginitis, balanitis and related genital infections, back pain, **diabetic ketoacidosis** (discontinue immediately and DO NOT restart); dizziness; dyslipidaemia; hypoglycaemia (in combination with insulin or sulfonylurea); increased risk of infection; rash; urinary disorders	Constipation; dry mouth; genital pruritus or vulvovaginal pruritus (ensure good hygiene): weight decreased, hypovolaemia, thirst	Angioedema: Fournier's gangrene (Rare but potentially life-threatening infection – discontinue. Urgent medical attention needed)

Frequency categories: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), very rare (< 1/10,000)

See MHRA alerts on DKA, Fournier's gangrene and lower limb amputation under 'further information for healthcare professionals' on page 11

Drug interactions

Below are some general drug interactions. This is not an exhaustive list. *For full details please refer to current Summary of Product Characteristics (SPC*): SPC for Dapagliflozin or SPC for Empagliflozin

Drug/Therapeutic group	Interaction
Insulin and insulin secretagogues	Insulin and insulin secretagogues, such as sulphonylureas, cause hypoglycaemia. Therefore, a lower dose of insulin or an insulin secretagogue may be required to reduce the risk of hypoglycaemia when used in combination with dapagliflozin or empagliflozin in patients with type 2 diabetes mellitus
Diuretics	Dapagliflozin or empagliflozin may add to the diuretic effect of thiazide and loop diuretics and may increase the risk of dehydration and hypotension

Patient Counselling: Advice

Patient information has been produced by the dapagliflozin manufacturer and the empagliflozin manufacturer and can be used to counsel patients on what they need to watch out for:

- Foxiga® patient information booklet (includes sick day rules)
- Jardiance® medication guide (patient information includes advice on dehydration and ketoacidosis)

Advise patient against having a very carbohydrate restricted diet – dapagliflozin or empagliflozin should not be started in such patients.

Inform patients of the signs and symptoms of DKA, (including rapid weight loss, nausea or vomiting, abdominal pain, fast and deep breathing, 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.

GP/hospital to test for raised ketones in patients with signs and symptoms of DKA, even if plasma glucose levels are near-normal or normal.

Sick day rules

Temporarily withhold dapagliflozin or empagliflozin in patients who:

- are hospitalised for major surgery or acute serious illnesses (see MRHA 2020): blood ketone levels may be monitored (and be normal before restarting)
- also consider stopping in any other hospital admission until the patient is well/stable -if unsure, withhold and seek advice from senior member of the team
- develop volume depletion until the depletion is corrected
- are not eating or drinking with inter-current conditions that may lead to volume depletion (e.g., vomiting /diarrhoea)
- have a major infection

Treatment may be restarted once the patient's condition has stabilised, and they are eating normally for at least 24 hours (providing no new contra-indications exist)

Further information for health care professionals

- Forxiga® (dapagliflozin) Information for UK Healthcare Professionals
- Jardiance® (empagliflozin) Information for UK Healthcare Professionals
- MHRA April 2016 -SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis
- MHRA Feb 2019 - SGLT2 inhibitors: reports of Fournier's gangrene (necrotising fasciitis of the genitalia or perineum)
- MHRA March 2017 - SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation (mainly toes)
- MHRA March 2020 - SGLT2 inhibitors: monitor ketones in blood during treatment interruption for surgical procedures or acute serious medical illness
- SPC for Dapagliflozin
- SPC for Canagliflozin
- SPC for Empagliflozin
- SPC for Ertugliflozin

References

1. Heerspink HJL et al. Dapagliflozin in patients with chronic kidney disease. N Engl J Med 2020; 383:1436-1446. https://www.nejm.org/doi/full/10.1056/NEJMoa2024816

Glossary of terms

HFrEF- Heart failure with reduced ejection fraction

BP- Blood pressure

SGLT2i - Sodium glucose co-transporter II inhibitor

ACEi - Angiotensin converting enzyme inhibitor

ARB – Angiotensin receptor blocker

ARNI – Angiotensin receptor-neprilysin inhibitor