HERTFORDSHIRE MEDICINES MANAGEMENT COMMITTEE (HMMC)
NICE TECHNOLOGY APPRAISALS – RECOMMENDED

NICE TAs 390, 288, 418: DAPAGLIFLOZIN THERAPY FOR TREATING TYPE 2 DIABETES (T2DM)
RECOMMENDED FOR RESTRICTED USE

Names: generic (trade)	What is it?	Indication	Date decision last revised	Decision status	NICE / SMC Guidance
Dapagliflozin (Forxiga®)	Sodium-glucose co-transporter 2 inhibitor	Treatment of type 2 diabetes (T2DM)	January 2017 (update of September 2016)	Final	NICE TAs 288, 390, 418 – recommended for restricted use. SMC – accepted for restricted use.

HMMC Recommendation, in line with NICE technology appraisal guidance 288, 390 and 418:

RECOMMENDED FOR RESTRICTED USE AS AN OPTION FOR TREATING T2DM:

In monotherapy: Dapagliflozin as monotherapy is recommended as an option for treating type 2 diabetes in adults for whom metformin is contraindicated or not tolerated and when diet and exercise alone do not provide adequate glycaemic control, only if:

- A dipeptidyl peptidase-4 (DPP-4) inhibitor would otherwise be prescribed and
- A sulfonylurea or pioglitazone is not appropriate.

Only continue if the person has had a reduction of at least 5.5 mmol/mol (0.5%) in HbA1c in 6 months
Initiation can be undertaken by primary, community or secondary care.

In a dual therapy regimen: in combination with metformin (as an alternative to pioglitazone and dipeptidyl peptidase-4 inhibitors [gliptins]):

- instead of a sulfonylurea as second-line therapy to first-line metformin when control of blood glucose remains or becomes inadequate (HbA1c ≥ 48 mmol/mol [6.5%], or higher level agreed with patient) if:
  - the person is at significant risk of hypoglycaemia or its consequences (for example, older people and people in certain jobs [for example, those working at heights or with heavy machinery] or people in certain social circumstances [for example, those living alone]), OR
  - the person does not tolerate a sulfonylurea or a sulfonylurea is contraindicated.
- only continue if the person has had a reduction of at least 5.5 mmol/mol (0.5%) in HbA1c in 6 months
- initiation can be undertaken by primary, community or secondary care.

In a triple therapy regimen in combination with metformin and a sulfonylurea **ONLY**:

- only continue if the person has had a reduction of at least 5.5 mmol/mol (0.5%) in HbA1c in 6 months.
- initiation should be undertaken by community or secondary care specialists or by GPs where appropriate

In combination with insulin with or without other antidiabetic drugs (metformin +/- sulfonylurea):

- only continue if the person has had a reduction of at least 5.5 mmol/mol (0.5%) in HbA1c in 6 months
- initiation should be undertaken by community or secondary care specialists or by GPs with expertise in the treatment of patients with T2DM with insulin.

Background information, costs, monitoring, contra-indications and adverse-events

- Dapagliflozin is now licensed and recommended by NICE as monotherapy, dual therapy and triple therapy.
- **Costs – The SGLT2 inhibitors, (empagliflozin, canagliflozin and dapagliflozin) are currently the highest cost oral antidiabetic drugs (excluding tolbutamide).**
- Dapagliflozin is usually taken at a dose of 10mg once daily.

Renal function

- Efficacy of dapagliflozin is dependent on renal function, and efficacy is reduced in patients who have moderate renal impairment and likely absent in patients with severe renal impairment. **Dapagliflozin is not recommended for use in patients with moderate to severe renal impairment** (patients with creatinine clearance [CrCl] < 60 ml/min or eGFR < 60 ml/min/1.73 m^2). **Monitoring of renal function is recommended as follows**:
  - Prior to initiation of dapagliflozin and at least annually thereafter
  - Prior to initiation of concomitant medicinal products that may reduce renal function and periodically thereafter
  - For renal function approaching moderate renal impairment, at least 2 to 4 times per year. If renal function

falls below CrCl < 60 ml/min or eGFR < 60 ml/min/1.73 m^2, dapagliflozin treatment should be discontinued.

Hepatic impairment

- No dosage adjustment is necessary for patients with mild or moderate hepatic impairment. In patients with severe hepatic impairment, a starting dose of 5 mg is recommended. If well tolerated, the dose may be increased to 10 mg

Dapagliflozin is not recommended for use in patients 75 years and older.

- In subjects ≥ 65 years of age, a higher proportion treated with dapagliflozin had adverse reactions related to volume depletion, renal impairment or failure vs placebo.

Common adverse reactions include urinary tract and genital infections.

- There is an increased risk of hypoglycaemia when combined with insulin or sulfonylureas.
- Dapagliflozin is **not recommended for use in patients concomitantly treated with pioglitazone** (precautionary measure as a result of concerns about bladder cancer rates for both drugs).

Dapagliflozin has not been studied in combination with glucagon-like peptide 1 (GLP-1) analogues.

- MHRA Drug Safety update June 2015 reports that serious and life-threatening cases of diabetic ketoacidosis have been reported in patients taking sodium-glucose co-transporter 2 (SGLT2) inhibitors (canagliflozin, dapagliflozin or empagliflozin). It advises to test for raised ketones in patients with acidosis symptoms, even if plasma glucose levels are near-normal,
- MHRA Drug Safety Update April 2016 on DKA advises:
    - **not to restart** treatment with any SGLT2 inhibitor in patients who experienced DKA during use, unless another cause for DKA was identified and resolved
    - **interrupt treatment** with the SGLT2 inhibitor in patients who are hospitalised for major surgery or acute serious illnesses; treatment may be restarted once the patient's condition has stabilised

Refer to Summary of Product Characteristics for further information on dapagliflozin http://www.medicines.org.uk/emc/medicine/27188 and the MHRA Drug Safety Update https://www.gov.uk/drug-safety-update/sglt2-inhibitors-updated-advice-on-the-risk-of-diabetic-ketoacidosis

- There is currently no cardiovascular safety outcome data for dapagliflozin and canagliflozin.

Reference:

NICE TA 288: Type 2 diabetes - Dapagliflozin combination therapy, June 2013 http://guidance.nice.org.uk/TA288
NICE TA 390: Type 2 diabetes - Dapagliflozin monotherapy, May 2016 https://www.nice.org.uk/guidance/ta390
NICE TA 418: Type 2 diabetes - Dapagliflozin triple therapy, Nov 2016 https://www.nice.org.uk/guidance/ta418