### 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**

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<th>Names:</th>
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<td>Dapagliflozin (Forxiga®)</td>
<td>Sodium-glucose co-transporter 2 inhibitor</td>
<td>Treatment of type 2 diabetes (T2DM)</td>
<td>January 2017 (update of September 2016)</td>
<td>Final</td>
<td>NICE TAs 288, 390, 418 – recommended for restricted use. SMC – accepted for restricted use.</td>
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**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 with expertise in the treatment of patients with T2DM.

**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 m²). **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 m², 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


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

**Reference:**


NICE TA 390: Type 2 diabetes - Dapagliflozin monotherapy, May 2016 [https://www.nice.org.uk/guidance/ta390](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](https://www.nice.org.uk/guidance/ta418)