This policy statement is approved by Halton, Knowsley, Liverpool, South Sefton, Southport and Formby, St Helens, Warrington, and Wirral CCGs

Ha Kn Li SS SF SH Wa Wi

Pan Mersey
Area Prescribing Committee

DAPAGLIFLOZIN tablets (Forxiga®) WITH INSULIN for the treatment of type 1 diabetes

The Pan Mersey Area Prescribing Committee recommends the prescribing of DAPAGLIFLOZIN tablets (Forxiga®) WITH INSULIN, for the treatment of type 1 diabetes mellitus in accordance with NICE TA597.

AMBER patient retained by specialist

NICE technology appraisal (TA) 597 recommends dapagliflozin tablets with insulin as an option for treating type 1 diabetes in adults with a body mass index (BMI) of at least 27 kg/m^2, when insulin alone does not provide adequate glycaemic control despite optimal insulin therapy, only if:

- they are on insulin doses of 0.5 units/kg of body weight/day or more, **and**
- they have completed a structured education programme that is evidence based, quality assured, delivered by trained educators and includes information about diabetic ketoacidosis, such as:
  - how to recognise its risk factors, signs and symptoms
  - how and when to monitor blood ketone levels
  - what actions to take for elevated blood ketones, **and**
- **treatment is started and supervised by a consultant physician specialising in endocrinology and diabetes treatment, and haemoglobin A1c (HbA1c) levels are assessed after 6 months and regularly after this.**

Dapagliflozin should be stopped if there has not been a sustained improvement in glycaemic control (that is, a fall in HbA1c level of about 0.3% or 3 mmol/mol).[1]

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

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Effectiveness[1]

The main evidence for dapagliflozin came from 2 trials, DEPICT-1 and DEPICT-2. These trials compared dapagliflozin plus insulin therapy at 2 doses (5 mg [licensed] or 10 mg [unlicensed]) with placebo plus insulin therapy over 52 weeks. They were randomised and double-blind and included a total of 1,591 patients with inadequately controlled type 1 diabetes despite optimised insulin therapy and HbA1c levels ranging from 7.5% (58.5 mmol/mol) to 10.5% (91.0 mmol/mol). Patients starting on systemic corticosteroid therapy were excluded from the trials. The primary endpoint in both trials was change in HbA1c from baseline at 24 weeks.
NICE focused only on the data for the licensed dose of dapagliflozin and in a subgroup of patients who were on average 45 years old and had an average BMI of 32 kg/m^2. Also, 54% were women, 6% smoked, 43% were on an insulin pump and 49% were on a renin-angiotensin-aldosterone system (RAAS) inhibitor. Patients had type 1 diabetes for an average of 21 years, had an average baseline HbA1c level of 8.4% (68 mmol/mol) and used an average insulin dose of 0.8 units/kg of body weight/day.

Adjusted mean change from baseline in HbA1c and weight at 24 and 52 weeks in the DEPICT trials (pooled results, full analysis set, BMI 27 kg/m^2 or more).

Outcome		24weeks		52weeks	
		Dapagliflozin 5mg plus insulin	Placebo plus insulin	Dapagliflozin 5mg plus insulin	Placebo plus insulin
Change in HbA1c	Percentage points, %	−0.44	−0.01	−0.26	0.08
	Difference from placebo	−0.44 (95% CI −0.55 to −0.32)		−0.34 (95% CI −0.48 to −0.20)	
Change in weight	%	−3.11	−0.01	−3.42	0.49
	Difference from placebo	−3.10 (95% CI −3.89 to −2.31)		−3.89 (95% CI −4.67 to −3.11)	

Evidence from the clinical trials shows small improvements in blood glucose (HbA1c levels) and weight loss, and very small improvements in quality of life, when dapagliflozin plus insulin is compared with placebo plus insulin in adults with type 1 diabetes and inadequate blood glucose control despite optimised insulin therapy.

Safety[2]

See Forxiga 5 mg SPC for full details.
See also MHRA alerts: SGLT2 inhibitors: updated advice on the risk of diabetic ketoacidosis
SGLT2 inhibitors: updated advice on increased risk of lower-limb amputation
SGLT2 inhibitors: reports of Fournier's gangrene

Diabetic ketoacidosis (DKA): In type 1 diabetes mellitus studies with dapagliflozin, patients had a higher number of DKA events compared with the placebo group. Patients should have completed a structured education programme that covers DKA.
Renal impairment: The glycaemic efficacy of dapagliflozin is dependent on renal function. Efficacy is reduced in patients who have moderate renal impairment and is likely absent in patients with severe renal impairment. In subjects with glomerular filtration rate (GFR < 60 mL/min), a higher proportion of subjects treated with dapagliflozin had adverse reactions of increase in creatinine, phosphorus, parathyroid hormone (PTH) and hypotension, compared with placebo. Dapagliflozin should not be initiated in patients with a GFR < 60 mL/min and should be discontinued at GFR persistently below 45 mL/min. Dapagliflozin has not been studied in severe renal impairment (GFR < 30 mL/min) or end-stage renal disease.

Cost[1]

The NICE costing template assumes uptake will be low and only 10% of the eligible population will be treated with an SGLT-2 inhibitor, and 40% of patients who commence on treatment will stop at 6 months. Estimated cost impact: £749 per 100,000 population for 2019/20, rising to £5,893 per 100,000 population by 2023/24.

Patient factors[2]

Renal function should be monitored prior to initiation of dapagliflozin and at least yearly thereafter. Additional monitoring is recommended prior to initiation of concomitant medicines that may reduce renal function and periodically thereafter. For renal function with GFR < 60mL/min, monitoring is recommended at least 2 to 4 times per year.

Prescribing information[2]

The dose in type 1 diabetes is 5 mg once daily. Dapagliflozin must only be administered as an adjunct to insulin.

Before initiating treatment with dapagliflozin:

- Risk factors for (DKA) should be assessed.
- It should be ensured that ketone levels are normal. If ketones are elevated (blood beta-hydroxybutyrate reading greater than 0.6 mmol/L or urine ketones one plus (+)), treatment with dapagliflozin should not be started until the ketone levels are normal.
- It should be ensured that the patient demonstrates the ability to monitor ketone levels.
- It is recommended that patients obtain several baseline ketone levels over one to two weeks prior to initiation of dapagliflozin therapy, and patients should become familiar with how their behaviours and circumstances affect their ketone levels.
- Patients should be informed, in a dedicated education session, on the risk of DKA, how to recognise DKA risk factors, signs or symptoms, how and when to monitor ketone levels and what actions to take at elevated ketone readings.
- Correction of volume depletion prior to initiation of dapagliflozin is recommended in patients with this condition.

In order to avoid hypoglycaemia with the first dose of dapagliflozin, a 20% reduction in the first mealtime bolus insulin may be considered. Subsequent bolus doses should be adjusted individually based on blood glucose results. No reduction in basal insulin is recommended when initiating dapagliflozin. Subsequently, basal insulin should be adjusted based on blood glucose results. When needed, insulin dose reduction should be done cautiously to avoid ketosis and DKA.

Ketone monitoring during treatment:

During the initial one to two weeks of treatment with dapagliflozin, ketones should be monitored on a regular basis, then the frequency of ketone level testing should be individualized, according to the patient's lifestyle and/or risk factors.

Patients should be informed about what actions to take if ketone levels are elevated.

Implementation notes[1]

Treatment should be initiated and supervised by a consultant physician specialising in endocrinology and diabetes. At initiation, the hospital will prescribe for the first 6 weeks. A hospital review of treatment will take place at one month. If treatment is to continue, a letter will be sent to the GP detailing the outcome of the review and requesting the GP to take over prescribing.

Refer to the accompanying Pathway for addition of SGLT2 inhibitors to insulin therapy for patients with type 1 diabetes for further guidance on specialist initiation and review.

References

1. National Institute for Health and Clinical Excellence. Technology Appraisal 597; Dapagliflozin with insulin for treating type 1 diabetes, 28 August 2019, last updated 12 February 2020. Accessed 17 February 2020.
2. AstraZeneca UK Limited. Summary of Product Characteristics: Forxiga 5 mg film-coated tablets, 31 July 2019. Accessed 07 September 2019.