Commissioning Support Dapagliflozin (*Forxiga®▼*)

For treatment of type 2 diabetes

Commissioning guidance:

Commissioners may wish to bear the following in mind when considering the commissioning of dapagliflozin:

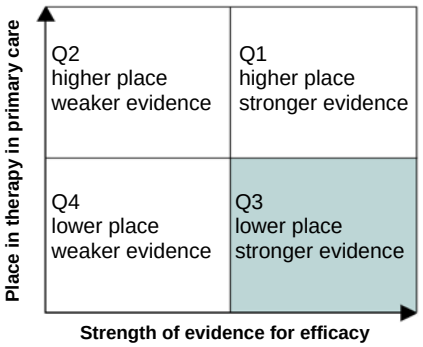
- Its place in the local care pathway should be defined by local Drug & Therapeutics or Area Prescribing Committees.
- In the absence of such local guidance, it is the opinion of the committee that dapagliflozin may be suitable as a third-line agent following treatment with a DPP-4 inhibitor (gliptin').
- It has potential as an alternative treatment in patients with type 2 diabetes who are obese.
- Current draft NICE guidance on dapagliflozin does not recommend its use because the appraisal committee require further information from the manufacturer regarding the efficacy and cost-effectiveness of the treatment.

Prescribing guidance: Category B (Q3) **Expected BNF: 6.1.2**

Dapagliflozin should be initiated by a practitioner with a special interest in diabetes. Following initiation, it is suitable for prescribing in primary care.

Category B: suitable for restricted prescribing under defined conditions

Q3 rating: The evidence for the efficacy of dapagliflozin was considered to be relatively strong. In seven RCTs, it was shown to be more effective at decreasing glycosylated haemoglobin (HbA_{1c}) levels than placebo as monotherapy, and as add-on therapy to metformin, glimepiride, pioglitazone and insulin. As add-on therapy to metformin it was non-inferior to a combination of metformin and glipizide. There is however, no longer-term outcome data for this treatment. The place in therapy of dapagliflozin has not yet been established.



The Q rating relates to the drug's position on the effectiveness indicator grid. *The strength of the evidence is determined by the quality and quantity of studies that show significant efficacy of the drug compared with placebo or alternative therapy. Its place in therapy in primary care takes into account safety and practical aspects of using the drug in primary care, alternative options, relevant NICE guidance, and the need for secondary care input.*

Description of technology

Dapagliflozin is the first in a new class of oral antidiabetic agents that selectively inhibit the human renal sodium glucose co-transporter type 2 (SGLT2), the major transporter responsible for renal glucose re-absorption. Dapagliflozin lowers plasma glucose by inhibiting the renal re-absorption of glucose in the proximal tubule, thereby promoting its urinary excretion. It is licensed for use in adults aged 18 years and older with type 2 diabetes mellitus to improve glycaemic control as:

- monotherapy when diet and exercise alone do not provide adequate glycaemic control in patients for whom metformin is considered inappropriate due to intolerance or
- add-on therapy in combination with other glucose-lowering medicinal products including insulin, when these, together with diet and exercise, do not provide adequate glycaemic control.

Background

Diabetes mellitus is a common chronic disease, associated with markedly increased morbidity and mortality. The majority of people in the UK with diabetes mellitus (~90%) have type 2 diabetes,[1] which is associated with serious long-term microvascular and macrovascular complications. Patients with type 2 diabetes are two to five times more likely to suffer cardiovascular morbidity.[2]

Dietary and lifestyle modifications form the mainstays of therapy for type 2 diabetes, but 50 to 70% of patients will also require an antidiabetic drug. Drug treatments currently available include sulphonylureas, metformin, pioglitazone, acarbose, repaglinide, nateglinide, DPP-4 inhibitors ("gliptins"), exenatide, liraglutide and insulin.

Clinical evidence for efficacy and safety

Eight fully published multicentre, phase III RCTs (n = 4,657) assessed the efficacy and safety of oral dapagliflozin 2.5 mg, 5 mg, or 10 mg once daily as monotherapy (1 trial), or as part of a dual or triple therapy regimen in patients with type 2 diabetes whose glycosylated haemoglobin levels (HbA_{1c}) were not well controlled with current therapy (7 trials). Seven trials used a placebo comparator; the eighth trial was an active comparator trial.[3-8]

The primary outcome in all the trials was the change

in HbA_{1c} from baseline to the end of the study. Secondary outcomes included the proportion of patients achieving a therapeutic response (HbA_{1c} < 53 mmol/mol [7%]) and the change from baseline in fasting plasma glucose levels (FPG) and bodyweight.

In the dapagliflozin as ***monotherapy*** trial,[3] dapagliflozin at doses of 5 mg and 10 mg daily lowered HbA_{1c} levels significantly more than placebo after 24 weeks' treatment (placebo-subtracted decreases of 5.9 and 7.3 mmol/mol [0.54% and 0.66%] respectively from baseline, $p < 0.001$).[3] FPG levels were also significantly lowered in the dapagliflozin 5 mg and 10 mg groups compared with placebo ($p < 0.001$). There was no significant difference between the dapagliflozin 2.5 mg dose group and placebo for those outcomes. Mean bodyweight decreased in all patients during the trial with no significant difference between dapagliflozin and placebo.

As ***dual or triple therapy,*** dapagliflozin 5 mg or 10 mg daily was evaluated in combination with metformin extended-release (XR) formulation in 2 trials (1,236 treatment-naïve patients, duration 24 weeks)[5]; and at doses of 2.5 mg to 10 mg in combination with standard metformin in a further trial involving 534 patients over 24 weeks.[4] Dapagliflozin was also evaluated: as dual therapy with pioglitazone or glimepiride,[6,7] compared with pioglitazone or glimepiride plus placebo; and as dual or triple therapy with insulin ± oral antidiabetic drugs (OADs) compared with placebo plus insulin ± oral antidiabetic drugs (OADs).[8]

- In all six trials after 24 weeks' treatment (or 52 weeks in one trial[8]), the combination treatment showed greater decreases in HbA_{1c} levels from baseline than placebo plus individual components. Placebo-subtracted mean decreases in HbA_{1c} for the groups receiving dual or triple therapy were in the range 4.4 to 9.5 mmol/mol [0.4 to 0.86%] in these trials.
- Across the trials, results were similar for fasting plasma glucose decreases compared with placebo.
- Bodyweight decreases were in the range 2 to 3 kg for dapagliflozin plus metformin-treated patients and 0.9 to 2 kg for dapagliflozin plus glimepiride-treated patients, or dapagliflozin plus insulin. In combination with pioglitazone, only patients in the dapagliflozin 10 mg-treated group showed a mean decrease in bodyweight of 0.14 kg. Patients treated with dapagliflozin 5 mg or placebo plus pioglitazone showed a mean weight gain over the trial of 0.09 to 1.64 kg.

In the only ***active comparator*** trial,[9] a combination of dapagliflozin plus metformin was compared with glipizide plus metformin in 801 patients over 52 weeks. In that trial, doses were titrated to target FPG levels over the initial 18 weeks to a maximum of 10 mg for dapagliflozin-treated patients or 20 mg for glipizide-treated patients.

Results of the trial showed that the combination of metformin plus dapagliflozin was non-inferior to metformin plus glipizide. There was also no significant difference in the proportion of patients that showed a response to treatment (HbA_{1c} < 53 mmol/mol [7%]). Significantly more metformin plus glipizide-treated patients had at least one hypoglycaemic episode compared with metformin plus dapagliflozin-treated patients (40.8% *vs.* 3.5%, $p < 0.0001$).

Adverse events

In the trials reviewed, the most commonly reported events leading to discontinuation in patients treated with dapagliflozin 10 mg were increased blood creatinine (0.4%), urinary tract infections (0.3%), nausea (0.2%), dizziness (0.2%), and rash (0.2%).

Considerations for cost impact

- According to QOF 2011/12 data,[10] the estimated number of patients with diabetes mellitus in the West Midlands is 298,514. About 90% of these will have type 2 diabetes,[11] equating to a total of 268,663 potential recipients.
- At current prices, a year's treatment with dapagliflozin 10 mg daily costs £477.

References

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Launch date: November 2012 Manufacturer: Bristol Myers Squibb-AstraZeneca EEIG *Ltd*

WARNING: This sheet should be read in conjunction with the Summary of Product Characteristics

This guidance is based upon the published information available in English at the time the drug was considered. It remains open to review in the event of significant new evidence emerging.

NICE GUIDANCE ON DAPAGLIFLOZIN WAS NOT AVAILABLE AT TIME OF PUBLICATION OF THIS GUIDANCE

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