Having more options available for treating diabetes allows clinicians to tailor therapy for patients to achieve better glycaemic control

**Dapagliflozin**

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The search for new ways to treat diabetes has intensified over recent years with various new drugs being launched and two new classes of medicine being developed. Although each class comes with its own limitations and adverse effect profile, they also give clinicians more options to tailor and optimise therapy.

Dapagliflozin (Forxiga) was developed jointly by Bristol-Myers Squibb and AstraZeneca. In November 2012, it became the first sodium-glucose co-transporter 2 (SGLT2) inhibitor to be made available in the UK. It has a novel insulin-independent mechanism of action that targets the kidneys.

**Mechanism of action**

The possibility of altering plasma glucose levels by modifying renal excretion of glucose originated from the discovery of phlorizin. Although this molecule could not be developed as a medicine, it was shown to normalise fasting and fed glucose levels in diabetic rats. Glucose is usually filtered in the kidney and reabsorbed via active transport by SGLT1 and SGLT2. The latter is a high-capacity, low-affinity carrier responsible for approximately 90% of the reabsorbed glucose.

When SGLT2 is blocked by dapagliflozin, some of the filtered glucose is excreted in the urine. As well as decreasing blood glucose levels, this may cause moderate weight loss and a slight decrease in blood pressure. Osmotic diuresis is believed to contribute to these secondary effects, although the weight loss is possibly maintained by fat mass reduction due to glucosuria.

**Licensing**

Dapagliflozin is approved as monotherapy for patients intolerant of metformin or in combination with several other antidiabetic medicines, including insulin. The recommended dose is 10mg once daily with or without food, meaning it can be taken at a time that suits the patient. The cost of treatment is £36.59 per month — comparable to the cost of the glucagon-like peptide-1 (GLP-1) agonists and the dipeptidyl peptidase-4 (DPP-4) inhibitors.

**Evidence**

Dapagliflozin’s marketing authorisation was granted based on an extensive clinical development programme consisting of 12 phase III trials. These examined dapagliflozin as monotherapy and in combination with several other antidiabetic medicines, including metformin, sulphonylureas, pioglitazone and insulin. Its effect on weight loss and use in moderate renal failure were also investigated.

Although over 5,000 patients participated in the trials, the majority of participants (84%) were white American or European; only 10% were Asian and 3% were of black origin. The US Food and Drug Administration notes this as concerning, given the high rate of diabetes in non-white ethnicities.

The primary endpoint in the studies was change in HbA1c from baseline at 24 weeks — a common endpoint in diabetes trials. Some studies were extended for a further 78 weeks. Nonetheless, it cannot be assumed that a reduction in HbA1c will result in improved clinical outcomes, such as reduced mortality or fewer vascular complications.

The mean reduction in HbA1c throughout the development programme was consistently statistically significant, and ranged from 0.4% to 0.8%. This is similar to that achieved by pioglitazone and DPP-4 inhibitors. Elements of key trials from the licence submission are detailed in a document produced by the London New Drugs Group (available from www.nelm.nhs.uk) and summarised in Box 1 (p24).

**Special groups**

**Renal impairment** Dapagliflozin requires a good level of renal function to work. Efficacy is reduced in patients who have moderate renal impairment and is probably absent in patients with severe renal impairment. It is not licensed for use in patients with a creatinine clearance below 60ml/min. However, no dose adjustment is needed for patients with mild renal impairment.

**Hepatic impairment** Dose adjustment is unnecessary for patients with mild or moderate hepatic impairment. In patients with severe impairment, a starting dose of 5mg is recommended. This can be increased to 10mg if tolerated.

**Older people** In general, no dose adjustment is recommended based on age.

**VERDICT**

Dapagliflozin is the first in a new class of antidiabetic drug that can be used as monotherapy or in combination with other antidiabetic medicines, including insulin. It is associated with a decrease in HbA1c, and has the potential to cause weight loss and decrease blood pressure.

There are some safety concerns and patients should be profiled before use to minimise the increased risk of infection and potential increased risk of cancer.

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However, the mean age studied in the trials was 56 years; 21% of patients were at least 65 years old and only 5% were at least 75 years old. Due to its lack of exposure to patients ≥65 years of age, dapagliflozin is not currently recommended for use in this patient group.

Also, older patients are more at risk of renal impairment and blood volume depletion, and are often treated with medicines such as loop diuretics and angiotensin-converting enzyme (ACE) inhibitors (which can worsen renal function).

**Safety issues**

Although it was granted European marketing authorisation, dapagliflozin was not recommended for approval by the FDA because of concerns over its adverse effect profile. Further clinical data have been requested by the FDA to allow better assessment of the risks. Nevertheless, dapagliflozin did pass the cardiovascular screening that is now requested by the FDA for all new diabetes medicines.

The European Medicines Agency’s Committee for Medicinal Products for Human Use, however, believes that the commonly seen side effects are manageable. It has recommended that further studies investigating the potential cancer risks (see below) be carried out, but that the benefits of dapagliflozin outweigh the risks.

The manufacturer plans to conduct post-marketing trials to evaluate the safety profile.

**Urinary and genital tract infections**

A common finding during clinical trials was that urinary tract infections and genital tract infections (GTIs) were statistically more common in the dapagliflozin-treated groups, with the incidence of GTIs being dose-related. The infections appeared to be mild and responded to standard therapy. However, the trials were not of sufficient duration to consider the effect of repeated infections and the risk of developing resistant organisms with repeated treatment.

**Hypoglycaemia**

The incidence of hypoglycaemia was low but increased with concurrent sulphonylurea or insulin therapy. In a trial examining monotherapy, there were no cases of significant hypoglycaemia. Lowering the sulphonylurea or insulin dose may reduce the risk of hypoglycaemic events.

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**Box 1: Summary of key trials**

<table>
<thead>
<tr>
<th>STUDY</th>
<th>DESCRIPTION</th>
<th>LIMITATIONS</th>
<th>KEY FINDINGS</th>
<th>CLINICAL SIGNIFICANCE/PRACTICAL NOTES</th>
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<tbody>
<tr>
<td>Nauck et al</td>
<td>Add-on to metformin; dapagliflozin (2.5–10mg) versus sulphonylurea (glipizide 5–20mg/day)</td>
<td>Non-inferiority design therefore unable to prove that it is clinically better than sulphonylurea; Patients were allowed treatment with other oral antidiabetic at half maximal dose (triple therapy) but no further details given</td>
<td>Both dapagliflozin and glipizide reduced HbA1c by 0.52% but with different profiles of glucose alteration</td>
<td>Equivalent efficacy to glipizide as second-line therapy; Showed weight loss versus weight gain with sulphonylurea, which may indicate a place in therapy for patients with higher BMI; Significant reduction in hypoglycaemic events compared with sulphonylurea</td>
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<tr>
<td>Jabbour et al</td>
<td>Add-on to dipeptidyl peptidase-4 inhibitor (sitagliptin) with or without metformin; dapagliflozin (10mg) versus placebo</td>
<td>Trial yet to be published and there are limited details on study design</td>
<td>Greater reduction in HbA1c at 24 weeks seen with dapagliflozin treatment compared with placebo in dual and triple therapy; results maintained at week 48</td>
<td>Significant HbA1c reduction seen for triple therapy compared with placebo; Only trial that looks at use with DPP-4 inhibitor, so shows this combination could have potential if sulphonylurea cannot be used; This is not a common drug combination used in the UK and is not recommended by current NICE guidance</td>
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<tr>
<td>Wilding et al</td>
<td>Add-on to insulin ≥30 units ± up to two oral antidiabetics; dapagliflozin (2.5mg, 5mg or 10mg) versus placebo</td>
<td>Insulin doses not titrated to target, although this was to enable interpretation of the effect of dapagliflozin</td>
<td>HbA1c reduction was statistically higher for all doses compared with placebo; these were sustained to week 104</td>
<td>Demonstrated statistically significant benefit over placebo; Higher rates of hypoglycaemia in comparison with placebo demonstrating a possible need for insulin dose reduction</td>
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<tr>
<td>Bolinder et al</td>
<td>Body composition measurement; dapagliflozin (10mg) versus placebo in patients inadequately controlled on metformin</td>
<td>Significant differences between male and female populations studied; Patients with body weight over 120kg were excluded which means those with the highest BMI cannot be included in the conclusions; The study did not determine precise mechanism of dapagliflozin weight loss, and its effects on food intake and satiety are unknown</td>
<td>Mean weight loss of 2kg above placebo; proportion of patients achieving weight reduction of at least 5% was 26.2%</td>
<td>Greater effect seen in men than women; weight loss was mainly accounted for by fat loss rather than water; Although this does not indicate significant benefits over other therapies (eg, glucagon-like peptide-1 agonists) it does offer weight loss benefits at an earlier stage in therapy and without the restrictions placed on GLP-1 agonists</td>
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Malignancy
An analysis of the adverse effects that occurred during clinical trials suggested there was an imbalance in the occurrence of both bladder cancer (10 cases) and breast cancer (nine cases). The trials were not of adequate design, size or scope to detect a significant risk difference between dapagliflozin and comparators for these types of cancer. However, the FDA determined that the number of observed breast and bladder cancers in the dapagliflozin-treated group exceeded the expected number of cases in the general diabetic population.

Hepatic impairment
There were at least eight cases of deranged liver function during the phase III trials which included raised serum alanine transaminase and bilirubin test results. Only one case was thought to be related to dapagliflozin.

Interactions
Few interactions have been reported during the pharmacokinetic studies that have been carried out. A lack of effect on the cytochrome P450 system indicates that interactions are not expected with drugs metabolised by these enzymes. No clinically significant changes were seen when dapagliflozin was administered with other enzyme inducers and inhibitors.

As mentioned earlier, patients treated with medicines that affect renal function, such as ACE inhibitors or loop diuretics, should be started on dapagliflozin cautiously.

Place in therapy
Pharmacists should ensure that dapagliflozin use is suitable for individual patients (see Box 2). Dapagliflozin will probably become yet another third-line therapy option for diabetes, alongside DPP-4 inhibitors, GLP-1 agonists and thiazolidinediones. However, with the growing concern regarding the hypoglycaemia risk of sulphonylureas, the manufacturer of dapagliflozin will probably promote the drug’s use earlier in the course of diabetes — as an alternative for patients in whom sulphonylureas are contraindicated.

Such use would be logical, given the restrictions on treatment caused by age and renal function, and be within the product licence. Furthermore, the weight loss seen during trials would be an added benefit. However, dapagliflozin does not have the strength of evidence to support it replacing metformin or sulphonylureas as first- and second-line options.

Nonetheless, its new mode of action allows prescribers another option to tailor therapy to meet individual needs. It also presents an opportunity to prescribe with insulin due to its insulin-independent mechanism and insulin-sparing effects.

There are many third-line options and it requires careful consideration of each patient and his or her comorbidities to select the most appropriate treatment. Having additional options means there are more ways for patients to achieve the best possible glycaemic control.

References