New drugs

Dapagliflozin

Approved indication: type 2 diabetes
Forxiga (Bristol-Myers)
10 mg film-coated tablets
Australian Medicines Handbook section 10.1

In diabetes, changes in insulin resistance and secretion result in hyperglycaemia. The glucose in the blood enters the glomerular filtrate, but most of it is reabsorbed. This reabsorption involves the sodium-glucose co-transporter in the proximal tubules. Inhibiting this co-transporter should therefore increase glucose excretion and reduce hyperglycaemia. Dapagliflozin is the first sodium-glucose co-transporter inhibitor to be marketed for diabetes.

The drug is taken once a day. Although fat decreases absorption, the dose can be taken with or without food. Most of the dose is metabolised and most of the metabolites are excreted in the urine. Dapagliflozin is contraindicated if renal function is moderately or severely impaired (creatinine clearance below 60 mL/min). The effect of the drug on the developing kidney also precludes its use in pregnancy and lactation. Dapagliflozin should not be used by patients with severe hepatic impairment. No clinically significant interactions in the metabolism of dapagliflozin and other drugs have been identified.

Dapagliflozin has been studied as monotherapy in previously untreated patients whose type 2 diabetes was inadequately controlled by diet and exercise. The 559 patients were randomised to take one of six different dose regimens of dapagliflozin or a placebo. After 24 weeks the glycated haemoglobin (HbA1c) had fallen by 0.58–0.89% (units from baseline) in the dapagliflozin groups and by 0.23% in the placebo group. This difference was statistically significant for the 5 mg and 10 mg doses of dapagliflozin.[1] The 10 mg dose has been recommended for use in Australia.

The Australian approval for dapagliflozin allows it to be used as monotherapy only in patients who cannot tolerate metformin, but it can be used as initial therapy in combination with metformin. Dapagliflozin was compared with extended-release metformin in two trials involving a total of 1244 previously untreated patients who had HbA1c concentrations of 7.5–12% despite diet and exercise. They were randomised to take dapagliflozin, metformin or both. One trial studied dapagliflozin 5 mg and the other studied 10 mg. Over 24 weeks HbA1c reduced in all treatment groups with the combined regimen having the greatest effect. The effect of dapagliflozin 10 mg on HbA1c was not inferior to the effect of metformin. On average, patients taking dapagliflozin lost more weight than those taking metformin (Table 1).[2]

Dapagliflozin has also been studied in patients whose type 2 diabetes was not well controlled with metformin alone (HbA1c 7–10%). The 546 patients were randomised to add a daily dose of dapagliflozin 2.5 mg, 5 mg, 10 mg or a placebo. After 24 weeks HbA1c concentrations had fallen significantly more, in the patients taking dapagliflozin, than the 0.3% reduction in the placebo group. The reductions were 0.67% with 2.5 mg, 0.7% with 5 mg and 0.84% with 10 mg. Significantly more of the patients taking

Some of the views expressed in the following notes on newly approved products should be regarded as tentative, as there may be limited published data and little experience in Australia of their safety or efficacy. However, the Editorial Executive Committee believes that comments made in good faith at an early stage may still be of value. As a result of fuller experience, initial comments may need to be modified. The Committee is prepared to do this. Before new drugs are prescribed, the Committee believes it is important that full information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

Table 1 **Dapagliflozin and extended-release metformin for untreated type 2 diabetes** [2]

	Study 1			Study 2		
	Dapagliflozin 5 mg	**Metformin**	**Dapagliflozin 5 mg with metformin**	**Dapagliflozin 10 mg**	**Metformin**	**Dapagliflozin 10 mg with metformin**
Number of patients	203	201	194	219	208	211
Baseline mean HbA1c	9.14%	9.14%	9.21%	9.03%	9.03%	9.10%
Mean HbA1c at 24 weeks	7.96%	7.79%	7.13%	7.59%	7.6%	7.10%
Mean decrease in HbA1c	1.19%	1.35%	2.05%	1.45%	1.44%	1.98%
Baseline mean weight	86.2 kg	85.6 kg	84.1 kg	88.5 kg	87.2 kg	88.4 kg
Mean weight reduction at 24 weeks	2.61 kg	1.29 kg	2.66 kg	2.73 kg	1.36 kg	3.33 kg

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dapagliflozin 10 mg reached an HbA1c of 7% or less than in the placebo group (40.6% vs 25.9%).[3]

Another option when metformin alone is ineffective is to add a sulfonylurea. This strategy has been compared with adding dapagliflozin in a 52-week trial of 814 patients with HbA1c concentrations of 6.5–10%. At the end of the year the addition of either glipizide or dapagliflozin had reduced HbA1c by a mean of 0.52%. While this outcome was equivalent, patients taking glipizide gained an average of 1.44 kg, but those taking dapagliflozin lost 3.22 kg.[4]

Dapagliflozin has also been assessed as an add-on treatment in patients whose diabetes was not controlled (HbA1c 7–10%) by a sulfonylurea. A total of 597 patients taking glimepiride were randomised to add dapagliflozin 2.5 mg, 5 mg, 10 mg or a placebo. After 24 weeks HbA1c had fallen by 0.13% in the placebo group, and in the dapagliflozin groups by 0.58% with 2.5 mg, 0.63% with 5 mg and 0.82% with 10 mg. All the patients lost weight. Those taking dapagliflozin 10 mg lost an average of 2.26 kg compared with a loss of 0.72 kg in the placebo group.[5]

Some patients with type 2 diabetes use insulin as well as oral antidiabetic drugs. The effect of adding dapagliflozin to such regimens was studied in a placebo-controlled trial of 71 patients. In this trial dapagliflozin 10 mg and 20 mg were used and the patients had their doses of insulin halved. After 12 weeks, HbA1c concentrations had increased by 0.09% in the placebo group, but decreased by 0.61% with 10 mg dapagliflozin and by 0.69% with 20 mg.[6]

Increasing glucose excretion causes an osmotic diuresis. This can be a problem in patients who are volume depleted or are taking loop diuretics. Glycosuria also increases the risk of urinary tract infections. In the clinical trials 4.8% of patients taking dapagliflozin 10 mg developed genital infections, such as vulvovaginitis or balanitis, compared with 0.9% of the placebo group. When used alone dapagliflozin does not appear to cause significant hypoglycaemia,[1] however the risk increases in combination with a sulfonylurea.[5]

Dapagliflozin is the first of a new class of drugs. In addition to reducing HbA1c and weight, it also lowers systolic blood pressure by 1–5 mmHg. These effects could be beneficial, but longer-term studies will be needed to see if dapagliflozin improves the outcomes for patients with type 2 diabetes. These studies will also need to assess the safety of dapagliflozin. In the trials the relative risk of bladder, breast and prostate cancer was slightly increased. Until long-term data are available, dapagliflozin should probably only be used as an adjunct to treatment with drugs, such as metformin, which have more evidence to support them.

T T manufacturer provided additional useful information

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2011;34:26–7.

* At the time the comment was prepared, information about this drug was available on the website of the Food and Drug Administration in the USA (www.fda.gov).

A At the time the comment was prepared, information about this drug was available on the website of the Therapeutic Goods Administration (www.tga.gov.au/industry/pm-auspar.htm)