New drugs

Empagliflozin

Approved indication: type 2 diabetes
Jardiance (Boehringer Ingelheim)
10 mg and 25 mg film-coated tablets
Australian Medicines Handbook section 10.1.5

Empagliflozin is the third inhibitor of the sodium-glucose co-transporter 2 (see Aust Prescr 2014;37:14-16 and 2014;37:17-20) to be approved for the treatment of adults with type 2 diabetes. Canagliflozin and dapagliflozin are already available in Australia. By inhibiting renal reabsorption of glucose, the drugs increase glucose excretion thereby decreasing blood glucose.

Empagliflozin is rapidly absorbed and there is an immediate increase in the excretion of glucose which continues for at least 24 hours. The elimination half-life is approximately 12 hours with excretion in urine and faeces. There is some metabolism, but this does not involve the cytochrome P450 system. Empagliflozin is a substrate for the P-glycoprotein transporter, but it is unlikely that it will cause interactions with other substrates. Renal and hepatic impairment will increase plasma concentrations of empagliflozin, but no dose adjustment is recommended. However, empagliflozin is contraindicated if the eGFR is 45 mL/min/1.73 m^2 or less.

A phase III placebo-controlled trial randomised 899 previously untreated patients to take once-daily empagliflozin 10 mg or 25 mg or sitagliptin 100 mg. These patients had a mean HbA1c of 63 mmol/mol (7.88%). After 24 weeks this had been significantly reduced by the active treatments (see Table 1). The proportion of patients achieving a concentration below 53 mmol/mol (7%) was 12% with placebo, 35% with empagliflozin 10 mg, 44% with 25 mg and 38% with sitagliptin. Patients taking empagliflozin 10 mg lost 2.26 kg in weight and those taking 25 mg lost 2.48 kg while there was no significant weight loss with placebo or sitagliptin.[1]

Like other sodium-glucose co-transporter 2 inhibitors, empagliflozin has also been studied in combination with other drugs for diabetes (see Table 1). It is most likely to be used in this way, unless the patient has an intolerance of metformin.

Table 1 **Effect of once-daily empagliflozin on glycated haemoglobin (HbA1c)**

Trial	Duration	Treatment	Mean change in HbA1c (%) from baseline
Roden et al[1] (monotherapy)	24 weeks	placebo	+0.08
		empagliflozin 10 mg	−0.66
		empagliflozin 25 mg	−0.78
		sitagliptin 100 mg	−0.66
Häring et al[2]	24 weeks	metformin plus	
		placebo	−0.13
		empagliflozin 10 mg	−0.70
		empagliflozin 25 mg	−0.77
Rosenstock et al[3]	12 weeks	metformin plus	
		placebo	+0.15
		empagliflozin 10 mg	−0.56
		empagliflozin 25 mg	−0.55
		sitagliptin 100 mg	−0.45
Ridderstråle et al[4]	104 weeks	metformin plus	
		empagliflozin 25 mg	−0.66
		glimepiride 1–4 mg	−0.55
Häring et al[5]	24 weeks	metformin and sulfonylurea plus	
		placebo	−0.17
		empagliflozin 10 mg	−0.82
		empagliflozin 25 mg	−0.77

Some of the views expressed in the following notes on newly approved products should be regarded as preliminary, as there may be limited published data at the time of publication, 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. Before new drugs are prescribed, the Committee believes it is important that more detailed information is obtained from the manufacturer's approved product information, a drug information centre or some other appropriate source.

NEW DRUGS

Empagliflozin was added to the treatment of patients who had a mean HbA1c of at least 53 mmol/mol (7%) despite treatment with metformin. A placebo was given to 207 patients, while 217 added empagliflozin 10 mg and 213 added empagliflozin 25 mg. After 24 weeks the mean HbA1c fell by 1.4 mmol/mol with placebo, 7.7 mmol/mol with empagliflozin 10 mg and by 8.4 mmol/mol with 25 mg. In percentage units, the difference from placebo was 0.57% with empagliflozin 10 mg and 0.64% with empagliflozin 25 mg.[2]

In another study of patients with diabetes that was not completely controlled by metformin, 495 were randomised to add either empagliflozin 1 mg, 5 mg, 10 mg, 25 mg or 50 mg, or a placebo or open-label sitagliptin 100 mg daily. Apart from the 1 mg dose, all the active treatments produced a significant reduction in HbA1c by 12 weeks. Adding empagliflozin 10 mg reduced the mean HbA1c from 63 mmol/mol (7.9%) to approximately 57 mmol/mol (7.34%). The proportion of patients achieving an HbA1c of 53 mmol/mol (7%) or less was 15.5% with placebo, 38% with empagliflozin 10 mg and 33.8% with sitagliptin. Body weight reduced by 1.2 kg in the control group and by 2.7 kg with 10 mg empagliflozin.[3]

Another study compared empagliflozin with glimepiride in patients with diabetes that was inadequately controlled by diet, exercise and metformin. The mean HbA1c at baseline was 63 mmol/mol (7.92%) in the 769 patients randomised to add empagliflozin and in the 780 randomised to add glimepiride. After 104 weeks the mean reduction in HbA1c was 0.66% with empagliflozin and 0.55% with glimepiride. This showed that the effect of empagliflozin was statistically superior to glimepiride. Empagliflozin also reduced weight and blood pressure.[4]

Empagliflozin has also been studied in patients with diabetes that was not well controlled by metformin and a sulfonylurea. In one trial 669 patients were randomised to add empagliflozin 10 mg, 25 mg or a placebo to their regimen. After 24 weeks the HbA1c concentration had been significantly reduced by empagliflozin. Expressed as percentage units, the reductions were 0.82% with 10 mg, 0.77% with 25 mg and 0.17% with placebo. At the start of the study the mean HbA1c was 65 mmol/mol (8.1%). While 9.3% of the patients in the placebo group achieved a concentration below 53 mmol/mol (7%), this was reached by 26.3% of the empagliflozin 10 mg group and 32.2% of the 25 mg group. There was a weight loss of 2.16 kg with empagliflozin 10 mg and 2.39 kg with 25 mg, compared with 0.39 kg in the placebo group.[5]

A study of empagliflozin as an add-on to basal insulin found significant reductions in HbA1c over 78 weeks. In the group of 169 patients who added 10 mg empagliflozin the HbA1c fell by 0.48% from a baseline of 8.26% (67 mmol/mol), while in the 170 patients who added a placebo it fell by 0.02% from a baseline of 8.1% (65 mmol/mol).[6]

There has been a systematic review of 10 studies of empagliflozin involving 6203 people. The results suggest that empagliflozin 25 mg has similar effects on HbA1c as metformin and sitagliptin. It also reduces weight and blood pressure (see Table 2).[7]

Although empagliflozin increases the amount of glucose in the urine, the increase in urinary tract infections was not significantly different from placebo in the systematic review.[7] However, a different pooled analysis did find a significant increase. There is also a significant increase in genital tract infections compared with placebo.[7] The osmotic diuresis caused by glucose can lead to volume depletion and decreased renal function.

While the incidence of hypoglycaemia is no different from placebo with monotherapy it rises when empagliflozin is combined with other treatments.[7] When combined with metformin and a sulfonylurea, the incidence of hypoglycaemia was 16.1% with empagliflozin 10 mg and 11.5% with 25 mg daily.[5] In combination with insulin it was 19.5% with empagliflozin 10 mg and 28.4% with 25 mg daily.

Due to a lack of data, empagliflozin is not recommended for children or during pregnancy and lactation.

Prescribers now have a variety of drugs to consider when a patient's type 2 diabetes cannot be controlled

Table 2 **Meta-analysis of ten trials of empagliflozin for type 2 diabetes** [7]

Outcome measure	Outcome for empagliflozin compared to placebo	
	10 mg once daily	25 mg once daily
Change in glycated haemoglobin (HbA1c)	–0.62%	–0.66%
Odds ratio for patients achieving HbA1c below 53 mmol/mol (7%)	3.83	4.4
Change in weight	–1.85 kg	–1.84 kg
Change in systolic blood pressure	–3.49 mmHg	–4.19 mmHg
Change in diastolic blood pressure	–1.28 mmHg	–1.88 mmHg

by diet, exercise and metformin. If the prescriber adds a sodium-glucose co-transporter 2 inhibitor there is also a choice of drugs. All the members of the class reduce HbA1c and body weight, but increase the risk of genitourinary infection. There has been a concern about a possible higher risk of cancer in patients taking dapagliflozin, but it is too early to say if there will be a similar concern with empagliflozin. Although empagliflozin reduces the concentration of HbA1c, it is also too early to know the drug's effect on clinical outcomes.

T manufacturer provided the product information

REFERENCES *†

1. Roden M, Weng J, Eilbracht J, Delafont B, Kim G, Woerle HJ, et al. Empagliflozin monotherapy with sitagliptin as an active comparator in patients with type 2 diabetes: a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Diabetes Endocrinol 2013;1:208-19.
2. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Broedl UC, et al; EMPA-REG MET Trial Investigators. Empagliflozin as add-on to metformin in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2014;37:1650-9.
3. Rosenstock J, Seman LJ, Jelaska A, Hantel S, Pinnetti S, Hach T, et al. Efficacy and safety of empagliflozin, a sodium glucose cotransporter 2 (SGLT2) inhibitor, as add-on to metformin in type 2 diabetes with mild hyperglycaemia. Diabetes Obes Metab 2013;15:1154-60.
4. Ridderstråle M, Andersen KR, Zeller C, Kim G, Woerle HJ, Broedl UC; EMPA-REG H2H-SU trial investigators. Comparison of empagliflozin and glimepiride as add-on to metformin in patients with type 2 diabetes: a 104-week randomised, active-controlled, double-blind, phase 3 trial. Lancet Diabetes Endocrinol 2014;2:691-700.
5. Häring HU, Merker L, Seewaldt-Becker E, Weimer M, Meinicke T, Woerle HJ, et al; EMPA-REG METSU Trial Investigators. Empagliflozin as add-on to metformin plus sulfonylurea in patients with type 2 diabetes: a 24-week, randomized, double-blind, placebo-controlled trial. Diabetes Care 2013;36:3396-404.
6. Rosenstock J, Jelaska A, Wang F, Kim G, Broedl U, Woerle HJ, et al. Empagliflozin as add on to basal insulin for 78 weeks improves glycemic control with weight loss in insulin-treated type 2 diabetes (T2DM). Can J Diabetes 2013;37 Suppl 4:S32.
7. Liakos A, Karagiannis T, Athanasiadou E, Sarigianni M, Mainou M, Papatheodorou K, et al. Efficacy and safety of empagliflozin for type 2 diabetes: a systematic review and meta-analysis. Diabetes Obes Metab 2014;16:984-93.

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The Transparency score (T) is explained in 'New drugs: T-score for transparency', Aust Prescr 2014;37:27.

* 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)

† At the time the comment was prepared, a scientific discussion about this drug was available on the website of the European Medicines Agency (www.ema.europa.eu)