New drugs

Canagliflozin

Approved indication: type 2 diabetes
Invokana (Janssen-Cilag)
100 mg, 300 mg tablets
Australian Medicines Handbook section 10.1

Canagliflozin is the second sodium-glucose co-transporter inhibitor to be approved in Australia. Like dapagliflozin (Aust Prescr 2013;36:174-9), it reduces renal reabsorption of glucose resulting in increased excretion in the urine. The fall in the renal threshold for glucose excretion reduces blood glucose.

A single dose of canagliflozin will suppress the renal threshold for at least 24 hours. Although food does not affect bioavailability, taking canagliflozin before breakfast will reduce postprandial glucose concentrations. As canagliflozin is mainly metabolised by glucuronidation, there is a potential for its efficacy to be reduced by enzyme-inducing drugs such as phenytoin and rifampicin. An interaction with digoxin increases the concentration of digoxin. Approximately one third of the canagliflozin metabolites are excreted in the urine and there is a need to check renal function before and during treatment as canagliflozin can decrease the glomerular filtration rate (GFR). The increases in serum urea and creatinine will decline after treatment is stopped.

Efficacy declines below an estimated GFR of 60 mL/min/1.73 m^2 and adverse effects increase, so canagliflozin should not be used below 45 mL/min/1.73 m^2. There is a risk of hyperkalaemia in patients with moderate renal impairment, particularly if they are taking ACE inhibitors or potassium-sparing diuretics. Canagliflozin is also associated with increases in serum magnesium and phosphate.

Canagliflozin has been studied as monotherapy in patients with type 2 diabetes that has not been controlled by diet and exercise. One placebo-controlled trial randomised 587 patients to take canagliflozin 100 mg or 300 mg for 26 weeks. Their mean glycated haemoglobin (HbA1c) at the start of the study was approximately 8.0% (64 mmol/mol). At the end of the study HbA1c had increased by 0.14% in the placebo group, but decreased by 0.77% with canagliflozin 100 mg and by 1.03% with 300 mg. An HbA1c below 7.0% (53 mmol/mol) was achieved by 62.4% of the canagliflozin 300 mg group and 44.5% of the 100 mg group, but only 20.6% of the placebo group. The patients on active treatment lost an average of 2.5–3.4 kg while the weight loss in the placebo group was 0.5 kg.[1]

Canagliflozin has also been studied in combination with other drugs for diabetes, however, at the time of writing not all of these trials have been published in full. A placebo-controlled, dose-ranging study tried five different doses in 386 patients who had mean HbA1c concentrations of 7.6–8.0% (60–64 mmol/mol) despite treatment with metformin. After 12 weeks the absolute fall in HbA1c was 0.76% with canagliflozin 100 mg and 0.92% with 300 mg daily compared with a fall of 0.22% in the placebo group.[2] This statistically significant difference was confirmed in a 26-week study involving 906 patients.

Canagliflozin was compared to sitagliptin in 1284 patients who had diabetes which was not controlled by metformin. The average HbA1c concentration was 7.9–8.0% (63–64 mmol/mol) at the start of the study. After 26 weeks HbA1c was reduced by 0.79% with canagliflozin 100 mg, 0.94% with canagliflozin 300 mg and by 0.82% with sitagliptin 100 mg compared with a reduction of 0.17% with placebo. The patients in the placebo group were then switched to sitagliptin. After a total of 52 weeks the mean reductions in HbA1c from baseline were 0.73% with sitagliptin and 0.73% with canagliflozin 100 mg. Canagliflozin 300 mg resulted in a reduction of 0.88% which was statistically superior to sitagliptin.[3]

Another trial studied patients with diabetes that was not well controlled by metformin and a sulfonylurea. A group of 378 patients added canagliflozin 300 mg daily while another 378 added sitagliptin 100 mg daily. These patients had a mean HbA1c concentration of 8.1% (65 mmol/mol). After a year this had declined by 1.03% (11.3 mmol/mol) with canagliflozin and by 0.66% (7.2 mmol/mol) with sitagliptin. At the end of the study, 47.6% of the canagliflozin group and 35.3% of the sitagliptin group had HbA1c concentrations less than 7% (53 mmol/mol). Sitagliptin had little effect on blood pressure and weight, whereas patients taking canagliflozin had a fall of 5.1 mmHg in systolic blood pressure and lost 2.3 kg.[4]

In another year-long trial involving 1452 patients, canagliflozin had a similar effect to glimepiride when added to metformin. The mean HbA1c concentration declined, from 7.8% (62 mmol/mol), by 0.82% with

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.

NEW DRUGS

canagliflozin 100 mg, 0.93% with canagliflozin 300 mg and by 0.81% with glimepiride.[5] Canagliflozin can also cause additional reductions in HbA1c when glycaemic control cannot be achieved by a combination of metformin and pioglitazone.

Canagliflozin has been studied as an add-on therapy to regimens which included insulin for the treatment of type 2 diabetes. The 1718 patients were taking an average of 83 units of insulin each day. Adding canagliflozin 100 mg reduced HbA1c by 0.63% from a mean of 8.33%, while 300 mg reduced it by 0.72% from a mean of 8.27%. In a control group, adding a placebo to insulin had no significant effect on HbA1c after 18 weeks.

Several of the adverse effects of canagliflozin can be predicted from its mechanism of action. The glycosuria is associated with an increase in genital fungal infections and the osmotic diuresis can cause volume depletion. People over 75 years old and those using loop diuretics have an increased risk of dizziness and orthostatic hypotension. Hypoglycaemia is mainly a problem when canagliflozin is combined with a sulfonylurea or insulin. When canagliflozin was added to a combination of metformin and a sulfonylurea, 43.2% of patients developed hypoglycaemia and in 4% this was severe.[4]

There are few published data on how canagliflozin influences cardiovascular outcomes, but it does increase concentrations of low density lipoprotein cholesterol. A study investigating the cardiovascular effects of canagliflozin found more cardiovascular events in the first 30 days of treatment with canagliflozin (13/2886 patients) than with placebo (1/1441 patients). These early events could be related to volume depletion. In an analysis of the results of nine trials there was a higher hazard ratio for strokes in patients taking canagliflozin, but this difference was not statistically significant.

The safety of canagliflozin in pregnancy and lactation is unknown. In animal studies, renal development has been affected.

While canagliflozin has been studied as monotherapy, in Australia this indication is limited to patients who cannot tolerate or have a contraindication to metformin. Canagliflozin is therefore most likely to be used as an add-on therapy. Prescribers now have an array of oral drugs to consider when type 2 diabetes cannot be controlled by metformin and a sulfonylurea, in addition to diet and exercise. Although the drugs all have an effect on the concentration of HbA1c, it is not clear which drug has the best long-term outcomes or has advantages over starting insulin. Canagliflozin may have an efficacy advantage over sitagliptin as add-on therapy.[4]

T T manufacturer provided additional useful information

REFERENCES *

1. Stenlöf K, Cefalu WT, Kim KA, Alba M, Usiskin K, Tong C, et al. Efficacy and safety of canagliflozin monotherapy in subjects with type 2 diabetes mellitus inadequately controlled with diet and exercise. Diabetes Obes Metab 2013;15:372-82.
2. Rosenstock J, Aggarwal N, Polidori D, Zhao Y, Arbit D, Usiskin K, et al. Dose-ranging effects of canagliflozin, a sodium-glucose cotransporter 2 inhibitor, as add-on to metformin in subjects with type 2 diabetes. Diabetes Care 2012;35:1232-8.
3. Lavalle-González FJ, Januszewicz A, Davidson J, Tong C, Qiu R, Canovatchel W, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. Diabetologia. Epub 2013 Sep 13.
4. Schernthaner G, Gross JL, Rosenstock J, Guarisco M, Fu M, Yee J, et al. Canagliflozin compared with sitagliptin for patients with type 2 diabetes who do not have adequate glycemic control with metformin plus sulfonylurea: a 52-week randomized trial. Diabetes Care 2013;36:2508-15.
5. Cefalu WT, Leiter LA, Yoon KH, Arias P, Niskanen L, Xie J, et al. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. Lancet 2013;382:941-50.

First published online 26 November 2013

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).