Pharmacotherapeutic report, summary

Canagliflozin (Invokana®) for the treatment of adults with 'type 2 diabetes mellitus'

Recommendation by Zorginstituut Nederland dated 24 March 2014, based on an evaluation by the WAR (Scientific Advisory Committee).

The WAR has approved a pharmacotherapeutic report for the medicine canagliflozin (Invokana®) in film-coated tablets with 100 mg/300 mg active ingredient. In determining its therapeutic value, add-on therapy in a two-fold combination with metformin was compared with the addition of an SU-derivative, sitagliptin, dapagliflozin or pioglitazone to metformin. They reached the following conclusion.
- the therapeutic value of canagliflozin in combination with metformin for the treatment of type 2 diabetes mellitus is equivalent to that of an SU-derivative, DPP-4 inhibitors, dapagliflozin or pioglitazone.

Medicine. Canagliflozin. (Invokana®), film-coated tablet 100 mg and 300 mg for oral use
Registered indication. 'Used in adults aged 18 years and older with type 2 diabetes mellitus (type 2 DM), to improve glycaemic control, to be used as monotherapy in cases where metformin is considered inappropriate, and in two-fold combination with oral glucose-lowering medicinal products and/or insulin if this treatment – together with diet and exercise – does not provide adequate glycaemic control.
Posology. 100-300 mg 1x/day, orally, as monotherapy or as add-on in two-fold combination with an oral antidiabetic drug or insulin.
Mechanism of action. Canagliflozin is a representative of a relatively new class of oral antidiabetic drugs (OAD), the SGLT2-inhibitors ('sodium glucose co-transporter 2'-inhibitors). SGLT2 is the most important carrier for the reabsorption of glucose from the glomerular filtrate. By inhibiting the renal glucose reabsorption, glucose is excreted via the urine (glucosuria). This results in a lower glycaemic value. The amount of glucose excreted via the kidneys under the influence of canagliflozin depends on the glucose concentration in the blood and on the glomerular filtration rate (GFR). The elimination of glucose via urine goes hand-in-hand with loss of calories and weight loss. The effect of canagliflozin is independent of the β-cell function and insulin sensitivity.
Specific details. The registration-holder is asking for reimbursement when canagliflozin is used in two-fold combination with metformin, not for use in monotherapy or in combination with insulin.

Summary of the therapeutic value

Intended effects. Two actively controlled, non-inferiority studies show that the addition of canagliflozin to metformin in two-fold therapy contributes to a clinically significant improvement in glycaemic control, comparable with the reduction after the addition of glimepiride (average HbA1c reduction of -0.8% vs. -0.8% respectively) or the addition of sitagliptin 100 mg (-0.7% vs -0.7% respectively) in patients who are insufficiently regulated on optimum doses of metformin monotherapy. The addition of canagliflozin 100 mg and 300 mg to metformin leads to a statistically significant weight loss of ca. 4-5%, larger than seen with the addition of glimepiride (1% weight increase) or the addition of sitagliptin (1% weight loss). The differences in weight change when canagliflozin is added compared to addition of glimepiride persist for up to and including 104 weeks. Studies with a longer follow-up duration are needed to be able to determine the effects of canagliflozin on long-term outcomes such as mortality, disease-related mortality and morbidity. Based on indirect comparisons, the addition of canagliflozin 100 mg to metformin after 52 weeks leads to a decrease in HbA1c that is comparable with the decrease after the addition of dapagliflozin 10 mg to metformin.
It has been established, on basis of earlier assessments, that the effects on Hb1Ac are compared by the addition of either dapagliflozin, pioglitazone or DPP-4 inhibitors.

This means that the same conclusion applies to canagliflozin 100 mg. The addition of canagliflozin 300 mg to metformin leads to a reduction in HbA1c that is statistically significantly larger than the reduction due to the addition of dapagliflozin 10 mg, both of which were compared with the addition of an SU-derivative.

Unintended effects. The total incidence of side effects during treatment with canagliflozin was comparable with the incidence of side effects in the placebo arm. Characteristic for the side effects profile of canagliflozin are genital infections, urinary tract infections and hypoglycaemia. Vulvovaginal candidiasis occurs in about 10% of the women who undergo treatment with canagliflozin. Balanitis often occurs in men. The mechanism of action of canagliflozin does not itself lead to hypoglycaemia, but when canagliflozin is combined with insulin or an SU-derivative – medicines that can cause hypoglycaemia – the risk of hypoglycaemias increases considerably. The safety profile of canagliflozin is similar to that of dapagliflozin: the type, severity and frequencies of the reported side effects are comparable. Based on the above findings, the adverse reactions of canagliflozin and dapagliflozin can be regarded as comparable.

Experience. Experience with canagliflozin is limited, as is experience with dapagliflozin (marketed as of the end of 2012). Ample experience has been obtained with SU-derivatives and pioglitazone. These products have been marketed for more than 10 years. Sitagliptin became available in 2007. Sufficient experience has been obtained with this drug.

Applicability. There are no major differences in applicability – which is broad – between canagliflozin and dapagliflozin. Similarly to dapagliflozin, canagliflozin can enhance the effect of diuretics. The efficacy of both drugs depends on the renal function. Efficacy may be reduced in patients with moderate–severe renal failure. Efficacy may be absent in patients with severe renal failure or ESRD. The applicability of canagliflozin is greater than that of pioglitazone, but smaller than that of sitagliptin (DDP4-inhibitor).

Ease of use. There are no major differences between canagliflozin, dapagliflozin, pioglitazone, DPP-4 inhibitors and SU-derivatives. All these drugs are administered orally.

Final conclusion on therapeutic value.

Based on direct and indirect comparisons, the addition of canagliflozin 100 mg to metformin in two-fold therapy results in a reduction in HbA1c that is comparable with the effect after adding the SU-derivative glimepiride, the DPP-4 inhibitor sitagliptin 100 mg and dapagliflozin 10 mg in patients who are insufficiently regulated on optimum doses of metformin monotherapy. The addition of canagliflozin 300 mg to metformin results in a statistically significant larger reduction than the addition of dapagliflozin 10 mg, both of which were compared with the addition of an SU-derivative. Regarding the profile, the adverse effects are comparable with those of dapagliflozin. Regarding the severity, the adverse effects are comparable with those of sitagliptin. The safety of canagliflozin during long-term use has not been determined. The therapeutic value of canagliflozin, added to metformin in a two-fold combination for the treatment of adult patients with type 2 DM is equal to that of SU-derivatives, DPP-4 inhibitors, pioglitazone and dapagliflozin. Unlike for the SU-derivatives, no data are available for canagliflozin on the effects of preventing complications of type 2 DM in the long term.