Type 2 diabetes mellitus: Added benefit of canagliflozin is not proven

June 17 2014

Canagliflozin (trade name: Invokana) has been approved since November 2013 as monotherapy and in various combination therapies for adults with type 2 diabetes mellitus when diet and exercise alone do not provide adequate glycaemic control. In an early benefit assessment pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) now examined whether this new drug alone (monotherapy) or in combination with other blood-glucose lowering drugs offers an added benefit over the appropriate comparator therapy. No added benefit can be derived from the dossier, however, because the manufacturer did not present any suitable data for any of the possible therapeutic indications.

Monotherapy or combination therapy possible

Canagliflozin is approved as monotherapy in adults with type 2 diabetes mellitus when diet and exercise alone do not provide adequate glycaemic control and the use of metformin is considered inappropriate due to intolerance or contraindications.

The combination of the new drug with one or several other blood-glucose lowering drugs (including insulin) is indicated when current medication, together with diet and exercise, does not provide adequate glycaemic control.

G-BA specified appropriate comparator therapy

The Federal Joint Committee (G-BA) specified a different appropriate comparator therapy for each of four different therapeutic indications:

When canagliflozin is used as monotherapy, sulfonylurea (glibenclamide or glimepiride) is the appropriate comparator therapy.

For the dual combination of canagliflozin with another blood-glucose lowering drug (except insulin), this is metformin plus a sulfonylurea (glibenclamide or glimepiride).

In combination with at least two other blood-glucose lowering drugs, canagliflozin is compared with metformin plus human insulin.

When canagliflozin is combined with insulin (with or without an oral antidiabetic), metformin plus human insulin is also the appropriate comparator therapy.

No suitable data

The manufacturer identified no comparative study for the monotherapy and for the combination with insulin. One study in comparison with a placebo was available for the dual combination of canagliflozin plus sulfonylurea and one such study for the triple combination of canagliflozin plus metformin plus sulfonylurea. However, the manufacturer could not derive an added benefit from the study results, neither using direct nor using indirect comparisons. Hence no added benefit is proven for these therapeutic indications.

Different therapeutic strategies

The manufacturer claimed an added benefit only for the dual combination of canagliflozin plus metformin. As specified by the G-BA, it used a sulfonylurea plus metformin as a comparison: The three-arm randomized approval study (DIA3009) cited by the manufacturer in its dossier compared canagliflozin (100 mg or 300 mg) and glimepiride, each in combination with metformin.

All patients continued their prior therapy with metformin in a stable dose as concomitant treatment. Administration of canagliflozin and glimepiride differed, however: Whereas glimepiride was gradually increased in five dose levels (titration) until blood glucose (HbA1c) reached near-normal levels, the daily dose in the two canagliflozin arms was not changed. Only sham titration, also in five "steps", was envisaged in the canagliflozin arms to maintain blinding.

Because of this, the study not only compared the effects of two drugs, but also two different therapeutic strategies with each other. Hence possible differences in treatment results cannot be clearly attributed to the drugs or the therapeutic strategies, i.e. the one-sided specification of target blood glucose levels in the treatment with glimepiride.

Results not interpretable

In the first 18 weeks of the study, blood-glucose lowering differed considerably between the treatment groups: Blood glucose was lowered more in the glimepiride arm than in the canagliflozin arms. In this study phase, the proportion of patients with hypoglycaemia was also larger under glimepiride than under canagliflozin treatment. It remains unclear, however, whether the effects can be attributed to the different drugs or the different therapeutic strategies. The study results can therefore not be used for the assessment of the added benefit of canagliflozin plus metformin versus the appropriate comparator therapy.

Hence the dossier contained no study results that prove an added benefit of canagliflozin for any of the existing indications.

G-BA decides on the extent of added benefit

The dossier assessment is part of the overall procedure for early benefit assessments supervised by the G-BA. After publication of the manufacturer's dossier and IQWiG's assessment, the G-BA conducts a commenting procedure, which may provide further information and result in a change to the benefit assessment. The G-BA then decides on the extent of the added benefit, thus completing the early benefit assessment.

Provided by Institute for Quality and Efficiency in Health Care