Empagliflozin in type 2 diabetes: Added benefit not proven

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Empagliflozin (trade name Jardiance) has been approved since May 2014 for adults with type 2 diabetes mellitus in whom diet and exercise alone do not provide adequate glycaemic control. The German Institute for Quality and Efficiency in Health Care (IQWiG) examined in a dossier assessment whether the drug offers an added benefit over the appropriate comparator therapies in these patient groups.

According to the findings, such an added benefit is not proven: For four of five research questions, the manufacturer presented no relevant data in its dossier. For the fifth research question, on the one hand, it presented data from a direct comparison, in which empagliflozin was initially administered at a larger dose than recommended by the approval. Moreover, the study arms not only differed in the drug combination, but also in the therapeutic strategy. On the other hand, the manufacturer conducted two indirect comparisons based on an incomplete study pool and on studies that were unsuitable for the assessment.

Subindications Result in Five Research Questions

Empagliflozin is approved as monotherapy for patients who do not tolerate metformin. It is approved as add-on therapy in combination with other blood-glucose lowering drugs including insulin when these, together with diet and exercise, do not provide adequate glycaemic control.

The Federal Joint Committee (G-BA) specified different appropriate comparator therapies for the subindications, resulting in a total of five comparisons: empagliflozin as monotherapy versus a sulfonylurea (A), in combination with metformin versus metformin and a sulfonylurea (B1), in combination with another blood-glucose lowering drug also in comparison with metformin and sulfonylurea (B2), in combination with at least two other blood-glucose lowering drugs in comparison with metformin and human insulin (C) and in combination with insulin also in comparison with metformin plus human insulin (D).

For Four Research Questions, No Relevant Data Were Submitted

The manufacturer postulated an added benefit, which was partly considerable and partly non-quantifiable, for the research questions A, B2, C and D, but submitted no relevant data. An added benefit of empagliflozin versus the appropriate comparator therapies is therefore not proven in these cases.

Strict Target Levels Only in Comparator Arm

The manufacturer used one direct and two indirect comparisons to answer research question B1. In Study 1245.28, it compared empagliflozin with the sulfonylurea glimepiride. However, patients in the comparator arm received 1 to 4 mg glimepiride, without having sufficient flexibility, based on uniform HbA1c target levels. Dosing in the empagliflozin arm, in contrast, was consistently 25 mg daily. Hence the comparison not only referred to two drugs, but additionally to two therapeutic strategies.

In the first phase of the two-year study, blood glucose levels in the comparator arm decreased more rapidly and many more hypoglycaemias

occurred than in the empagliflozin arm. More hypoglycaemias were also recorded in the glimepiride in the second half of the study, but it cannot be excluded that these hypoglycaemias also included events that were caused by the different therapeutic strategies.

Starting Dose Too High

In addition, the constant administration of 25 mg empagliflozin in the study is equivalent to 2.5 times the starting dose recommended in the approval. The blood-glucose lowering effectiveness of 10 mg empagliflozin cannot be assessed from the study.

Overall, the results of Study 1245.28 could not be interpreted with sufficient certainty. Regardless of this, the study showed no overall advantage of empagliflozin because although there were fewer hypoglycaemias under empagliflozin, there were also more genital infections and renal and urinary disorders as well as generally more serious adverse events than under glimepiride.

Indirect Comparisons Also not Informative

In the first of the two indirect comparisons, empagliflozin 25 mg plus metformin was the so-called common comparator, which was compared with empagliflozin 10 mg plus metformin in Study 1275.1, and with glimepiride 1 to 4 mg plus metformin in the aforementioned Study 1245.28. However, the manufacturer did not consider Study 1245.23/1245.31, which was also relevant. In addition, the comparison of two treatment regimens in Study 1245.28 made it impossible to clearly attribute the effect to the drug.

In the second indirect comparison, the pharmaceutical company also used a study that was unsuitable for the assessment because different

treatment regimens were used in the two study arms with a target blood glucose level being specified only in the comparator arm. Data from the same study were already submitted in a dossier on linagliptin, for which also no added benefit is proven for this reason, among others. IQWiG therefore concluded: An added benefit of empagliflozin is not proven.

G-BA Decides on the Extent of Added Benefit

The dossier assessment is part of the overall procedure for early benefit assessments according to the Act on the Reform of the Market for Medicinal Products (AMNOG) 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.

More information: www.iqwig.de/download/A14-26_E … ertung-35a-SGB-V.pdf

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