Empagliflozin, alone or in combination, in type 2 diabetes: Added benefit again 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. In 2014, the German Institute for Quality and Efficiency in Health Care (IQWiG) concluded in its dossier assessment that an added benefit of the drug in comparison with the appropriate comparator therapies was not proven. Partly, the drug manufacturer had presented no relevant data; partly not only the drugs, but also the therapeutic strategies differed; in addition, the indirect comparisons were based on studies unsuitable for the assessment.

The manufacturer now requested a new benefit assessment due to "new scientific findings", and submitted two dossiers: one for empagliflozin alone, and one for empagliflozin in combination with metformin. IQWiG determined in both early benefit assessments that the dossiers still contained no data and analyses relevant or suitable for the research questions. Hence an added benefit of empagliflozin alone or in combination with metformin in comparison with the appropriate comparator therapies is still not proven. The analyses of the large study EMPA-REG-Outcome additionally submitted were unsuitable for an assessment of the added benefit in Germany.

Same studies, same problems

Both the single agent and the combination of empagliflozin with metformin are approved alone or in combination with other blood-glucose lowering drugs including insulin. According to the Federal Joint Committee (G-BA), this resulted in three and four research questions respectively. The manufacturer again presented no relevant data for five of these seven research questions so that an added benefit is not proven. One study of direct comparison as well as several studies for indirect comparisons, all of which had already been cited in the dossier or in the commenting procedure in 2014, were available for the other two research questions.

The assessment of the data from the indirect comparison was incomplete with regard to content, although it had been known to the manufacturer since the first dossier assessment which patient-relevant outcomes were important. In particular, there was no information on specific adverse events for which a disadvantage of empagliflozin versus the comparator therapy was shown. The information provided on one of the indirect comparisons had the same deficiency; furthermore, there were contradictions to the clinical study reports. The second indirect comparison was not evaluable because the studies compared were not sufficiently similar and because therapeutic strategies instead of drugs were compared with one another again.

Hence there was no hint of an added benefit of empagliflozin in comparison with the appropriate comparator therapies for the single agent or for the fixed combination.

Study EMPA-REG-Outcome unsuitable for the assessment of the added benefit

Both dossiers additionally contained a description of the EMPA-REG-Outcome study used by the manufacturer to answer a question posed by the manufacturer itself, i.e. whether empagliflozin (alone or with

metformin) in addition to standard treatment offers an added benefit for patients at high cardiovascular risk in comparison with standard treatment alone plus placebo.

The antidiabetic therapy in this study cannot be considered standard treatment, however: The blood-glucose lowering treatment was not escalated appropriately and the upper threshold values mentioned in guidelines were not consistently respected. And even if treatment was escalated, this was mostly done as emergency treatment, but not as part of a planned treatment expansion.

Effects in favour of empagliflozin mainly in Latin America and Asia

Moreover, marked regional differences were notable: Effects in favour of empagliflozin mainly occurred in study centres in Latin America and Asia, whereas in Europe, partly advantages and partly disadvantages of empagliflozin were shown. Finally, the study addressed neither the G-BA's research questions nor the appropriate comparator therapies specified there.

Thomas Kaiser, Head of the IQWiG Drug Assessment Department, commented on this attempt by the manufacturer to prove an added benefit for at least certain patients: "This is a wasted opportunity. It should be welcomed that studies of this size and this duration, which are therefore potentially informative, are conducted. But it was conducted with obvious deficiencies. Experts had pinned high hopes on this study, particularly as, in contrast to other large outcome studies, it appeared to produce positive results at first glance. A thorough analysis of the study and the results in European participants did not confirm this impression, however."

G-BA decides on the extent of added benefit

The dossier assessments are part of the early benefit assessment according to the Act on the Reform of the Market for Medicinal Products (AMNOG) supervised by the G-BA. After publication of the dossier assessments, the G-BA conducts commenting procedures and makes final decisions on the extent of the added benefit.

More information: www.iqwig.de/download/A16-12_E … ertung-35a-SGB-V.pdf
www.iqwig.de/download/A16-13_E … ertung-35a-SGB-V.pdf

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