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Added benefit of the fixed combination of dapagliflozin and metformin is not proven

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The fixed combination of the drugs dapagliflozin and metformin (trade name: Xigduo) has been approved since January 2014 for adults with type 2 diabetes in whom diet and exercise 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 combination offers an added benefit over the appropriate comparator therapy. No such added benefit can be derived from the dossier, however, because the drug manufacturer did not present any suitable data for any of the possible therapeutic indications.

Monotherapy or combination therapy possible

Dapagliflozin is approved both alone and in combination with other blood-glucose lowering drugs, including insulin. IQWiG already published an early benefit assessment of dapagliflozin as monotherapy in March 2013. The Institute concluded in this assessment that an added benefit was not proven because of a lack of suitable data.

The fixed combination with metformin is an option for patients who are already taking dapagliflozin and metformin as separate tablets or for patients or who do not benefit sufficiently from the commonly used drug metformin. It can also be used together with other blood-glucose lowering drugs, including insulin, if metformin and these drugs are

insufficient.

G-BA specified appropriate comparator therapy

The Federal Joint Committee (G-BA) specified a different appropriate comparator therapy for each of three different indications: For the fixed combination alone, this appropriate comparator therapy was a sulfonylurea (glibenclamide or glimepiride) plus metformin. When the fixed combination is administered together with insulin or other blood-glucose lowering drugs, the appropriate comparator therapy was human insulin plus metformin. The G-BA additionally commissioned IQWiG to also assess not only studies on glibenclamide and glimepiride, but also on glipizide – in each case combined with metformin – in the first research question.

Drugs were not used in compliance with their approval

The drug manufacturer presented results of a study that directly compared the fixed combination with glipizide plus metformin. In this study, however, which had already been the basis for its dossier on the monotherapy, the drugs were not used according to the specifications in the approval – both in the intervention and in the control arm. It remained unclear whether the same effects would have been observed if the drugs had been administered in compliance with the Summary of Product Characteristics. At any rate, the study results cannot be interpreted with regard to the approval-compliant use.

Insulin therapy could not be optimized

For the second research question, in which the fixed combination was to be complemented with insulin, the manufacturer used three studies,

which it had also already cited in the dossier on the monotherapy. However, their results could also not be used for assessing the added benefit. The main reason for this is that the insulin therapy could not be tailored sufficiently to the individual patient: Even though their current insulin therapy was insufficient, patients were neither supposed to change the insulin nor to adapt the dose. But to be able to draw conclusions about the added benefit, the fixed combination would have to be compared with other strategies for optimizing treatment, for example optimizing insulin use.

Not tailoring treatment to the individual patient does not meet the current standard of diabetological practice anyway. Instead, insulin therapy is optimized for the individual patient so that hyperglycaemia and hypoglycaemia do not occur in the first place. So in the study, insulin was not used in a way that would be necessary and appropriate in this indication.

No study identified

For the third research question, in which dapagliflozin plus metformin were combined with other blood-glucose lowering drugs, the manufacturer identified no study in comparison with human insulin plus metformin.

Hence the dossier did not contain any study results for any of the three indications that would be suitable to prove an added benefit.

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

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