Added benefit of dapagliflozin is not proven

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Dapagliflozin (trade name: Forxiga) has been approved in Germany since November 2012 for the treatment of type 2 diabetes mellitus. 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) examined whether this new drug offers an added benefit over the current standard therapy. No such added benefit can be derived from the dossier, however, because the drug manufacturer did not present any relevant data for any of the possible therapeutic indications of dapagliflozin.

Monotherapy or combination therapy possible

Dapagliflozin is approved both as monotherapy and in combination with other blood-glucose lowering drugs, including insulin. As monotherapy it is an option for patients who do not tolerate metformin. Dapagliflozin can also be used as combination therapy, either together with metformin or with sulfonylureas if either of these two drugs alone is insufficient to control blood sugar. Dapagliflozin can also be combined with insulin if the target blood sugar levels cannot be achieved with insulin alone. Other combinations with oral antidiabetics are possible, but these were not presented by the manufacturer in its dossier.

G-BA specified appropriate comparator therapy

The Federal Joint Committee (G-BA) specified a sulfonylurea (glibenclamide or glimepiride) as appropriate comparator therapy for the dapagliflozin monotherapy. The combination therapy of dapagliflozin

and metformin was also to be compared with one of these two drugs (each supplemented with metformin). The combination of dapagliflozin with a sulfonylurea was to be tested against metformin in combination with one of the sulfonylureas glibenclamide or glimepiride. According to the G-BA's specifications, the combination of dapagliflozin and insulin was to be compared either with human insulin and metformin, or, if metformin was unsuitable, with human insulin alone.

Monotherapy: patients did not receive approval-compliant treatment

The manufacturer did not submit any direct comparative study between dapagliflozin and one of the sulfonylureas. Instead, it conducted an adjusted indirect comparison based on several studies. In principle, such indirect comparisons can be suitable to prove an added benefit. But the patients in the studies used by the manufacturer were not treated according to the approval status of dapagliflozin as monotherapy because the vast majority were not intolerant to metformin.

Combination with metformin: manufacturer compared with glipizide

Regarding the combination therapy with metformin, the pharmaceutical company did not submit any study that compared dapagliflozin with glibenclamide or glimepiride as the G-BA had specified. Instead, it cited a study that compared dapagliflozin plus metformin with glipizide plus metformin. However, this sulfonylurea has no longer been approved in Germany since 2007. In addition, the manufacturer did not provide sufficient proof in its dossier that glipizide is equivalent to the other two sulfonylureas.

Combination with sulfonylureas: studies were

unsuitable

As to the combination therapy with sulfonylureas, the company did not draw on a direct comparative study, but on an adjusted indirect comparison. However, the studies it used were unsuitable: in one case, the glibenclamide dose exceeded the maximum dose approved in Germany, in another case, the drug glipizide, which is not approved in Germany, was used.

Combination with insulin: therapy could not be optimized for the individual patient

Regarding the indication dapagliflozin combined with insulin, the manufacturer used three studies. However, the results of these studies cannot be used for the assessment of 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 combination with dapagliflozin 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. In fact, insulin therapy is optimized for the individual patient so that hyperglycaemia and hypoglycaemia do not occur in the first place. So in the studies insulin was not used in a way that would be necessary and appropriate in this indication.

Hence the dossier did not contain study results for any of the four therapeutic 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