Added benefit of lixisenatide is not proven

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Lixisenatide (trade name: Lyxumia) has been approved in Germany since February 2013 for the treatment of type 2 diabetes mellitus in combination with oral blood-glucose lowering drugs or basal insulin when these, together with 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) 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 suitable data for any of the possible therapeutic indications of lixisenatide.

G-BA specified appropriate comparator therapy

Lixisenatide is approved in combination with other blood-glucose lowering drugs, including basal insulin. Depending on the type of prior treatment, there are different subindications within the therapeutic indication for the use of lixisenatide, for which the Federal Joint Committee (G-BA) specified different comparator therapies. For the combination of lixisenatide with metformin, sulfonylurea (glibenclamide or glimepiride) plus metformin is the appropriate comparator therapy.

Two subpopulations are differentiated for the subindication "lixisenatide plus sulfonylurea" regarding the appropriate comparator therapy: For patients for whom metformin is suitable, the comparison is made with the combination of metformin and sulfonylurea. For patients who do not tolerate metformin, the comparison is made with human insulin. A sulfonylurea may be given in addition to human insulin if this is necessary for the individual patient.

The triple combination of lixisenatide with metformin and sulfonylurea is to be compared with human insulin (if applicable, plus metformin). If lixisenatide is combined with basal insulin with or without metformin, the appropriate comparator therapy specified is also human insulin (if applicable, plus metformin).

Manufacturer deviated from appropriate comparator therapy

In the subindication "lixisenatide plus metformin", the manufacturer additionally defined two specific patient groups, for which it specified comparator therapies deviating from the G-BA. In both cases, the manufacturer did not give sufficient reasons for deviating from the comparator therapy defined by the G-BA.

The manufacturer confined itself to a certain part of the specified comparator therapy in the subindications "lixisenatide plus sulfonylurea" when metformin is unsuitable, and "lixisenatide plus basal insulin (if applicable, plus metformin)": It only made a comparison with basal insulin or with intensified conventional insulin treatment instead of considering all treatment options with human insulin. It therefore also only presented data for this comparison.

The manufacturer compared the triple combination "lixisenatide plus metformin plus sulfonylurea" with basal insulin plus metformin plus sulfonylurea. IQWiG did not accept the reasons given by the manufacturer for the deviation, either, because this treatment option is not advisable from a medical point of view because of more frequent side effects, among other things.

Indirect comparisons unsuitable

The manufacturer did not present a direct comparative study between lixisenatide and the appropriate comparator therapy for any of the four subindications mentioned.

For two subindications, it conducted adjusted indirect comparisons based on several studies. In principle, such indirect comparisons can be suitable to prove an added benefit. The three studies it used for the combination of lixisenatide with metformin

were unsuitable, however: In two cases, sulfonylureas were not used according to their approval status, and in one case, the study participants differed considerably from the patients in the lixisenatide study, including with regards to baseline blood glucose levels, age, and BMI. Hence treatment effects from the indirect comparison could not be interpreted.

As to the combination of lixisenatide and basal insulin (if applicable, plus metformin), the pharmaceutical company also drew on an adjusted indirect comparison. But the four studies with intermediate comparators were also unsuitable for this comparison because of different patient populations, deviating aims of treatment, and heterogeneous comparator therapies, among other things. Hence the treatment effects could also not be interpreted.

The manufacturer itself did not identify any relevant studies for lixisenatide in dual combination with sulfonylurea versus the appropriate comparator therapy. In the triple combination with metformin plus sulfonylurea, it deviated from the appropriate comparator therapy and did not present any relevant studies.

Hence the dossier did not contain any 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.

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