Linagliptin: Once again, no proof of added benefit

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Linagliptin (trade name Trajenta) has been approved since August 2011 to improve blood glucose control in adults with type 2 diabetes. The assessment of the new dossier according to the German Act on the Reform of the Market for Medicinal Products (AMNOG) again showed that no added benefit of the drug over the appropriate comparator therapy (ACT) can be determined, because the pharmaceutical company has not submitted any relevant studies. This is the conclusion of the report by the German Institute for Quality and Efficiency in Health Care (IQWiG) published on 3rd December 2012.

First assessment negative because the comparator therapy deviated from the one specified

In its first early benefit assessment dated January 2012, IQWiG was unable to determine any added benefit because the pharmaceutical company (Boehringer Ingelheim) had chosen sitagliptin as comparator therapy in its first dossier instead of the ACT (a sulfonylurea) specified by the Federal Joint Committee (G-BA). A decision based on the IQWiG report was made by the G-BA on 29th March 2012.

Company can submit a new dossier in the transitional period

On the basis of an exemption clause since enshrined in the German Social Code Book V (§35a Paragraph 5b), during a transitional period up

to the end of 2012, companies are allowed to apply for a new assessment at any time if the added benefit is considered unproven due to incomplete evidence. The G-BA decided to allow a corresponding application for linagliptin and commissioned IQWiG to assess the new dossier submitted by the company. Linagliptin is the first drug to be re-assessed according to this rule.

Approval status distinguishes between three treatment situations

The ACT (the sulfonylureas glibenclamide and glimepiride) specified by the G-BA differs according to which of three treatment situations applies: firstly, where linagliptin is given alone (monotherapy) as a substitute for metformin if the latter is not tolerated by patients or should not be taken because of impaired kidney function. In this case of monotherapy, the G-BA states that linagliptin is to be compared with a drug from the sulfonylurea class.

The second situation is dual therapy in which linagliptin is combined with metformin. This combination is indicated if treatment with metformin alone is insufficient to control blood glucose levels. In the case of such dual therapy with linagliptin, the added benefit is to be assessed in comparison with the combination of metformin and a sulfonylurea (glibenclamide or glimepiride).

The third situation is triple therapy in which a combination of linagliptin, metformin and a sulfonylurea is given. This is indicated if dual therapy of metformin and a sulfonylurea does not provide adequate treatment. The ACT for triple therapy was specified by the G-BA as a combination of human insulin and metformin.

Direct comparison with placebo is not sufficient

For monotherapy and triple therapy, the company did not submit any studies that tested linagliptin against the ACT. Although it presented the results of placebo-controlled studies in its dossier as supplementary information, in this case, however, the direct comparison with a dummy drug (placebo) is not suitable for proving an added benefit of one drug over another treatment.

Furthermore, the company also did not cite any studies that could be used for an indirect comparison. For methodological reasons, it did not consider that an indirect comparison could be carried out for the triple therapy.

The only study on dual therapy compared two treatment strategies

The company listed one study on dual therapy in which glimepiride and linagliptin - each combined with metformin - were tested against each other. In principle, this study could have been relevant. However, it did not simply compare two drugs with each other, but two different treatment strategies as well: whereas the glimepiride dose in the first phase of the study was to be adjusted (i.e. increased) until a near-normal level of blood glucose (HbA1c) was reached, no definite target value was specified in the linagliptin group. It is therefore unclear whether possible differences in the treatment results are attributable to the drugs or the treatment strategy, i.e. the unilateral specification of a target value. This study is therefore also unsuitable for deriving an added benefit.

Intensive reduction in blood glucose can increase the risk of strokes

Although it is not relevant for the assessment of the added benefit of linagliptin, this study nevertheless provided important information: in the

first phase of the study, in which the blood glucose levels in the glimepiride group were rapidly reduced to the desired near-normal range, not only was the number of hypoglycaemic episodes (times when blood glucose was too low) increased, but also the number of serious cerebral events, i.e. strokes, was far higher than in the comparator group, in which no target blood glucose value was specified.

"The results show once again that an intensive reduction in blood glucose values is achieved at the expense of substantial risks to health", commented Jürgen Windeler, the Director of IQWiG. "Furthermore, this result is to be attributed to the different treatment strategies rather than the drugs".

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