Saxagliptin and saxagliptin/metformin in type 2 diabetes: Added benefit not proven

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Saxagliptin (trade name: Onglyza) is approved for adults with type 2 diabetes mellitus whose blood-glucose levels are inadequately controlled by diet and exercise alone. The fixed combination with metformin is available under the trade name Komboglyze. Both the single agent and the fixed combination underwent early benefit assessments already in 2013, which were concluded with limited decisions by the Federal Joint Committee (G-BA). In 2015, the G-BA extended the period of the limited decision by one year.

As mandated in the Regulation for Early Benefit Assessment of New Pharmaceuticals, the drug manufacturer now submitted new dossiers after expiry of the decision. The Institute for Quality and Efficiency in Health Care (IQWiG) therefore reassessed whether the drug and the drug combination have advantages or disadvantages in comparison with the appropriate comparator therapies for the patients. The Institute concluded that an added benefit is not proven for the single agent or for the fixed combination.

Four appropriate comparator therapies

Saxagliptin can be combined with metformin and, depending on the therapeutic indication, with further drugs, particularly insulin and sulfonylureas. The G-BA therefore distinguished four research questions for the single agent and two research questions for the fixed combination and defined the appropriate comparator therapies, which consisted of

sulfonylureas, metformin, human insulin, and combinations of these drugs.

One study for all research questions

To prove an added benefit of the free and the fixed dual combination of saxagliptin plus metformin, the manufacturer used the same two studies IQWiG had already investigated in its first assessment and therefore did not analyse again (see dossier assessments A12-16 and A13-01 as well as addendum A13-14).

In addition to these studies, the manufacturer presented data from the SAVOR-TIMI 53 study for all research questions. This randomized controlled trial with patients at high cardiovascular risk, which lasted several years, had two goals: For permanent approval, it was to be excluded that more cardiovascular events occurred under saxagliptin than under placebo. For the benefit assessment, it was to be shown that saxagliptin reduced cardiovascular events in comparison with the comparator therapies.

Since patients with different pretreatments were included in the study, the total population of the study was mostly unsuitable for answering the individual research questions. The manufacturer therefore also presented analyses on subpopulations.

Analyses on subpopulations unsuitable for research questions

None of these analyses was suitable for the assessment of an added benefit, however. Subpopulations of very different sizes were chosen for several research questions. In one of the comparisons, for example, 1299 (15.7%) of the patients in the saxagliptin group were compared with 39

(0.5%) patients in the comparator group. With these large differences in proportions, the structural equality between the study arms required for an assessment is no longer guaranteed.

In addition, saxagliptin is approved for patients whose blood glucose levels are not adequately controlled by insulin alone or insulin plus metformin. Hence their previous antidiabetic treatment had to be optimized, not only in the saxagliptin arm, but also in the insulin arm. However, as the insulin dose in the corresponding comparator arm was notably increased in fewer than one third of the participants, either the appropriate comparator therapy was not adequately implemented, or a large proportion of these patients did not require treatment escalation. In this case, the prerequisite for use of saxagliptin was not met; the subpopulation was therefore unsuitable for the research question.

Overall, an added benefit of saxagliptin or saxagliptin/metformin was not proven for any of the six research questions in both dossiers.

Total population also allowed no conclusions on the G-BA's research questions

Due to the relevance of the SAVOR-TIMI 53 study for the therapeutic indication type 2 diabetes mellitus, IQWiG, besides the analyses relating to the research questions, also investigated the manufacturer's analyses on the total population of the study. In some outcomes, e.g. all-cause mortality or cardiovascular mortality, the study results showed no disadvantages or advantages of saxagliptin in comparison with placebo, each in addition to antidiabetic standard treatment. Regarding symptomatic hypoglycaemia and hospitalization due to cardiac failure, saxagliptin apparently had disadvantages.

However, no conclusions on an added benefit of saxagliptin or

saxagliptin/metformin in comparison with the comparator therapies specified by the G-BA could be derived from these results for several reasons. Most patients either did not receive adequate blood-glucose lowering treatment or received treatment that was not in compliance with the approval. It was also unclear how the approximately 40% patients with hypertension were treated - whether dosage of their blood-pressure lowering drugs was increased or whether they received additional drugs, for example. The data also suggested that the regional health care standards within the study population differed notably from one another so that the results are not immediately transferable to the German health care context.

G-BA decides on the extent of added benefit

The dossier assessment is 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 assessment, the G-BA conducts a commenting procedure and makes a final decision on the extent of the added benefit.

Provided by Institute for Quality and Efficiency in Health Care