

# Sitagliptin + metformin in type 2 diabetes: Added benefit over sulfonylurea + metformin

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Sitagliptin (trade names: Januvia and Xelevia) is approved for certain 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 names Janumet and Velmetia. 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 has advantages or disadvantages in comparison with the appropriate comparator therapies for the patients. The Institute concluded that there are hints of a partly non-quantifiable and partly considerable added benefit in comparison with sulfonylureas for the free and the fixed combination of [sitagliptin](#) and metformin. For all other uses, an added benefit is not proven.

## Numerous research questions

Sitagliptin can be combined with metformin and, depending on the

therapeutic indication, with further drugs, particularly insulin and sulfonylureas. The G-BA therefore distinguished five research questions for the single agent and three research questions for the fixed combination and defined the appropriate comparator therapies, which consisted of sulfonylureas, metformin, human insulin, and combinations of these drugs.

## **Sitagliptin monotherapy: added benefit not proven**

Regarding the question whether sitagliptin alone has an added benefit over the sulfonylureas glibenclamide or glimepiride, the manufacturer submitted the same unsuitable data as for the first assessment: Since the approval conditions of sitagliptin monotherapy were not fulfilled in the P251 study, i.e. intolerance or contraindication to metformin, an added benefit is not proven.

The same data as in the first assessment were also available for the comparison between sitagliptin and the sulfonylurea glipizide. However, since then the contraindication to metformin has been changed in such a way that the circle of patients for whom sitagliptin monotherapy is an option has narrowed. Yet the manufacturer presented no new analyses for this. Since the data were not interpretable, an added benefit of sitagliptin in comparison with this second comparator therapy is also not proven.

## **Added benefit also not proven in combination with sulfonylurea or insulin**

As the manufacturer identified no corresponding study, no added benefit is proven also for sitagliptin plus sulfonylurea and sitagliptin/metformin (free or fixed combination) plus sulfonylurea. Data from the study P260 were available for the combination of sitagliptin or sitagliptin plus

metformin with insulin. In the comparator arm of this study, insulin therapy was not escalated in a meaningful way, although it had been inadequate before. Hence these results were also not interpretable; an added benefit of the combination of sitagliptin and sitagliptin/metformin with insulin is therefore not proven.

## **Sitagliptin plus metformin: hints of added benefit**

The G-BA specified sulfonylurea plus metformin as appropriate comparator therapy for a free or fixed combination of sitagliptin and metformin. Besides studies with glibenclamide and glimepiride, also studies with glipizide were to be considered in a second research question.

For the first research question, particularly the data from the randomized controlled trial HARMONY 3 were relevant, where patients in the comparator arm received glimepiride in addition to metformin. In the outcome category "side effects", a hint of a positive effect of sitagliptin plus metformin versus glimepiride plus metformin was shown for symptomatic hypoglycaemia. The extent of this added benefit was non-quantifiable; it was at most considerable.

For the second research question, as in its earlier dossiers, the manufacturer submitted data from the P024 study, from which a hint of an added benefit in comparison with glipizide plus [metformin](#) was derived again. The extent of this hint was considerable for men and non-quantifiable for women. This only applied to patients in whom near-normal blood glucose levels are aimed at.

## **TECOS study allowed no conclusions on the G-BA's research questions**

In addition, the manufacturer presented results on the total population of the TECOS study. This randomized controlled trial investigated cardiovascular outcomes in patients with type 2 diabetes and established vascular disease. A combination of sitagliptin and existing antidiabetic therapy was compared with "usual diabetes care" in this study.

No conclusions for the research questions in both dossier assessments could be derived from the study for several reasons. The necessary comparisons with the appropriate comparator therapy specified by the G-BA were lacking. It cannot be assumed that there were uniform health care standards in the numerous countries involved in the study, so that the results cannot be simply transferred to the German [health care](#) context. In addition, the inclusion criteria suggested that the study was mostly conducted outside the approval of sitagliptin. The results overall raised doubts that the treatment of participants with inadequate blood glucose and blood pressure control was sufficiently escalated in the course of the study.

Overall, the analysis of the TECOS study showed an advantage of sitagliptin in comparison with "usual diabetes care" in the outcome "hospitalization due to hyperglycaemia" and a disadvantage in the outcome "retinopathy". No advantages or disadvantages were notable regarding all-cause mortality and cardiovascular mortality and morbidity; no conclusions were possible for several other outcomes.

## **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.

More English-language information will be available soon (extracts of the dossier assessments as well as easily understandable information on [informedhealth.org](http://informedhealth.org)). If you would like to be informed when these documents are available, please send an e-mail to [info@iqwig.de](mailto:info@iqwig.de).

Provided by Institute for Quality and Efficiency in Health Care

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