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Long struggle for appropriately processed manufacturer data leads to a new assessment of memantine

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After the manufacturer of the Alzheimer's drug memantine submitted a supplementary analysis of study data, the German Institute for Quality and Efficiency in Health Care (IQWiG) sees proof of a benefit of the drug for cognitive function, as well as indications of a benefit for activities of daily living, at least for a treatment period of 6 months. This changes the conclusions of the first IQWiG benefit assessment of 2009. IQWiG had repeatedly called upon the manufacturer Merz to provide a renewed analysis of study data appropriate to the research question.

IQWiG's Director Jürgen Windeler comments on the new assessment result: "As in many other projects, in the assessment of memantine the Institute was also confronted with gaps in the evidence. If this is the case, then we make suggestions as to how these gaps can be closed. Sometimes additional new studies are required; sometimes it suffices if the manufacturer provides or supplements data already available, as was the case for memantine. In the end, the additional effort paid off."

In Germany the drug memantine is marketed under the tradenames "Axura" and "Ebixa", and is approved for the treatment of moderate to severe Alzheimer's disease. In a first benefit assessment , prepared after commissioning by the Federal Joint Committee (G-BA) and published in September 2009, IQWiG found no proof that patients with Alzheimer's disease could benefit from memantine. However, among other things, relevant information on two studies was missing, which the

manufacturer had not provided to IQWiG.

At the beginning of 2010, Merz submitted the results of these two studies, as well as additional analyses of a larger number of studies, to the G-BA. IQWiG subsequently published a second assessment in the form of a working paper in August 2010. However, this did not change the conclusions of the first report. This was also due to the fact that IQWiG could not utilize the additional analyses as presented by Merz. For example, among other things, Merz had again failed to include all of the relevant studies. However, in its working paper IQWiG described how an appropriate analysis of the data could be performed.

These additional analyses, in which the data were processed appropriately, were finally submitted by Merz to the G-BA in October 2010. These were "responder analyses". In this type of analysis, a count is made of how many patients experience a notable improvement in their health status after treatment, i.e. are "responders".

For this purpose it is specified how big this difference has to be in a patient in order to be classified as an improvement. Then, both in the placebo and in the memantine groups, all patients are counted who at least achieved this improvement. In the case of a progressive disease such as Alzheimer's, the absence of deterioration may also be regarded as an improvement.

As the analysis now submitted shows, the number of patients whose short- and long-term memory (cognitive function) notably deteriorated over a period of at most 6 months was lower in the memantine group. IQWiG classifies this result as proof of a benefit.

Such a difference in favour of memantine was also shown for activities of daily living (e.g. concerning personal hygiene); however, this was considerably smaller. In addition, in contrast to the outcome "cognitive

function", the criteria according to which patients were classified as treatment responders have not proved themselves through year-long testing in studies. This leads to greater uncertainty in the interpretation of results. Consequently, overall IQWiG assumes an indication - not proof - of a benefit of treatment with memantine for this outcome.

It remains unclear whether memantine improves quality of life, as for this outcome the studies available still allow no conclusions to be drawn. The results for cognitive function and activities of daily living now submitted only apply with time restrictions, as none of the studies lasted longer than 6 months. "We still have no long-term studies. However, particularly for Alzheimer's drugs this type of study is urgently required, as they are usually taken for several years," says Jürgen Windeler.

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