Brivaracetam in epilepsy: Added benefit still not proven

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Brivaracetam (trade name: Briviact) has been approved since January 2016 as add-on therapy for adults and adolescents from 16 years of age with epileptic seizures. The German Institute for Quality and Efficiency in Health Care (IQWiG) had already examined the drug in an early benefit assessment published in May. For several reasons, the indirect comparisons presented by the drug manufacturer were unsuitable to assess an added benefit in comparison with the appropriate comparator therapy. Among other things, the manufacturer had not analysed all relevant outcomes. In the commenting procedure, the manufacturer presented a further indirect comparison.

In the addendum thereupon commissioned to IQWiG by the Federal Joint Committee (G-BA), the Institute has now concluded that this new indirect comparison is methodologically better. Among other things, the manufacturer has now analysed the missing outcomes. However, this indirect comparison submitted subsequently still fails to show an added benefit of brivaracetam over the appropriate comparator therapy.

New analyses only partly rectify the deficits

In its dossier assessment in May, IQWiG criticized that not all brivaracetam studies presented by the manufacturer were relevant for the benefit assessment, that the studies were insufficiently similar for informative indirect comparisons, that the manufacturer had not presented analyses of all relevant outcomes, and that the comparator

therapies had not been recognizably customized for the individual patient, as demanded by the G-BA.

The new indirect comparison submitted subsequently by the manufacturer addresses the first 3 points of criticism. The brivaracetam study is relevant for the research question, the studies used for the comparison are sufficiently similar to this study, and further patient-relevant outcomes are addressed. However, the problem remains unsolved that treatment in the control arms was not customized for the individual patient and thus does not correspond to the appropriate comparator therapy.

Non-inferiority of brivaracetam questionable

Independent of the question as to whether the appropriate comparator therapy specified by the G-BA was implemented, in the overall consideration, the indirect comparison shows no advantage of brivaracetam over lacosamide. Neither advantages nor disadvantages of brivaracetam were shown in the outcome categories "mortality" and "health-related quality of life" in comparison with lacosamide.

In the category "side effects", significant effects were shown in favour of brivaracetam (for serious adverse events and some specific adverse events, such as dizziness or eye disorders). However, the available data on the morbidity outcomes "seizure frequency", "50% responder rate" and "freedom of seizure", raise doubts that brivaracetam is at least equally effective as lacosamide. For seizure frequency, the one lacosamide study fails to show a clear advantage or disadvantage of brivaracetam, while the other shows a statistically significant disadvantage of the new drug compared with lacosamide. Both lacosamide studies also deliver heterogeneous results for the two other outcomes, which, however, do not lead to statistically significant advantages or disadvantages.

Overall, the indirect comparison therefore does not show an advantage of brivaracetam over the comparator therapy.

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 manufacturer's dossier and the IQWiG dossier assessment, the manufacturer submitted additional information in the commenting procedure. The G-BA subsequently commissioned IQWiG to assess the data subsequently submitted. IQWiG now presents this assessment in the form of an addendum. The G-BA makes a final decision on the extent of added benefit.

More information: www.g-ba.de/informationen/nutzenbewertung/218/

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