# Fingolimod in new therapeutic indication: Added benefit not proven

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The immunosuppressive drug fingolimod (trade name: Gilenya) was approved for an expanded therapeutic indication in May 2014: It is now also available for adults with highly active relapsing remitting multiple sclerosis (RRMS) who had received other pretreatment than interferon beta (IFN-β). In an early benefit assessment pursuant to the Act on the Reform of the Market for Medicinal Products (AMNOG), the German Institute for Quality and Efficiency in Health Care (IQWiG) examined whether the drug offers an added benefit over the appropriate comparator therapy in this patient group.

According to the findings, such an added benefit is not proven: For some of the patients, the drug manufacturer presented no data. For other patients, the available study data either showed no differences between the treatment groups, or the data were not evaluable.

## G-BA specifies appropriate comparator therapy

The Federal Joint Committee (G-BA) distinguishes between two patient groups for the assessment: In patients with highly active RRMS despite full previous treatment (no interferon beta), fingolimod was to be compared with glatiramer acetate or interferon beta. In patients with incomplete previous treatment, the G-BA distinguishes between two cases for the appropriate comparator therapy: In patients who had received glatiramer acetate, this medication was to be optimized and continued. In patients who had received a different drug, treatment was

to be changed to interferon beta or glatiramer acetate.

## Only data of few study participants relevant for the assessment

One relevant study was available for the early benefit assessment, an approval study on fingolimod (TRANSFORMS), which compared treatment with fingolimod versus treatment with IFN-β1a in adults with RRMS. However, the disease was rated as "highly active" in only nearly half of the 866 participants. Only 263 of these 402 patients had received full previous treatment.

Only 42 participants, i. e. a little less than five percent of the total study population, had not been treated with interferon beta (17 patients in the fingolimod arm, 25 in the interferon beta arm). However, only these patients correspond to the subpopulation relevant for this benefit assessment, because it is only this subpopulation that fingolimod had received expanded approval for. The informative value of the results was considerably limited because only data of few participants were evaluable.

## Differences between treatment arms not statistically significant

No deaths occurred during the total study duration of 12 weeks. There were differences between the fingolimod and the interferon beta group with regard to relapses and disability progression, but these were not statistically significant.

No evaluable data were available for the patient group for which fingolimod was newly approved regarding other aspects of the outcome "morbidity", e.g. fatigue or activities of daily living, and for the outcome

"health-related quality of life". One of the reasons for this is that different proportions of patients were not considered in the analysis.

There were group differences in side effects (serious adverse events and treatment discontinuation due to adverse events), which again were not statistically significant.

## Dossier without relevant study on patients with incomplete treatment

In its dossier, the manufacturer presented no relevant study for patients who had not received full previous treatment.

In summary, an added benefit of fingolimod is therefore not proven for patients with highly active relapsing remitting multiple sclerosis (RRMS) who had received a different pretreatment than interferon beta.

## Discrepancy between approval and study population

In 2011, fingolimod had been approved for two therapeutic indications: for rapidly progressive severe RRMS and for highly active RRMS that had been pretreated with interferon beta. For these two patient groups, IQWiG had published a dossier assessment according to AMNOG in January 2012.

In this first assessment the problem had already occurred that participants with different types of RRMS had been included in the relevant study, and that the authorities had then limited the approval to specific, relatively small patient groups. Since the first approval and assessment, the manufacturer apparently conducted no further studies for the expansion of approval.

# 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.

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