Perampanel for epilepsy: Still no proof of added benefit

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The drug perampanel (trade name Fycompa) has been approved since July 2012 as adjunctive ("add-on") therapy for adults and children aged 12 years and older with epileptic fits (seizures). In a new early benefit assessment according 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 perampanel offers an added benefit over the appropriate comparator therapy. However, such an added benefit cannot be derived from the new dossier either, as the drug manufacturer did not submit any relevant data for this comparison.

Already in the first dossier assessment in December 2012, there was no proof of an added benefit of perampanel because the manufacturer dossier provided no suitable data. The new assessment was conducted upon application of the manufacturer to the Federal Joint Committee (G-BA), which specifies the appropriate comparator therapy.

Appropriate comparator therapy expanded

Fits that affect only a small part of the brain are called "focal" or "partial seizures". In this type of fit, the muscle twitches and spasms remain limited to isolated parts of the body. However, such seizures may spread across the whole body and are then referred to as "secondary generalization". Perampanel is approved as add-on therapy for the treatment of partial seizures with or without secondary generalization in

people aged 12 years and older.

The G-BA approved the manufacturer's application for reassessment of the drug according to AMNOG because the appropriate comparator therapy had to be expanded following the change in the AMNOG Regulation for Early Benefit Assessment of New Pharmaceuticals (in §6 (1), Sentence 2, AM-NutzenV): Originally the more economical comparator therapy had to be chosen if several options were available, preferably a treatment with a fixed price. This regulation was dispensed with in 2013. If the G-BA specifies several options as appropriate comparator therapies, the manufacturer is now free to choose a therapy irrespective of the costs.

10 drugs possible as appropriate comparator therapies

The G-BA therefore specified 10 different drugs for the appropriate comparator therapy in form of an individual antiepileptic add-on therapy: gabapentin, lamotrigine, levetiracetam, oxcarbazepine, topiramate, valproic acid or zonisamide for all age groups, eslicarbazepine or pregabalin only for adults, or lacosamide only for patients aged 16 years or older. It depends on the basic and prior therapy as well as the reason for treatment switching which of these drugs is used. If a patient is known to have pharmacoresistance, intolerance or another contraindication to the chosen drug, this drug cannot be used.

Manufacturer limits its assessment to subpopulation

In its second dossier, the manufacturer wanted to prove the added benefit of perampanel as add-on therapy only for a certain part of the approval population: for patients with pharmacoresistant and continuing active epilepsy. In its dossier, the manufacturer defined these as patients

diagnosed with epilepsy for more than 5 years who, as add-on therapy in basic therapy, already receive at least one antiepileptic drug specified by the G-BA as appropriate comparator therapy.

The manufacturer justified this by claiming that, at first, new antiepileptics are mainly prescribed for resistant patients and in epilepsy centres or specialized practices. From the company's point of view, the manufacturer's proof of added benefit should preferably cover the population that is most likely to benefit from perampanel in the foreseeable future.

Comparisons with placebo instead of drugs

In the three relevant randomized controlled trials (RCTs) used by the manufacturer, each of three different dosages of perampanel is compared with a dummy drug (placebo): The patients either received perampanel as add-on therapy or placebo in addition to their ongoing basic therapy, which consisted of one to no more than three antiepileptics. At least one of the 10 drugs specified by the G-BA was part of the basic treatment.

The dose of antiepileptics of the basic therapy was not allowed to be changed during the treatment phase of 19 weeks. Hence there was no possibility to adapt or change the treatment of patients who continued to have epileptic seizures.

Appropriate comparator therapy not implemented

The manufacturer regarded the treatment in the subpopulation described to already be highly individual so that it could not be further improved by add-on therapy. Hence, from the company's point of view, the added benefit of perampanel as add-on therapy derives from the comparison

with placebo.

However, it was not presented in the dossier in a comprehensible way why none of the 10 drugs of the ACT should not be suitable as add-on therapy. The G-BA explicitly allowed the choice for the individual patient. There were also no indications that the study participants were no longer eligible for individual add-on therapy. In contrast, the study data suggest that not all options of drug treatment have been exhausted for these patients.

The appropriate comparator therapy was therefore not implemented in any of the studies presented. Hence the company again presented no relevant data for the assessment of the added benefit of perampanel. An added benefit of the drug is therefore still not proven.

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.

More information: An overview of the results of IQWiG's benefit assessment is given by a German-language executive summary. In addition, the website gesundheitsinformation.de, published by IQWiG, provides easily understandable and brief German-language information on perampanel.