IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Perampanel –

Benefit assessment according to § 35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Perampanel – Nutzenbewertung gemäß § 35a SGB V" [Version 1.0; Status: 13.12.2012]). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

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[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug perampanel. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to "the company"). The dossier was sent to IQWiG on 15.09.2012.

Research question

The assessment of the added benefit of perampanel in accordance with the approval status was undertaken for the following therapeutic indication: adjunctive (add-on) treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older.

The G-BA specified the following appropriate comparator therapy (ACT):

- Lamotrigine.
- In cases where lamotrigine is used as monotherapy, topiramate as add-on therapy is the ACT.

The company adhered to the ACT specified by the G-BA, but with the restriction that topiramate is not considered as an ACT for deriving the added benefit of perampanel. The company justified this approach on the basis of the G-BA's statement from the advisory discussion, "…a comparison versus lamotrigine as monotherapy would not be productive because of the planned therapeutic indication for perampanel as add-on therapy." Since topiramate is supposed to be ACT only in the specific case where lamotrigine is used as monotherapy, a comparison with topiramate would also not be productive.

This approach is not accepted. Topiramate is appropriate for use as comparator therapy if it is given as add-on therapy to a lamotrigine-containing basic therapy, provided perampanel is also given as add-on therapy to a lamotrigine-containing basic therapy.

The assessment was therefore carried out without restriction concerning the ACT, in accordance with the G-BA's specification.

The assessment was undertaken with respect to patient-relevant outcomes.

Results

The company did not include any direct comparative studies with perampanel versus lamotrigine. All the identified randomized controlled trials (RCTs) on perampanel were placebo-controlled and, by themselves, not adequate to demonstrate an added benefit

compared with the ACT. Nevertheless, on the basis of these studies, the company carried out a direct comparison with a subpopulation of patients who had received lamotrigine as part of their basic therapy. Thus, patients who had taken perampanel in addition to a lamotrigine-containing basic therapy were compared with patients who had received placebo in addition to a lamotrigine-containing basic therapy. The data presented constitute a comparison with placebo and are not suitable for answering the research question of the benefit assessment.

Furthermore, the company undertook an adjusted indirect comparison between perampanel and the ACT lamotrigine as add-on therapy. The company chose placebo as an intermediate comparator. Again, for perampanel, it included that subpopulation of patients from the 3 placebo-controlled approval studies who received perampanel or placebo in addition to a lamotrigine-containing basic therapy. For lamotrigine, the company included 2 placebo-controlled randomized studies, in which lamotrigine or placebo was given in addition to a basic therapy. The indirect comparison is also not suitable for answering the research question. It was not the required comparison (according to the specification of the ACT) between perampanel and lamotrigine, each as add-on to a basic therapy. Instead, the combination of perampanel and lamotrigine was compared with lamotrigine, in each case as add-on to a basic therapy of antiepileptic drugs. It should also be noted that in the studies on perampanel, the patients in the placebo group received lamotrigine as part of their basic therapy, which was not the case in the placebo groups of the studies on lamotrigine. Thus, the similarity of the intermediate comparator is also to be questioned.

The data submitted by the company are not relevant for the assessment of the added benefit of perampanel versus the ACT lamotrigine as add-on therapy.

The company undertook no comparison of perampanel and topiramate. Although it conducted a corresponding search for studies on topiramate and presented results on 2 placebo-controlled studies on topiramate, it did not include them in an indirect comparison with perampanel.

In summary, the dossier contains no relevant data for the research question of the benefit assessment, either for a direct comparison or for an indirect comparison with lamotrigine or topiramate. Hence there is no proof of an added benefit of perampanel over the ACT specified by the G-BA.

Extent and probability of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the extent and probability of the added benefit of the drug perampanel is assessed as follows:

The available data provide no proof of an added benefit of perampanel in comparison with the ACT specified by the G-BA. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

The decision regarding added benefit is made by the G-BA.

2.2 Research question

The assessment of the added benefit of perampanel in accordance with the approval status was carried out for the following therapeutic indication: "adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older" [3].

The G-BA specified the following ACT:

- Lamotrigine.
- In cases where lamotrigine is used as monotherapy, topiramate as add-on therapy is the ACT.

The company adhered to the ACT specified by the G-BA, but with the restriction that topiramate is not considered as the ACT for deriving the added benefit of perampanel. The company justified this approach on the basis of the G-BA's statement from the advisory discussion, "…a comparison versus lamotrigine as monotherapy would not be productive because of the planned therapeutic indication for perampanel as add-on therapy" (see Dossier Module 3, Section 3.1). Since topiramate is supposed to be ACT only in the specific case where lamotrigine is used as monotherapy, a comparison with topiramate would likewise not be productive.

This approach is not accepted. Topiramate is appropriate for use as comparator therapy if it is given as add-on therapy to a lamotrigine-containing basic therapy, provided perampanel is also given as add-on therapy to a lamotrigine-containing basic therapy (see also Section 2.7.1 of the full dossier assessment).

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or data not interpretable), see [1]. The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, no added benefit, or less benefit), see [2].

The assessment was therefore carried out without restriction concerning the ACT, in accordance with the G-BA's specification.

The assessment was undertaken with respect to patient-relevant outcomes.

Further information about the research question can be found in Module 3, Section 3.1 and in Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

- Studies on perampanel conducted and completed by the company up to 12.07.2012 (study list of the company)
- Results of a bibliographical literature search and a search in trial registries for studies on perampanel (last search 20.06.2012 in bibliographical databases and 26.06.2012 in trial registries, searches by the company)
- Results of a bibliographical literature search and a search in trial registries for studies on the ACT lamotrigine (last search 20.06.2012 in bibliographical databases and 26.06.2012 in trial registries, searches by the company).

The above-named steps for information retrieval identified no relevant direct comparative study for the present research question. The data submitted by the company for an indirect comparison of perampanel with lamotrigine are also unsuitable for answering the present research question. The reasons for this are as follows:

The company submitted no direct comparative studies on perampanel and the ACT. Nevertheless, it included data from 3 placebo-controlled RCTs in which perampanel was tested as add-on therapy in epilepsy patients aged 12 and over with partial seizures. Because of the placebo control, the studies are not, by themselves, adequate to demonstrate an added benefit over the ACT [4-7]. To enable conclusions on the added benefit of perampanel compared with lamotrigine to be drawn from these studies, the company used the results of their subpopulations. The subpopulations consisted of those patients who already received lamotrigine plus at least one other antiepileptic drug in their basic therapy. Thus, patients who received perampanel in addition to a lamotrigine-containing basic therapy were compared with patients given placebo in addition to a lamotrigine-containing basic therapy. This comparison is not suitable for assessing an added benefit over the ACT lamotrigine, since it corresponds to a comparison of perampanel versus placebo (see Section 2.7.2.1 of the full dossier assessment). Moreover, in this situation (lamotrigine is part of the basic therapy), topiramate is the ACT.

Furthermore, the company undertook an adjusted indirect comparison between perampanel and the ACT lamotrigine as add-on therapy. The company chose placebo (in addition to a basic therapy of one or several antiepileptic drugs) as intermediate comparator. For

perampanel the company included – as already done for the direct comparison – that subpopulation of patients from the 3 placebo-controlled approval studies who received perampanel or placebo in addition to a lamotrigine-containing basic therapy. For lamotrigine, the company included 2 placebo-controlled studies in which lamotrigine and placebo – each in addition to a basic therapy – were compared in epilepsy patients with partial seizures [8,9]. This indirect comparison is also not suitable for answering the research question of the benefit assessment (see also Section 2.7.2.1 of the full dossier assessment). The same arguments apply as for the direct comparison described above. The indirect comparison did not test (as was required in the specification of the ACT) the comparison of perampanel and lamotrigine, each as add-on to a basic therapy. Instead, the combination of perampanel and lamotrigine was compared with lamotrigine, in each case as add-on to a basic therapy of at least one other antiepileptic. Furthermore, topiramate and not lamotrigine was the ACT for the patients included on the perampanel side. It should also be noted that in the studies on perampanel, the patients in the placebo group received lamotrigine as part of their basic therapy (see also Module 4, Section 4.2.5.6 of the dossier), whereas this was not the case in the placebo groups of the studies on lamotrigine. Thus, the similarity of the common comparator ("placebo") is also to be questioned.

Indirect comparisons of perampanel with topiramate were not undertaken by the company as part of the dossier. Although the company declined to use topiramate as the ACT as specified by the G-BA (see Section 2.2), in Appendix 4-H; Section 4.3.2 of the dossier it presents the results of two studies on topiramate [10,11]. Since these studies were not used by the company for an indirect comparison and it is not clear from the information presented by the company whether or how many of the enrolled patients in those studies were treated with lamotrigine in the basic therapy, they cannot be taken into account for the benefit assessment.

Overall the company did not present any study data that are relevant for the research question of the benefit assessment. Therefore, no check of the completeness of the study pool submitted by the company was undertaken.

Further information about the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.4 Results concerning added benefit

No data relevant for the research question are available, either for a direct comparison or for an indirect comparison. Hence, there is no proof of an added benefit of perampanel over the ACT specified by the G-BA.

This deviates from the result of the company, which derived an added benefit of perampanel as add-on therapy from the comparative data it submitted.

Further information about the results concerning added benefit can be found in Module 4, Sections 4.3.1.4 of the dossier.

2.5 Extent and probability of the added benefit

The available data provide no proof of an added benefit of perampanel over the ACT specified by the G-BA. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company's assessment, which derived a major added benefit of perampanel over the ACT as add-on therapy of partial-onset seizures with or without secondarily generalized seizures.

The decision regarding added benefit is made by the G-BA.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.5 of the full dossier assessment

2.6 List of included studies

Not applicable, as the company did not present any study data in its dossier from which an added benefit of perampanel versus the ACT specified by the G-BA could be determined.

References for English extract

Please see full dossier assessment for full reference list.

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