

IQWiG Reports – Commission No. A14-16

**Perampanel –
Benefit assessment according
to §35a Social Code Book V¹**

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 August 2014). 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.

Publishing details

Publisher:

Institute for Quality and Efficiency in Health Care

Topic:

Perampanel – Benefit assessment according to §35a Social Code Book V

Commissioning agency:

Federal Joint Committee

Commission awarded on:

9 May 2014

Internal Commission No.:

A14-16

Address of publisher:

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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. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

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Keywords: perampanel, epilepsies – partial, benefit assessment

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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 referred to as “the company”). The dossier was sent to IQWiG on 9 May 2014.

Research question

The aim of this report was to assess the added benefit of perampanel as adjunctive (add-on) therapy of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older in comparison with the appropriate comparator therapy (ACT).

The G-BA specified the following ACT:

- an individual antiepileptic add-on therapy, if medically indicated and if no pharmacoresistance/intolerance and contraindications are known yet, with one of the following drugs:
eslicarbazepine (for adults) or gabapentin or lacosamide (for patients aged 16 years and older) or lamotrigine or levetiracetam or oxcarbazepine or pregabalin (for adults) or topiramate or valproic acid or zonisamide
The treatment is to be chosen by the doctor depending on the basic and prior therapy/therapies under consideration of the reason for treatment switching and any accompanying adverse events. The respective approval of the drugs is to be considered.

Limitation of the population

At first the company concurred with the ACT specified by the G-BA. However, it mentioned in its research question that the proof of added benefit of perampanel as add-on therapy was only to be conducted for a subpopulation of the approval population, which it referred to as subpopulation of patients with pharmacoresistant and continuing active epilepsy. The company defined this subpopulation as patients who, as add-on therapy in basic therapy, receive at least one antiepileptic drug specified by the G-BA as ACT, and whose epilepsy was diagnosed more than 5 years (> 60 months) ago.

Deviation from the ACT in the subpopulation

Deviating from the G-BA's specification, for this subpopulation, the company specified a comparator therapy in which the drugs specified by the G-BA are already understood to be part of an individual basic therapy. It postulated that treatment optimization with an add-on therapy is not possible in this patient population and that the added benefit results from a

comparison of perampanel as add-on therapy versus placebo. The company justified this by claiming that this does not put a focus on a specific antiepileptic from the list of the antiepileptics that are equally suitable for the ACT, but that each of them is an equal option at the same time (in the existing basic therapy). According to the company, this approach takes into account the fact that patients with pharmaco-resistant and continuing active epilepsy receive highly individual treatment, so that concentrating on one of the drugs would not correspond to the reality of treatment. This way the company conveyed the impression that the ACT specified by the G-BA does not allow for individual antiepileptic add-on therapy, and that the company had to deviate from it to allow individual treatment for the subpopulation it had chosen. The company therefore used a different interpretation of the G-BA's ACT explaining that this was understood to be part of the patients' individual effective basic therapy chosen by the doctor.

ACT specified by the G-BA also relevant for subpopulation

Contrary to the company's explanations, individual optimization of the drug treatment for patients with epilepsy who are not seizure-free despite antiepileptic treatment, is both reasonable and possible. This can be done, for example, by switching to a different antiepileptic treatment or by adding another antiepileptic drug to the existing treatment.

The company's deviation from the G-BA's ACT was not accepted. It was not comprehensible why none of the 10 drugs specified by the G-BA should not be an option as add-on therapy for the patients in the subpopulation defined by the company. Moreover, the G-BA's specification explicitly allowed patient-individual choice of a suitable add-on therapy, so that this argument also did not justify a deviating approach.

The present dossier assessment was conducted for all patients for whom perampanel is approved. The assessment was conducted versus the ACT specified by the G-BA both for the total population and for the subpopulation chosen by the company. The assessment was to be conducted based on patient-relevant outcomes and on randomized controlled trials (RCTs).

Results

The company presented no relevant data for the assessment of the added benefit of perampanel versus the ACT.

The study pool of the company to prove the added benefit of perampanel contains the 3 RCTs E2007-G000-304, E2007-G000-305 and E2007-G000-306. These studies were randomized, double-blind, placebo-controlled, multicentre studies with parallel group design. In the studies, the patients in the intervention groups took perampanel in different dosages as add-on therapy to their existing basic therapy of at least 1 to a maximum of 3 different antiepileptics. The patients in the comparator groups received placebo in addition to their existing basic therapy. The double-blind treatment phase of the studies was 19 weeks in each case. During the entire study duration, the existing treatment with antiepileptics was not to be changed. Dose adjustments were also not allowed. Other antiepileptics were only permitted as rescue

medication in severe and uncontrollable seizures. To assess the added benefit, the company selected those subpopulations from the 3 placebo-controlled studies in which at least one of the 10 drugs specified by the G-BA was already part of the existing basic therapy and whose epilepsy was diagnosed more than 5 years (> 60 months) ago.

No implementation of the ACT

None of the studies implemented the ACT specified by the G-BA. The patients in the comparator groups of the 3 studies received exclusively placebo in addition to their existing antiepileptic basic therapy. The patients who continued to have epileptic seizures despite their current basic therapy had no possibility to adapt or change their antiepileptic treatment.

However, there were no indications that the patients included were no longer eligible for individual antiepileptic add-on therapy. On the contrary, it has to be assumed that it would have been possible also for these patients to choose a suitable add-on therapy from the 10 possible drugs of the ACT. Hence the ACT specified by the G-BA was not implemented in any of the studies presented. There were also no indications that this is unsuitable for the subpopulation considered by the company.

All 3 studies (E2007-G000-304, E2007-G000-305 and E2007-G000-306) are therefore unsuitable to assess the added benefit versus the ACT specified by the G-BA.

Extent and probability of added benefit, patient groups with therapeutically important added benefit⁴

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

⁴ 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 conclusions 1 to 3 cannot be drawn from the available data), 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].

Table 2: Perampanel – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy	Extent and probability of added benefit
As add-on therapy of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older	An individual antiepileptic add-on therapy, if medically indicated and if no pharmacoresistance/intolerance and contraindications are known yet, with one of the following drugs: eslicarbazepine ^a or gabapentin or lacosamide ^b or lamotrigine or levetiracetam or oxcarbazepine or pregabalin ^a or topiramate or valproic acid or zonisamide The treatment is to be chosen by the doctor depending on the basic and prior therapy/therapies under consideration of the reason for treatment switching and any accompanying adverse events. The respective approval of the drugs is to be considered.	Added benefit not proven
a: For adults. b: For patients aged 16 years and older.		

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report was to assess the added benefit of perampanel as add-on therapy of partial-onset seizures with or without secondarily generalised seizures in patients with epilepsy aged 12 years and older in comparison with the ACT.

The G-BA specified the following ACT:

- an individual antiepileptic add-on therapy, if medically indicated and if no pharmacoresistance/intolerance and contraindications are known yet, with one of the following drugs:
eslicarbazepine (for adults) or gabapentin or lacosamide (for patients aged 16 years and older) or lamotrigine or levetiracetam or oxcarbazepine or pregabalin (for adults) or topiramate or valproic acid or zonisamide.
The treatment is to be chosen by the doctor depending on the basic and prior therapy/therapies under consideration of the reason for treatment switching and any accompanying adverse events. The respective approval of the drugs is to be considered.

Limitation of the population

At first the company concurred with the ACT specified by the G-BA. However, it mentioned in its research question that the proof of added benefit of perampanel as add-on therapy was only to be conducted for a subpopulation of the approval population, which it referred to as subpopulation of patients with pharmacoresistant and continuing active epilepsy. The company defined this subpopulation as patients who, as add-on therapy in basic therapy,

receive at least one antiepileptic drug specified by the G-BA as ACT, and whose epilepsy was diagnosed more than 5 years (> 60 months) ago. The company justified this limitation to a subpopulation of the approval population by claiming that, at first, new antiepileptics are mainly prescribed for resistant epilepsy patients and by experts in epilepsy centres or specialized practices. It wanted to provide proof in the population that, from the company's point of view, most closely corresponds to the patients who would benefit from perampanel in the foreseeable future.

Deviation from the ACT in the subpopulation

Deviating from the G-BA's specification, for this subpopulation, the company specified a comparator therapy in which the drugs specified by the G-BA are already understood to be part of an individual basic therapy. From the company's point of view, this basic therapy already constituted the optimum standard care for these patients. Hence the company postulated that treatment optimization with an add-on therapy is not possible in this patient population. Therefore, from the company's point of view, the added benefit results from the therapeutic benefit in patient-relevant outcomes achieved by perampanel as add-on therapy in comparison with placebo. The company justified this by claiming that this does not put a focus on a specific antiepileptic from the list of the antiepileptics that are equally suitable for the ACT, but that each of them is an equal option at the same time. According to the company, this approach takes into account the fact that patients with pharmaco-resistant and continuing active epilepsy receive highly individual treatment, so that concentrating on one of the drugs would not correspond to the reality of treatment. This way the company conveyed the impression that the ACT specified by the G-BA does not allow for individual antiepileptic add-on therapy, and that the company had to deviate from it to allow individual treatment for the subpopulation it had chosen.

Moreover, the company argued in Section 4.1 (Module 4A) that the existing drug treatment options were largely exhausted for patients with pharmaco-resistant and continuing active epilepsy. Expanding or switching the individual basic therapy under consideration of the antiepileptics currently approved for add-on therapy by the treating doctor was considered to be futile. The company therefore used a different interpretation of the G-BA's ACT explaining that this was understood to be part of the patients' individual effective basic therapy chosen by the doctor.

The company's deviation from the G-BA's ACT was not accepted. It is neither comprehensible why it should be no longer possible to optimize treatment for the subpopulation operationalized by the company, nor can the rationale be accepted that the G-BA's specification does not allow for individual treatment optimization.

ACT specified by the G-BA also relevant for subpopulation

Contrary to the company's explanations, individual optimization of the drug treatment for patients with epilepsy who are not seizure-free despite antiepileptic treatment, is both reasonable and possible [3,4]. This can be done, for example, by switching to a different

antiepileptic treatment or by adding another antiepileptic drug to the existing treatment. According to the German Society of Neurology guideline, chances of success to become seizure-free decrease after failure of the first treatment. However, it is not recommended to dispense with optimization of treatment. Instead, it is described that patients who appear to be pharmacoresistant can become seizure-free by using further drugs [4]. According to Kwan et al. [5], response to antiepileptic treatment is also influenced by the dynamic nature of epilepsy. Hence there is the possibility that an antiepileptic drug that has not been sufficiently effective in the past can be used successfully again at a later point in time.

Against this background, it was not comprehensible why none of the 10 drugs specified by the G-BA should not be an option as add-on therapy for the patients in the subpopulation defined by the company.

Moreover, the G-BA's specification explicitly allowed patient-individual choice of a suitable add-on therapy, so that this argument also did not justify a deviating approach.

The present dossier assessment was conducted for all patients for whom perampanel is approved. In principle, data can also be analysed for one part of the approval population, which would then allow to draw a conclusion on the added benefit for this subpopulation. The assessment was conducted versus the ACT specified by the G-BA both for the total population and for the subpopulation chosen by the company.

The assessment was to be conducted based on patient-relevant outcomes and on RCTs.

Further information about the research question can be found in Module 3A, Section 3.1, and Module 4A, 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

2.3.1 Information retrieval

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

Sources of the company in the dossier:

- study list on perampanel (studies completed up to 6 February 2014)
- bibliographical literature search on perampanel (last search on 13 February 2014)
- search in trial registries for studies on perampanel (last search on 13 February 2014)

To check the completeness of the study pool – referring to the time point of the first submission of the dossier:

- bibliographical literature search on perampanel (last search on 17 June 2014)
- search in trial registries for studies on perampanel (last search on 17 June 2014)

The company only used data that was already subject of its first dossier submission on 13 September 2012.

From the steps of information retrieval mentioned, the company identified 3 studies in the relevant therapeutic indication (E2007-G000-304 [6], E2007-G000-305 [7] and E2007-G000-306 [8]). These studies were unsuitable for the assessment of the added benefit of perampanel in comparison with the ACT specified by the G-BA. The reason for this was that the G-BA's ACT was not implemented in the studies. The 3 studies are described and the common reason for exclusion is explained in detail in the following Section 2.3.2.

Further information on the inclusion criteria for studies in this benefit assessment and the methods of information retrieval can be found in Module 4A, 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. Further information on the results of the information retrieval and the study pool derived from it can be found in Module 4A, Section 4.3.1.1 of the dossier and in Sections 2.7.2.3.1 and 2.7.2.3.2 of the full dossier assessment.

2.3.2 Description of the studies

Study design

The 3 studies on perampanel (E2007-G000-304, E2007-G000-305 and E2007-G000-306 [6-8]) were randomized, double-blind, placebo-controlled, multicentre studies with parallel group design. In all 3 studies, patients aged 12 years and older, diagnosed with epilepsy, who continued to have partial-onset seizures despite taking stable doses of up to 3 different antiepileptic drugs. In the studies, the patients in the intervention groups took perampanel in different dosages as add-on therapy to their existing basic therapy of at least 1 to a maximum of 3 different antiepileptics. The patients in the comparator groups received placebo in addition to their existing basic therapy. The double-blind treatment phase of the studies was 19 weeks in each case. During the entire study duration, the existing treatment with antiepileptics was not to be changed. Dose adjustments were also not allowed. Other antiepileptics were only permitted as rescue medication in severe and uncontrollable seizures.

No implementation of the ACT

As specified by the G-BA, the ACT of the present assessment is an individual antiepileptic add-on therapy, if medically indicated and if no pharmacoresistance/intolerance and contraindications are known yet, with one of the following drugs: eslicarbazepine (for adults) or gabapentin or lacosamide (for patients aged 16 years and older) or lamotrigine or levetiracetam or oxcarbazepine or pregabalin (for adults) or topiramate or valproic acid or zonisamide. The treatment is to be chosen by the doctor depending on the basic and prior therapy/therapies under consideration of the reason for treatment switching and any accompanying adverse events. The respective approval of the drugs is to be considered.

Hence, a possible direct comparison of perampanel versus an individual antiepileptic add-on therapy (chosen from the 10 drugs of the ACT) would be as follows:

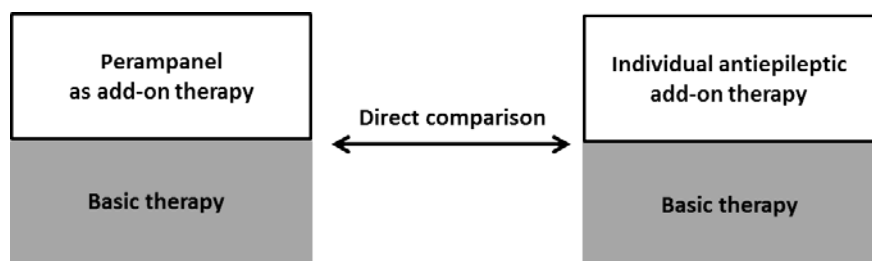


Figure 1: Possible direct comparison of perampanel with individual antiepileptic add-on therapy

Deviating from this, for the assessment of the added benefit, the company selected those subpopulations from the 3 placebo-controlled studies in which at least one of the 10 drugs specified by the G-BA was already part of the existing basic therapy and whose epilepsy was diagnosed more than 5 years (> 60 months) ago. The resulting comparison is represented in Figure 2. These subpopulations each constitute a proportion of 75% of the total study populations.

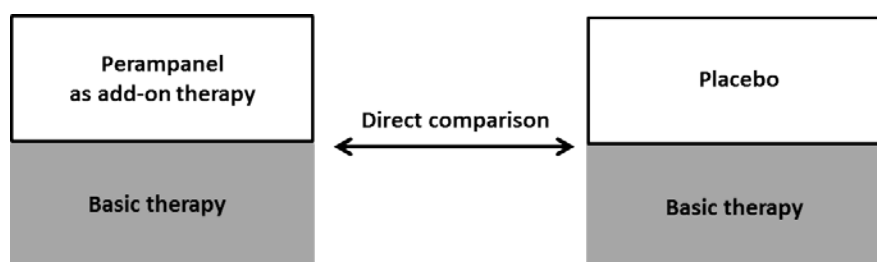


Figure 2: Direct comparison in the studies used by the company

None of the studies – E2007-G000-304, E2007-G000-305 and E2007-G000-306 – implemented the ACT specified by the G-BA.

The patients in the comparator groups of the 3 studies received exclusively placebo in addition to their existing antiepileptic basic therapy. The patients who continued to have epileptic seizures despite their current basic therapy had no possibility to adapt or change their antiepileptic treatment.

However, there were no indications that the patients included were no longer eligible for individual antiepileptic add-on therapy: They had received a median of 3 antiepileptic drugs for the treatment of their epilepsy in the last 5 years (at least 1 and no more than 12 antiepileptics), which suggests that not all drug options of an add-on therapy have been exhausted in a large proportion of these patients. On the contrary, it has to be assumed that it would have been possible also for these patients to choose a suitable add-on therapy from the 10 possible drugs of the ACT. Hence the ACT specified by the G-BA was not implemented in any of the studies presented. There were also no indications that this is unsuitable for the subpopulation considered.

All 3 studies (E2007-G000-304, E2007-G000-305 and E2007-G000-306) are therefore unsuitable to assess the added benefit versus the ACT specified by the G-BA.

Possible design of a direct comparative study versus the ACT

However, an RCT taking into account the ACT is feasible, and the following design is conceivable.

Patients with epilepsy aged 12 years and older who have partial-onset seizures with or without secondarily generalized seizures and who are not seizure-free despite their current antiepileptic treatment with at least 1 antiepileptic drug are included in the study. This concurs with the approved therapeutic indication of perampanel.

Before randomization, a doctor specifies for each patient the add-on therapy he or she would receive if allocated to the comparator group (individual antiepileptic add-on therapy). The doctor may consider known pharmacoresistance, intolerance and contraindications as well as basic and prior therapy/therapies of the patient as criteria for choosing the add-on therapy. The patients are then randomly assigned to 2 groups and treated according to their group allocation:

- intervention group: add-on therapy with perampanel
- comparator group: individual antiepileptic add-on therapy according to the doctor's choice (as specified before randomization)

This approach would allow to draw reliable conclusions on the added benefit of perampanel versus an alternative antiepileptic treatment according to the G-BA's specification on the ACT.

If necessary, this approach would also allow the analysis of subpopulations with regard to chosen comparator therapies. The study results of patients from the intervention group who would have received a certain drug if they had been allocated to the comparator group could be compared with the results of the patients who actually received this drug as their individual antiepileptic add-on therapy. As it was already specified for all patients before randomization which antiepileptic add-on therapy they would receive in case of allocation to the comparator group, these additional analyses could be conducted for all outcomes of the study.

Further information about the study design and the study populations can be found in Module 4A, Section 4.3.1.2.1 of the dossier, and in Section 2.7.2.3.2 of the full dossier assessment.

2.4 Results on added benefit

In its dossier, the company presented no suitable studies for the assessment of perampanel as add-on therapy versus the ACT specified by the G-BA. Since no relevant data for the benefit assessment were presented, there is no proof of added benefit of perampanel in comparison with the ACT specified by the G-BA.

This result deviates from that of the company, which derived an added benefit from the studies it included.

Further information about the results can be found in Module 4A, Section 4.3.1.3 of the dossier, and in Section 2.7.2.4 of the full dossier assessment.

2.5 Extent and probability of added benefit

The result of the assessment of the added benefit of perampanel in comparison with the ACT is shown in Table 3.

Table 3: Perampanel – extent and probability of added benefit

Therapeutic indication	Appropriate comparator therapy	Extent and probability of added benefit
As add-on therapy of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older	An individual antiepileptic add-on therapy, if medically indicated and if no pharmacoresistance/intolerance and contraindications are known yet, with one of the following drugs: eslicarbazepine ^a or gabapentin or lacosamide ^b or lamotrigine or levetiracetam or oxcarbazepine or pregabalin ^a or topiramate or valproic acid or zonisamide The treatment is to be chosen by the doctor depending on the basic and prior therapy/therapies under consideration of the reason for treatment switching and any accompanying adverse events. The respective approval of the drugs is to be considered.	Added benefit not proven
a: For adults. b: For patients aged 16 years and older.		

This deviates from the company's approach, which derived proof of considerable added benefit for perampanel for the subpopulation chosen by the company, which it referred to as patients with pharmacoresistant and continuing active epilepsy.

The G-BA decides on the added benefit.

2.6 List of included studies

The information usually provided here is not applicable as the studies included by the company were unsuitable for the assessment of the added benefit of perampanel versus the ACT specified by the G-BA for the reasons stated above.

References for English extract

Please see full dossier assessment for full reference list.

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