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Perampanel (epilepsy, 4 to < 12 years, partial-onset seizures) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Perampanel (Epilepsie, 4 bis < 12 Jahre, fokale Anfälle) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 March 2021). 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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Address of publisher
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

No advisor on medical and scientific questions was available for the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Ulrike Mikulić
- Katharina Biester
- Gertrud Egger
- Ulrich Grouven
- Marco Knelangen
- Christopher Kunigkeit
- Daniela Preukschat
- Corinna ten Thoren

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
EMA	European Medicines Agency
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)
SPC	Summary of Product Characteristics

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 is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 14 December 2020.

Research question

The aim of the present report is the assessment of the added benefit of perampanel in comparison with the appropriate comparator therapy (ACT) as adjunctive treatment in children from 4 to < 12 years of age with epilepsy with partial-onset seizures with or without secondarily generalized seizures.

For the benefit assessment, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of perampanel

Therapeutic indication	ACT[a]
Adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in children from 4 to < 12 years of age with epilepsy	Patient-specific antiepileptic adjunctive treatment, if medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance or contraindication is known, taking into account the following drugs: eslicarbazepine[b], gabapentin[c], lacosamide, lamotrigine, levetiracetam, oxcarbazepine[c], topiramate, valproic acid[d], zonisamide[c], brivaracetam
a. Presentation of the ACT specified by the G-BA. b. For children over 6 years of age. c. For children from 6 years of age. d. Valproic acid is not a regular option for adjunctive treatment in children and adolescents aged 4 to 11 years due to potential liver damage and teratogenicity. However, adjunctive treatment with valproic acid may be a possible option within the framework of an individual therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company largely followed the G-BA's specification of the ACT, but excluded the drug valproic acid as a treatment option. This approach is not appropriate because all drugs specified by the G-BA can be an option for individual antiepileptic adjunctive treatment. The benefit assessment was therefore conducted in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. A minimum duration of the maintenance therapy of 12 weeks was assumed.

Results

Concurring with the company, the check of the study pool did not produce any relevant randomized controlled trials (RCTs) for a direct or adjusted indirect comparison with the ACT. The company included the non-comparative, single-arm studies E2007-G000-311 and E2007-G000-232 on perampanel in its assessment. The company did not conduct an information retrieval for the ACT and accordingly did not present any data on the ACT. However, comparative data would be necessary to assess the added benefit of perampanel. For the E2007-G000-232 study, there is the additional fact that the 4-week maintenance phase is clearly too short. The evidence presented by the company is unsuitable for the assessment of the added benefit of perampanel in comparison with the ACT.

Irrespective of the fact that the company, as described above, did not present a comparison with the ACT, the conclusions drawn by the company, which compared results at the end of the study with the baseline phase, are not appropriate also because patient-specific adjustments of the previous antiepileptic therapy were not permitted for the baseline phase. Thus, the ACT in the sense of a patient-specific adjunctive treatment taking into account the drugs specified by the G-BA is also not represented in the baseline phase of the studies.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

No suitable data are available to assess the added benefit of perampanel compared with the ACT in children from 4 to < 12 years of age with epilepsy with or without secondarily generalized seizures. Hence, there is no hint of an added benefit of perampanel in comparison with the ACT; an added benefit is therefore not proven.

Table 3 presents a summary of the probability and extent of the added benefit of perampanel.

[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 conclusions 1 to 3 cannot be drawn from the available data). 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, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Perampanel – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in children from 4 to < 12 years of age with epilepsy	Patient-specific antiepileptic adjunctive treatment, if medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance or contraindication is known, taking into account the following drugs: eslicarbazepine[b], gabapentin[c], lacosamide, lamotrigine, levetiracetam, oxcarbazepine[c], topiramate, valproic acid[d], zonisamide[c], brivaracetam	Added benefit not proven

a. Presentation of the ACT specified by the G-BA.
b. For children over 6 years of age.
c. For children from 6 years of age.
d. Valproic acid is not a regular option for adjunctive treatment in children and adolescents aged 4 to 11 years due to potential liver damage and teratogenicity. However, adjunctive treatment with valproic acid may be a possible option within the framework of an individual therapy.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of perampanel in comparison with the ACT as adjunctive treatment in children from 4 to < 12 years of age with epilepsy with partial-onset seizures with or without secondarily generalized seizures.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of perampanel

Therapeutic indication	**ACT[a]**
Adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in children from 4 to < 12 years of age with epilepsy	Patient-specific antiepileptic adjunctive treatment, if medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance or contraindication is known, taking into account the following drugs: eslicarbazepine[b], gabapentin[c], lacosamide, lamotrigine, levetiracetam, oxcarbazepine[c], topiramate, valproic acid[d], zonisamide[c], brivaracetam
a. Presentation of the ACT specified by the G-BA. b. For children over 6 years of age. c. For children from 6 years of age. d. Valproic acid is not a regular option for adjunctive treatment in children and adolescents aged 4 to 11 years due to potential liver damage and teratogenicity. However, adjunctive treatment with valproic acid may be a possible option within the framework of an individual therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company largely followed the G-BA's specification of the ACT, but excluded the drug valproic acid as a treatment option. This approach is not appropriate because all drugs specified by the G-BA can be an option for individual antiepileptic adjunctive treatment. The benefit assessment was therefore conducted in comparison with the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. A minimum duration of the maintenance therapy of 12 weeks was assumed. This does not correspond to the inclusion criteria of the company, which imposed no restrictions regarding study duration.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on perampanel (status: 5 October 2020)
- bibliographical literature search on perampanel (last search on 23 September 2020)
- search in trial registries/trial results databases for studies on perampanel (last search on 30 September 2020)
- search on the G-BA website for perampanel (last search on 30 September 2020)

To check the completeness of the study pool:

- search in trial registries for studies on perampanel (last search on 18 December 2020)

Concurring with the company, the check of the study pool did not produce any relevant RCTs for a direct or an adjusted indirect comparison with the ACT.

The company did not compare individual arms from different studies. As justification, it stated that comparisons of individual treatment groups from different studies without reference to a common comparator are not a regular valid method of analysis and are therefore not usually suitable as a basis for an assessment of the added benefit.

Evidence provided by the company

In the Section "Further investigations" of the dossier, the company presented 2 non-comparative single-arm studies: E2007-G000-311 [3] and E2007-G000-232 [4]. These studies were the basis for the approval of perampanel in the present therapeutic indication. The data presented by the company are unsuitable for the derivation of an added benefit of perampanel in comparison with the ACT. This is justified below.

Study E2007-G000-311

Study E2007-G000-311 is a single-arm study in which perampanel was administered in addition to the existing basic therapy. A total of 180 children aged 4 to < 12 years with diagnosed epilepsy with partial-onset seizures with or without secondary generalization or with primary generalized tonic-clonic seizures were included in the study. Of the 180 children, 149 children had epilepsy with partial-onset seizures. According to the inclusion criterion of the study, patients must have had at least one partial-onset or primary generalized tonic-clonic seizure during the 12 weeks (4 weeks in Japan) before the start of the treatment phase despite their previous antiepileptic therapy.

The E2007-G000-311 study consisted of a 4-week pretreatment phase (hereinafter referred to as "baseline phase"), in which, among other things, the patients' seizure frequency under their previous antiepileptic therapy was recorded. This was followed by an 11-week titration phase and then a 12-week maintenance phase. In both study phases, the included patients received perampanel in addition to their previous antiepileptic therapy. This was followed by either a 4-week follow-up period (without treatment with perampanel) or switch to a single-arm extension study. In the titration phase, the dose of perampanel was increased at weekly intervals from 2 mg/day up to 8 mg/day. In children whose basic therapy included an enzyme-inducing antiepileptic drug, the starting dose was 4 mg/day and was increased to 12 mg/day. The maximum daily dose could be exceeded (up to 12 mg/day or 16 mg/day if an enzyme-inducing antiepileptic drug was co-administered) if the child tolerated the drug and was deemed likely to benefit from further dose increase.

The titration carried out in the study did not comply with the specifications of the Summary of Product Characteristics (SPC) of perampanel [5] for several reasons. For example, the intake of enzyme-inducing antiepileptic drugs is to be taken into account in the titration steps; however, this is not done in terms of the amount of the daily dose, but of the interval between the titration steps (every 2 weeks instead of weekly). In children with enzyme-inducing antiepileptic drugs in the basic therapy, the starting and maximum doses recommended in the SPC were exceeded in the specifications of the study (4 and at most 16 mg instead of 2 and at most 12 mg). In addition, dosing in children should be weight-adapted according to fixed weight ranges (< 20 kg, 20 kg to < 30 kg and ≥ 30 kg), which was not implemented in the E2007-G000-311study.

During the course of the study, the patients continued their previous antiepileptic therapy. According to the inclusion criterion of the study, this therapy had to consist of 1 to 3 antiepileptic drugs. Patient-specific dose changes, the addition or the discontinuation of drugs were not permitted during the entire course of the study. Besides, the dosages of the previous antiepileptic therapy had to be stable for at least 4 weeks before the start of the baseline phase. In the case where a new antiepileptic regimen had been initiated before the start of the baseline phase, the mandatory period of stable dosing was extended to at least 8 weeks.

The primary objective of the study was the assessment of the safety and tolerability of perampanel; other objectives included the recording of seizure frequency.

Study E2007-G000-232

As the study described above, study E2007-G000-232 is a single-arm study in which perampanel was administered in addition to the existing basic therapy. The study included children aged 2 to < 12 years with diagnosed epilepsy regardless of the type of seizure. According to the inclusion criterion of the study, patients must have had at least one seizure during the 4 weeks before the start of the study despite their previous antiepileptic therapy. Of the 50 study participants, 31 had epilepsy with partial-onset seizures and were between 4 and < 12 years old.

After a 2-week baseline phase in which, among other things, seizure frequency was recorded, the treatment phase of the study started. In this phase, the included patients received perampanel in addition to their previous antiepileptic therapy. The treatment phase consisted of a 7-week titration phase and a 4-week maintenance phase. This was followed by either a 4-week follow-up period or switch to a single-arm extension study. In the titration phase, the dose of perampanel, starting with a daily dose of 0.015 mg/kg, was increased at weekly intervals to a maximum daily dose of 0.18 mg/kg or until the maximum patient-specific tolerated dose was reached. The dosage was calculated using the dosage for adults with a body weight of 70 kg as a reference. The maximum daily dose allowed was 12 mg. The titration of perampanel did not comply with the specifications of the SPC for several reasons. In deviation from the weight ranges already mentioned above, the titration in the E2007-G000-232 study was per kg body weight. The starting dose of 0.015 mg/kg was notably lower in the study than the starting dose

of 1 mg/day or 2 mg for a body weight of 30 kg or more specified in the SPC. Furthermore, according to the SPC, the dose increase should only take place at weekly intervals if enzyme-inducing antiepileptic drugs are taken at the same time. This was not taken into account in the dosing specifications of the study.

During the course of the study, the patients continued to receive their previous antiepileptic therapy, which, according to the inclusion criteria, had to consist of 1 to 3 antiepileptic drugs. Patient-specific dose changes, the addition or the discontinuation of drugs were not permitted during the entire study. Besides, treatment with the previous antiepileptic therapy had to be ongoing for at least 2 months at the start of the baseline phase with the (respective) dose being stable for at least 4 weeks.

The primary objective of the study was to evaluate the pharmacokinetics of perampanel as an oral suspension; other objectives included the recording of seizure frequency and adverse events.

The company presented no comparison with the appropriate comparator therapy

The evidence presented by the company (only single-arm studies) is unsuitable for the assessment of the added benefit of perampanel in comparison with the ACT. The company did not conduct an information retrieval for the ACT and also did not present any data describing the efficacy or tolerability of the ACT. As described above, it justified its approach with the lack of validity of a comparison of individual arms from different studies. However, comparative data would be necessary to assess the added benefit of perampanel.

The company derived an added benefit of perampanel on the basis of the 2 single-arm studies E2007-G000-311 and E2007-G000-232 by considering results at the end of the study compared with the baseline phase. The company based its argument on an improvement in seizures, improvement in disease-related symptoms and the absence of impairment of age-appropriate development from perampanel. With regard to side effects, the company did not draw a comparison with the baseline phase, but described that the events that occurred during treatment with perampanel corresponded to the expected adverse events known for the drug perampanel. Irrespective of the fact that the company, as described above, did not present a comparison with the ACT, the conclusions drawn by the company are not appropriate also because patient-specific adjustments of the previous antiepileptic therapy were permitted neither in the baseline phase nor in the entire course of the study. Thus, the ACT in the sense of a patient-specific adjunctive treatment taking into account the drugs specified by the G-BA is also not represented in the baseline phase of the studies. Furthermore, there are also no indications that, at the time of enrolment, patients included in the study would no longer have been candidates for treatment optimization by means of an individual adjunctive treatment with one of the possible comparator therapies, e.g. due to pharmacoresistance or intolerance. Thus, about half of the children (55% in E2007-G000-311 and 56% in E2007-G000-232) were treated with 2 antiepileptic drugs at baseline and only about a quarter received the maximum possible number of 3 concomitant antiepileptic drugs. No information is available on previous therapies (before study inclusion).

Irrespective of the aspects mentioned, there are also no indications that there could be effects of perampanel in the single-arm studies of a magnitude that could not be explained by systematic bias alone. For the E2007-G000-232 study, there is the additional fact that the maintenance phase of only 4 weeks is clearly too short. In the present therapeutic indication, a minimum duration of the maintenance phase of 12 weeks is assumed for the benefit assessment in accordance with the European Medicines Agency (EMA) guidelines on clinical studies in epilepsy [6].

The points of criticism mentioned in the present assessment (lack of comparison with the ACT, lack of implementation of the requirements for patient-specific adjunctive treatment and too short duration of the maintenance phase) were already addressed in previous dossier assessments in the therapeutic indication [7,8].

2.4 Results on added benefit

No suitable data are available to assess the added benefit of perampanel compared with the ACT in children from 4 to < 12 years of age with epilepsy with or without secondarily generalized seizures. Hence, there is no hint of an added benefit of perampanel in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of perampanel in comparison with the ACT is summarized in Table 5.

Table 5: Perampanel – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adjunctive treatment of partial-onset seizures with or without secondarily generalized seizures in children from 4 to < 12 years of age with epilepsy	Patient-specific antiepileptic adjunctive treatment, if medically indicated and if no pharmacoresistance (in the sense of an insufficient response), intolerance or contraindication is known, taking into account the following drugs: eslicarbazepine[b], gabapentin[c], lacosamide, lamotrigine, levetiracetam, oxcarbazepine[c], topiramate, valproic acid[d], zonisamide[c], brivaracetam	Added benefit not proven
a. Presentation of the ACT specified by the G-BA. b. For children over 6 years of age. c. For children from 6 years of age. d. Valproic acid is not a regular option for adjunctive treatment in children and adolescents aged 4 to 11 years due to potential liver damage and teratogenicity. However, adjunctive treatment with valproic acid may be a possible option within the framework of an individual therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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