

IQWiG Reports – Commission No. A17-61

Perampanel (epilepsy) –

Benefit assessment according to §35a Social Code Book V¹

Extract

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
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. Assessment was based on a dossier of the company. The dossier was sent to IQWiG on 30 November 2017.

Research question

The aim of the present report was to assess the added benefit of perampanel as adjunctive therapy for primary generalized tonic-clonic seizures in adults and adolescents aged 12 years and older with idiopathic generalized epilepsy in comparison with the appropriate comparator therapy (ACT).

The ACT specified by the G-BA is shown in Table 2.

Table 2: Research question of the benefit assessment of perampanel

Research question	Subindication	ACT ^a
1	Adjunctive therapy for primary generalized tonic-clonic seizures in adults and adolescents aged 12 years and older with idiopathic generalized epilepsy	<p>an individual antiepileptic adjunctive therapy, if medically indicated and if no pharmacoresistance/intolerance and contraindications are known yet, with one of the following drugs: lamotrigine, levetiracetam, valproic acid^b, topiramate, clobazam</p> <p>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 AEs.</p> <p>The respective approval of the drugs is to be considered.</p>
<p>a: Presentation of the respective ACT specified by the G-BA. b: Due to its teratogenic potential, valproic acid is no regular option for the adjunctive therapy of primary generalized tonic-clonic seizures in female adolescents aged 12 years and older and women of childbearing age. However, adjunctive treatment with valproic acid can present a possible option within the framework of an individual therapy. ACT: appropriate comparator therapy; AEs: adverse events; G-BA: Federal Joint Committee</p>		

Deviation from the ACT

The company chose an individual antiepileptic treatment of physician's choice as comparator therapy without specifying it in detail in the first instance. Therewith, the company deviated from the ACT specified by the G-BA, which recommended individual antiepileptic adjunctive treatment of physician's choice and indicated lamotrigine, levetiracetam, valproic acid, topiramate or clobazam as drugs that are an option for adjunctive treatment in the therapeutic indication. There was no consultation prior to the procedure.

The company aimed to prove the added benefit of perampanel as adjunctive treatment to ongoing basic therapy in comparison with an ongoing individual basic therapy consisting of up to 3 antiepileptic drugs.

The company explained that the added benefit of a new adjunctive therapy in the present therapeutic indication in comparison with individual antiepileptic treatment specified by the attending physician was to be proved. A comparator therapy restricted to one or several specific drugs would not be expedient, because this way of proceeding might only insufficiently reflect the highly individual decisions for the therapeutic approaches in these patients. Therefore, the company deemed the consideration of the additional effect of perampanel in addition to an ongoing individual basic therapy as suitable to prove an added benefit.

In the company's opinion, perampanel is used only at a late point of the treatment cascade, chiefly in patients with refractory epilepsy. Most of the other drugs with comparable therapeutic indications in patients with many years of medical history had usually been used without success at this point in time.

The approach of the company was not followed. Individual optimization of the drug therapy is also possible and useful in patients who are not seizure-free despite their current antiepileptic treatment. This can be done, for example, by switching to another antiepileptic treatment or by adding another antiepileptic drug to the existing treatment. Individual treatment optimization is also possible, since the G-BA indicated several drugs as possible adjunctive treatment. Moreover, it was not clear from the information provided by the company that further treatment optimization with 1 of the 5 drugs specified by the G-BA was no longer an option for the patients of the study used by the company.

The benefit assessment was therefore conducted in comparison with the ACT specified by the G-BA, and for all patients in the therapeutic indication for whom perampanel is approved. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 12 weeks were relevant for the derivation of the added benefit.

Results

The company presented no relevant data for the assessment of the added benefit of perampanel in comparison with the ACT.

The company included the RCT 332 E2007-G000-332, in short 332, in its assessment. 164 patients aged 12 years and older with idiopathic generalized epilepsy and primary generalized tonic-clonic seizures were included in this study. Prior to randomization, the patients were not seizure-free despite taking up to 3 different antiepileptic drugs; reportedly, they had at least 3 primary generalized tonic-clonic seizures during the 8 weeks before randomization. They were administered either perampanel or placebo as study medication in addition to their ongoing antiepileptic basic therapy. Thereby, perampanel was administered as maintenance dose of

8 mg/day or, in case 8 mg were not tolerated, in lower doses. The maintenance phase was preceded by a 4-week titration phase up to an individual maximum dose of 8 mg/day, whereby the initial dose was 2 mg/day. In case of insufficient seizure control during the maintenance phase, the perampanel dose could be increased once by 2 mg, unless the maximum dose had been achieved during the titration phase. In case of intolerated side effects, the dose could be reduced once by 2 mg.

During the course of the study, the patients in both study arms received their ongoing antiepileptic treatment. Dose adjustment, addition of further drugs or discontinuation of drugs was not allowed during the study and at least 30 days before the start of the study. Administration of other antiepileptic drugs was only allowed as rescue medication.

No implementation of the ACT

Patients in the comparator group of the study received exclusively placebo in addition to their existing antiepileptic basic therapy, which was not allowed to be adjusted before and during the study.

However, there were no indications that the patients included were no longer eligible for individual add-on therapy with one of the 5 possible comparator therapies for treatment optimization. Hence, the ACT specified by the G-BA was not implemented in the study presented by the company.

The study 332 was therefore unsuitable for the assessment of the added benefit of perampanel in comparison with the ACT specified by the G-BA.

Conduction of a study for the derivation of an added benefit was possible

Study 332 ended in May 2014, and thus more than 3 years before the present dossier was submitted. Given the G-BA's previous decision on perampanel of 2014, it would have been absolutely possible to conduct a study with a maintenance phase of at least 12 weeks within this period, permitting a comparison of perampanel with an individual add-on therapy. In such study, the add-on therapy each patient would receive in case of allocation to the comparator group would be determined by the attending physician prior to randomization. After randomization the patients are treated in accordance with their group allocation:

- intervention group: add-on therapy with perampanel;
- Comparator group: individual antiepileptic add-on therapy with one of the drugs levetiracetam, lamotrigine, topiramate, valproic acid or clobazam according to the physician's choice (as specified before randomization).

Probability and extent of added benefit, patient groups with therapeutically important added benefit³

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

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

Table 3: Perampanel – probability and extent of added benefit

Subindication	ACT ^a	Probability and extent of added benefit
Adjunctive therapy for primary generalized tonic-clonic seizures in adults and adolescents aged 12 years and older with idiopathic generalized epilepsy	<p>an individual antiepileptic adjunctive therapy, if medically indicated and if no pharmacoresistance/intolerance and contraindications are known yet, with one of the following drugs: lamotrigine, levetiracetam, valproic acid^b, topiramate, clobazam</p> <p>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.</p> <p>The respective approval of the drugs is to be considered.</p>	Added benefit not proven
<p>a: Presentation of the respective ACT specified by the G-BA. b: Due to its teratogenic potential, valproic acid is no regular option for the adjunctive therapy of primary generalized tonic-clonic seizures in female adolescents aged 12 years and older and women of childbearing age. However, adjunctive treatment with valproic acid can present a possible option within the framework of an individual therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee</p>		

The G-BA decides on the added benefit.

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].

2.2 Research question

The aim of the present report was to assess the added benefit of perampanel as adjunctive therapy for primary generalized tonic-clonic seizures in adults and adolescents aged 12 years and older with idiopathic generalized epilepsy in comparison with the ACT.

The ACT specified by the G-BA is shown in Table 4.

Table 4: Research question of the benefit assessment of perampanel

Research question	Subindication	ACT ^a
1	Adjunctive therapy for primary generalized tonic-clonic seizures in adults and adolescents aged 12 years and older with idiopathic generalized epilepsy	<p>an individual antiepileptic adjunctive therapy, if medically indicated and if no pharmacoresistance/intolerance and contraindications are known yet, with one of the following drugs: lamotrigine, levetiracetam, valproic acid^b, topiramate, clobazam</p> <p>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.</p> <p>The respective approval of the drugs is to be considered.</p>
<p>a: Presentation of the respective ACT specified by the G-BA. b: Due to its teratogenic potential, valproic acid is no regular option for the adjunctive therapy of primary generalized tonic-clonic seizures in female adolescents aged 12 years and older and women of childbearing age. However, adjunctive treatment with valproic acid can present a possible option within the framework of an individual therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee</p>		

The company chose an individual antiepileptic treatment of physician's choice as comparator therapy without specifying it in detail in the first instance. Therewith, the company deviated from the ACT specified by the G-BA, which recommended individual antiepileptic adjunctive treatment of physician's choice and indicated lamotrigine, levetiracetam, valproic acid, topiramate or clobazam as drugs that are an option for adjunctive treatment in the therapeutic indication. There was no consultation prior to the procedure.

The company aimed to prove the added benefit of perampanel as adjunctive treatment to ongoing basic therapy in comparison with an ongoing individual basic therapy consisting of up to 3 antiepileptic drugs. This approach was not followed. The reasons are described below:

In accordance with the approval, perampanel is used as add-on therapy [3], i.e., when patients are not seizure-free despite their current treatment and optimization of ongoing therapy is considered necessary.

The company explained that the added benefit of a new adjunctive therapy in the present therapeutic indication in comparison with individual antiepileptic treatment specified by the

attending physician was to be proved. A comparator therapy restricted to one or several specific drugs would not be expedient, because this way of proceeding might only insufficiently reflect the highly individual decisions for the therapeutic approaches in these patients. Therefore, the company deemed the consideration of the additional effect of perampanel in addition to an ongoing individual basic therapy as suitable to prove an added benefit.

However, this approach does not represent the comparison requested by the G-BA. The G-BA described that “treatment [...] is to be chosen according to the physician’s choice depending on the basic and prior therapy/therapies under consideration of the reason for treatment switching” (see Table 4), i.e. ongoing treatment had to be adjusted using 1 of the 5 specified drugs. Individual treatment optimization is also possible, since the G-BA indicated several drugs as possible adjunctive treatment. The company’s argumentation does not provide information on the usefulness of the unchanged continuation of the ongoing basic therapy in the sense of the ACT. In its decision on an earlier benefit assessment of perampanel, the G-BA already explained that comparison of an adjunctive treatment (as add-on to ongoing basic therapy) with an ongoing, obviously inadequate, but unchanged basic therapy alone is insufficient for the derivation of an added benefit. Adjustment of the ongoing treatment is required instead [4].

In the company’s opinion, perampanel is used only at a late point of the treatment cascade in practice, chiefly in patients with refractory epilepsy. Most of the other drugs with comparable therapeutic indications in patients with many years of medical history had usually been used at this point in time.

Approval of perampanel does not support this argumentation. According to the current SPC, perampanel is approved as adjunctive treatment for patients with primary generalized tonic-clonic seizures in adults and adolescents aged 12 years and older with idiopathic generalized epilepsy. Usage of the drug is not restricted to a population with long-standing medical histories or for whom all other therapy options have been exhausted [3].

Moreover, the company argued that due to the SPCs mandatory for Germany and to national as well as international guidelines only the drugs levetiracetam, lamotrigine and topiramate had a therapeutic indication sufficiently similar to that of perampanel. Sufficient clinical evidence from studies that are comparable with regard to content and acceptable with regard to quality was only available for these 3 drugs. Moreover, they were normally used much earlier in the therapy and were thus no alternative drugs in the sense of an ACT. Usually, they had rather been part of a basic therapy or had already been stopped due to lacking success. In this respect, the company referred to the basic therapy in the study it included.

The company’s arguments do not hold true. In addition to the 3 drugs mentioned by the company, the G-BA also specified clobazam and valproic acid as possible ACT. Both drugs have been approved without restriction in the present therapeutic indication [5,6]. The company did not prove that only insufficient evidence was available for other drugs than levetiracetam, lamotrigine and topiramate, e.g. with a systematic search.

In summary, the comparator therapy chosen by the company was unsuitable to demonstrate an added benefit of perampanel as adjunctive therapy for primary generalized tonic-clonic seizures in adults and adolescents aged 12 years and older with idiopathic generalized epilepsy. The benefit assessment was therefore conducted in comparison with the ACT specified by the G-BA, and for all patients in the therapeutic indication for whom perampanel is approved.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 12 weeks were relevant for the derivation of the added benefit. This concurs with the company's inclusion criteria.

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 (status: 5 October 2017)
- bibliographical literature search on perampanel (last search on 29 September 2017)
- search in trial registries for studies on perampanel (last search on 29 September 2017)

To check the completeness of the study pool:

- search in trial registries for studies on perampanel (last search on 14 December 2017)

No relevant study was identified from the check.

The company included study 332 E2007-G000-332, in short 332, in its assessment [7]. This study was unsuitable for the assessment of the added benefit of perampanel. This is justified in the following sections.

2.3.2 Description of the study included by the company

Study design

Study 332 is a randomized controlled trial (RCT) on the comparison of perampanel with placebo, each in addition to ongoing antiepileptic treatment. 164 patients aged 12 years and older with idiopathic generalized epilepsy and primary generalized tonic-clonic seizures were included in this study. Deviating from this, persons under 18 years of age were not included in Germany. Prior to randomization, the patients were not seizure-free despite taking up to 3 different antiepileptic drugs; reportedly, they had at least 3 primary generalized tonic-clonic seizures during the 8 weeks before randomization. Perampanel was administered as maintenance dose of 8 mg/day or, in case 8 mg were not tolerated, in lower doses. The maintenance dose was administered over a period of 13 weeks. This maintenance phase was

preceded by a 4-week titration phase up to an individual maximum dose of 8 mg/day, whereby the initial dose was 2 mg/day. In case of insufficient seizure control during the maintenance phase, the perampanel dose could be increased once by 2 mg, unless the maximum dose had been achieved during the titration phase. In case of intolerated side effects, the dose could be reduced once by 2 mg.

During the course of the study, the patients in both study arms received their ongoing antiepileptic treatment. Dose adjustment, addition of further drugs or discontinuation of drugs was not allowed during the study and at least 30 days before the start of the study. Administration of other antiepileptic drugs was only allowed as rescue medication.

Primary outcomes of the study were the percentage of patients who reached a reduction in primary generalized tonic-clonic seizure frequency per 28 days by at least 50% compared with the start of the study, and the percentage change in primary generalized tonic-clonic seizure frequency per 28 days compared with the baseline value. Further patient-relevant outcomes were, for instance, the proportion of seizure-free patients, the percentage change in seizure frequency during the maintenance phase, health-related quality of life and side effects of treatment.

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:

- lamotrigine, levetiracetam, valproic acid, topiramate, clobazam.

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 (AEs). The respective approval of the products is to be considered.

Hence, a possible direct comparison of perampanel versus an individual antiepileptic add-on therapy (chosen from the 5 drugs of the ACT) would be as follows:

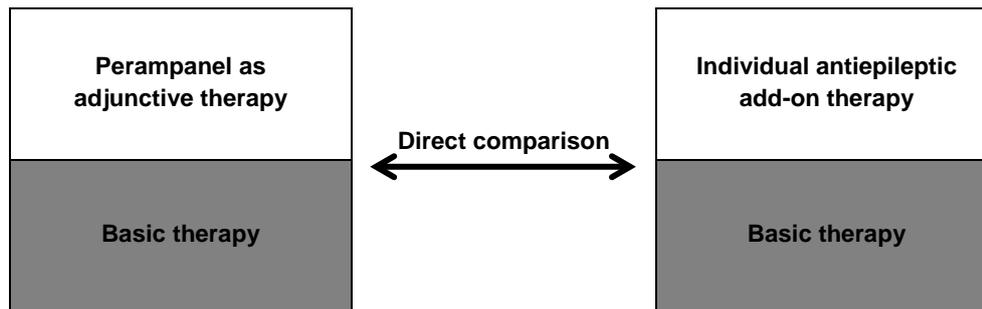


Figure 1: Possible direct comparison of perampanel with individual antiepileptic add-on therapy

Deviating from this, the company included a study for the assessment of the added benefit that compared perampanel as adjunctive treatment to ongoing antiepileptic treatment with ongoing antiepileptic treatment that could not be optimized for the individual patient. Consequentially, only placebo was administered as control. This corresponds to the comparison shown in Figure 2.

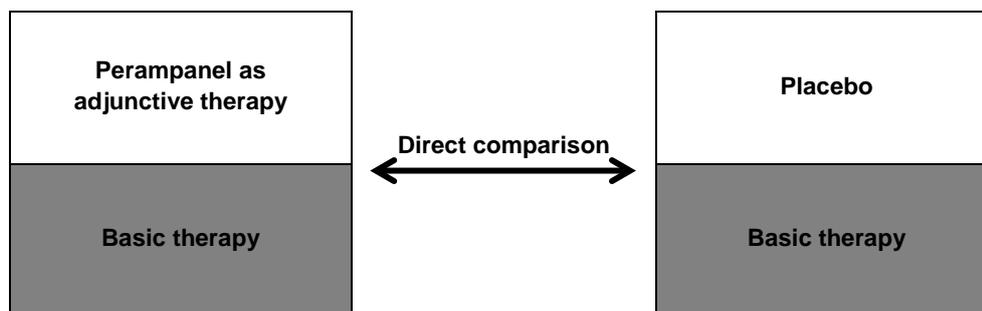


Figure 2: Direct comparison in study 332 used by the company

In the previous assessment of perampanel, the G-BA already pointed out that individual optimization of the drug therapy was possible and useful also in patients who are not seizure-free despite their current antiepileptic treatment [4]. This can be done, for example, by switching to another antiepileptic treatment or by adding another antiepileptic drug to the existing treatment. According to the German Society of Neurology (Deutsche Gesellschaft für Neurologie, DGN) 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 pharmacoresistant patients can also become seizure-free by using further drugs [4,8]. There was no such choice in study 332. Patients in the comparator group received exclusively placebo in addition to their ongoing antiepileptic basic therapy, which was not allowed to be adjusted before and during the study.

However, there were no indications that the patients included were no longer eligible for individual add-on therapy with one of the 5 possible comparator therapies. The dossier of the company does not include documentation of the pharmacoresistance, e.g. according to the International League Against Epilepsy (ILAE) as noted by the G-BA in 2014 [4].

From the information on the antiepileptic treatment provided by the company it can be learned that at the start of the study around one third of the study participants received only one antiepileptic drug in their basic therapy, roughly one half of them received 2 antiepileptic drugs, and 20% received the permitted maximum number of 3 products. At the start of the study, the drugs of the ACT were used at different frequencies: around 39% of the patients (both study arms) received lamotrigine, 37% (perampanel group) or 26% (comparator group) received levetiracetam, valproic acid was administered to 34% (both study arms), 22% (perampanel group) or 9% (comparator group) received topiramate and 4% of the patients received clobazam (both study arms). However, in module 4 B of its dossier, the company presented no information on antiepileptic treatments the patients had received before they were included in the study. Average time since first diagnosis of epilepsy amounted to 16 (perampanel group) or 19 years (comparator group) in the treatment arms, with standard deviations of 11 or 13 years. Therefore, some patients must be assumed to have extensive medication histories. However, it was not sufficiently clear from the data in the company's dossier whether the drugs of the ACT were actually no treatment option for a decisive proportion of the patients, for instance, because they had already received and discontinued these drugs before the start of the study. Nor is it clear how many patients received none of the drugs specified by the G-BA at the start of the study.

At least, the information on antiepileptic treatments at the start of the study do not indicate that these products could not be used in the majority of the study participants. This might be the case when a decisive proportion of patients had already received drugs of the ACT or were ineligible for treatment with any of the drugs for other reasons. Such information was not available in the company's dossier, however.

In summary, study 332 was unsuitable for the assessment of the added benefit of perampanel in comparison with the ACT specified by the G-BA.

Possible design of a direct comparative study versus the ACT

An RCT involving appropriate implementation of the ACT is feasible. In such a study, the add-on therapy each patient would receive in case of allocation to the comparator group would be determined by the attending physician prior to randomization. Criteria such as prior therapies, ongoing basic treatment, pharmacoresistance, tolerability and contraindications can be considered in this step. After randomization the patients are treated in accordance with their group allocation:

- intervention group: add-on therapy with perampanel;
- Comparator group: individual antiepileptic add-on therapy with one of the drugs levetiracetam, lamotrigine, topiramate, valproic acid or clobazam according to the physician's choice (as specified before randomization).

For further information see benefit assessment A14-16 on perampanel of 13 August 2014 [9].

Study 332 ended in May 2014, and thus more than 3 years before the present dossier was submitted. Given the G-BA's previous decision on perampanel [4], it would have been absolutely possible to conduct a study with the design outlined in Section 2.3 and a maintenance phase of at least 12 weeks.

Summary

The placebo-controlled study 332 presented by the company is unsuitable to prove an added benefit in comparison with the ACT. The study design did not allow adjustment of the therapy in the comparator arm, therefore perampanel as adjunctive treatment to antiepileptic basic treatment was compared with ongoing antiepileptic treatment, only controlled by placebo. This does not concur with the ACT specified by the G-BA. A study that is relevant for the present benefit assessment is basically possible. Individual optimization of the ongoing antiepileptic treatment using lamotrigine, levetiracetam, topiramate, valproic acid or clobazam would have to take place in the comparator group of such study.

2.4 Results on added benefit

The company presented no relevant data on the assessment of the added benefit of perampanel as adjunctive therapy for primary generalized tonic-clonic seizures in adults and adolescents aged 12 years and older with idiopathic generalized epilepsy are not available. Hence, there was no hint of an added benefit perampanel in comparison with the ACT. An added benefit is therefore not proven.

This deviates from the assessment of the company, which derived an added benefit from the study it included.

2.5 Probability and extent of added benefit

Relevant data on the assessment of the added benefit of perampanel as adjunctive therapy for primary generalized tonic-clonic seizures in adults and adolescents aged 12 years and older with idiopathic generalized epilepsy are not available.

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

Subindication	ACT ^a	Probability and extent of added benefit
Adjunctive therapy for primary generalized tonic-clonic seizures in adults and adolescents aged 12 years and older with idiopathic generalized epilepsy	<p>An individual antiepileptic adjunctive therapy, if medically indicated and if no pharmacoresistance/intolerance and contraindications are known yet, with one of the following drugs: lamotrigine, levetiracetam, valproic acid^b, topiramate, clobazam</p> <p>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.</p> <p>The respective approval of the drugs is to be considered.</p>	Added benefit not proven
<p>a: Presentation of the respective ACT specified by the G-BA. b: Due to its teratogenic potential, valproic acid is no regular option for the adjunctive therapy of primary generalized tonic-clonic seizures in female adolescents aged 12 years and older and women of childbearing age. However, adjunctive treatment with valproic acid can present a possible option within the framework of an individual therapy. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee</p>		

The assessment described above deviates from that of the company, which derived an indication of at least considerable added benefit in its dossier.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

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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