Cannabidiol (tuberous sclerosis)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Part I: Benefit assessment

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

I 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)
SPC	Summary of Product Characteristics

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug cannabidiol. 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 4 December 2023.

Research question

The aim of this report is to assess the added benefit of cannabidiol as an adjunctive therapy compared with an individualized adjunctive antiepileptic therapy as appropriate comparator therapy (ACT) in patients aged 2 years and older with seizures associated with tuberous sclerosis.

The research question presented in Table 2 is derived from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of cannabidiol

Therapeutic indication	**ACT**[a]
Adjunctive therapy in patients aged 2 years and older with seizures associated with tuberous sclerosis[b]	An individualized adjunctive antiepileptic therapy[c] taking into account the type of seizures[d] occurring, the basic and previous therapy (therapies) and any associated side effects choosing from ▪ brivaracetam, carbamazepine, cenobamate, clonazepam[e], eslicarbazepine, everolimus, gabapentin, lacosamide, lamotrigine, levetiracetam, nitrazepam[e], oxcarbazepine, perampanel, pregabalin, topiramate, valproic acid[f], vigabatrin[e],zonisamide, glucocorticoids (prednisone or prednisolone)[e], tetracosactide (ACTH)[e]

a. Presented is the ACT specified by the G-BA.
b. It is assumed that for patients with tuberous sclerosis who are eligible for treatment with cannabidiol, epilepsy surgery is not indicated at the current time of treatment. The implementation of dietary measures can be considered as part of the treatment of the disease in question. Against this background, patients in both study arms should have the opportunity to take advantage of appropriate nutritional advice or to continue a diet already started before the start of the study during the study.
c. For the implementation of individualized therapy in a direct comparative study, according to the G-BA, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). When implementing the ACT in the context of a clinical study, it must be ensured that the patient-specific choice of the adjunctive antiepileptic treatment is described as specifically as possible by criteria (e.g. by documenting the respective previous therapies, the reasons for a treatment discontinuation or a treatment switch). Usually, combination therapies are used in this therapeutic indication. If monotherapy is indicated in the comparator arm, this must be justified in the dossier. The unchanged continuation of an inadequate therapy does not correspond to the implementation of the ACT if there is still the option of optimization. Simply adjusting the dosage of a previously stable inadequate antiepileptic therapy does not regularly correspond to the ACT.
d. The disease profile of tuberous sclerosis typically includes focal or secondary generalised seizures and infantile spasms. Drugs that are explicitly approved for the treatment of these seizure types or for epilepsy in general can therefore also be considered as part of the ACT, provided there are no contraindications for tuberous sclerosis. As the approved therapeutic indication for cannabidiol is very general and not explicitly aimed at a "last-line" therapeutic situation, it is assumed that antiepileptic drugs for the treatment of focal seizures, which guidelines only recommend for the last line of therapy, such as phenytoin and phenobarbital, are only used in individual cases in the present therapeutic indication.
e. Vigabatrin is particularly recommended for the treatment of infantile spasms, possibly in combination with glucocorticoids (prednisone or prednisolone) or tetracosactide (ACTH). The benzodiazepines clonazepam and nitrazepam are also approved for infantile spasms and may be used if there is an inadequate response to the drugs mentioned.
f. Due to its teratogenic potential, valproic acid is not a regular option for the adjunctive treatment of focal seizures in women of childbearing age. However, adjunctive treatment with valproic acid may be a possible option within the framework of an individualized therapy.

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

The company followed the G-BA's specification on the ACT. However, the company differs in part in the naming of individual drugs to be used under it. The company states that the majority of patients with tuberous sclerosis have a treatment-refractory course that does not

allow further individualized improvement with the existing seizure-suppressant drugs. Therefore, the company also considers placebo-controlled studies to be an adequate study design for representing the G-BA's ACT. The approach of the company is not appropriate. The benefit assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of the maintenance therapy of 12 weeks were used for deriving any added benefit.

Results

No relevant study was identified from the check of the completeness of the study pool. Deviating from this, the company identified the placebo-controlled RCT GWEP1521 and included it in its assessment. The study is a blinded RCT comparing cannabidiol with placebo, each in addition to the previous seizure-suppressant basic therapy. It included patients aged 1 to 65 years with a clinical diagnosis of tuberous sclerosis whose epilepsy was not fully controlled by the seizure-suppressant therapy available at the time of inclusion in the study. This study is not suitable for demonstrating an added benefit over the ACT. The study design did not allow therapy adjustment in the comparator arm at any time, so that cannabidiol as an adjunctive therapy to a seizure-suppressant basic therapy was only compared with an ongoing seizure-suppressant therapy. The implementation of an individualized therapy as ACT is therefore not given.

Results on added benefit

No suitable data are available for assessing the added benefit of cannabidiol as adjunctive treatment in comparison with the ACT in patients aged 2 years and older with seizures associated with tuberous sclerosis. There is no hint of an added benefit of cannabidiol in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 shows a summary of probability and extent of the added benefit of cannabidiol.

[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: Cannabidiol – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adjunctive therapy in patients 2 years of age and older with seizures associated with tuberous sclerosis[b]	An individualized adjunctive antiepileptic therapyc taking into account the type of seizures[d] occurring, the basic and previous therapy (therapies) and any associated side effects choosing from ▪ brivaracetam, carbamazepine, cenobamate, clonazepame, eslicarbazepine, everolimus, gabapentin, lacosamide, lamotrigine, levetiracetam, nitrazepame, oxcarbazepine, perampanel, pregabalin, topiramate, valproic acidf, vigabatrine,zonisamide, glucocorticoids (prednisone or prednisolone)[e], tetracosactide (ACTH)e	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that for patients with tuberous sclerosis who are eligible for treatment with cannabidiol, epilepsy surgery is not indicated at the current time of treatment. The implementation of dietary measures can be considered as part of the treatment of the disease in question. Against this background, patients in both study arms should have the opportunity to take advantage of appropriate nutritional advice or to continue a diet already started before the start of the study during the study.
c. For the implementation of individualized therapy in a direct comparative study, according to the G-BA, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). When implementing the ACT in the context of a clinical study, it must be ensured that the patient-specific choice of the adjunctive antiepileptic treatment is described as specifically as possible by criteria (e.g. by documenting the respective previous therapies, the reasons for a treatment discontinuation or a treatment switch). Usually, combination therapies are used in this therapeutic indication. If monotherapy is indicated in the comparator arm, this must be justified in the dossier. The unchanged continuation of an inadequate therapy does not correspond to the implementation of the ACT if there is still the option of optimization. Simply adjusting the dosage of a previously stable inadequate antiepileptic therapy does not regularly correspond to the ACT.
d. The disease profile of tuberous sclerosis typically includes focal or secondary generalised seizures and infantile spasms. Drugs that are explicitly approved for the treatment of these seizure types or for epilepsy in general can therefore also be considered as part of the ACT, provided there are no contraindications for tuberous sclerosis. As the approved therapeutic indication for cannabidiol is very general and not explicitly aimed at a "last-line" therapeutic situation, it is assumed that antiepileptic drugs for the treatment of focal seizures, which guidelines only recommend for the last line of therapy, such as phenytoin and phenobarbital, are only used in individual cases in the present therapeutic indication.
e. Vigabatrin is particularly recommended for the treatment of infantile spasms, possibly in combination with glucocorticoids (prednisone or prednisolone) or tetracosactide (ACTH). The benzodiazepines clonazepam and nitrazepam are also approved for infantile spasms and may be used if there is an inadequate response to the drugs mentioned.
f. Due to its teratogenic potential, valproic acid is not a regular option for the adjunctive treatment of focal seizures in women of childbearing age. However, adjunctive treatment with valproic acid may be a possible option within the framework of an individualized therapy.

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

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment departs from the results of the G-BA's assessment conducted as part of the extension of the therapeutic indication in 2021, where the G-BA had determined a non-quantifiable added benefit of cannabidiol. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

I 2 Research question

The aim of this report is to assess the added benefit of cannabidiol as an adjunctive therapy compared with an individualized antiepileptic therapy as ACT in patients aged 2 years and older with seizures associated with tuberous sclerosis.

The research question presented in Table 4 is derived from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of cannabidiol

Therapeutic indication	**ACT[a]**
Adjunctive therapy in patients 2 years of age and older with seizures associated with tuberous sclerosis[b]	An individualized adjunctive antiepileptic therapyc taking into account the type of seizures[d] occurring, the basic and previous therapy (therapies) and any associated side effects choosing from ▪ brivaracetam, carbamazepine, cenobamate, clonazepame, eslicarbazepine, everolimus, gabapentin, lacosamide, lamotrigine, levetiracetam, nitrazepame, oxcarbazepine, perampanel, pregabalin, topiramate, valproic acidf, vigabatrine,zonisamide, glucocorticoids (prednisone or prednisolone)[e], tetracosactide (ACTH)[e]

a. Presented is the ACT specified by the G-BA.
b. It is assumed that for patients with tuberous sclerosis who are eligible for treatment with cannabidiol, epilepsy surgery is not indicated at the current time of treatment. The implementation of dietary measures can be considered as part of the treatment of the disease in question. Against this background, patients in both study arms should have the opportunity to take advantage of appropriate nutritional advice or to continue a diet already started before the start of the study during the study.
c. For the implementation of individualized therapy in a direct comparative study, according to the G-BA, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). When implementing the ACT in the context of a clinical study, it must be ensured that the patient-specific choice of the adjunctive antiepileptic treatment is described as specifically as possible by criteria (e.g. by documenting the respective previous therapies, the reasons for a treatment discontinuation or a treatment switch). Usually, combination therapies are used in this therapeutic indication. If monotherapy is indicated in the comparator arm, this must be justified in the dossier. The unchanged continuation of an inadequate therapy does not correspond to the implementation of the ACT if there is still the option of optimization. Simply adjusting the dosage of a previously stable inadequate antiepileptic therapy does not regularly correspond to the ACT.
d. The disease profile of tuberous sclerosis typically includes focal or secondary generalised seizures and infantile spasms. Drugs that are explicitly approved for the treatment of these seizure types or for epilepsy in general can therefore also be considered as part of the ACT, provided there are no contraindications for tuberous sclerosis. As the approved therapeutic indication for cannabidiol is very general and not explicitly aimed at a "last-line" therapeutic situation, it is assumed that antiepileptic drugs for the treatment of focal seizures, which guidelines only recommend for the last line of therapy, such as phenytoin and phenobarbital, are only used in individual cases in the present therapeutic indication.
e. Vigabatrin is particularly recommended for the treatment of infantile spasms, possibly in combination with glucocorticoids (prednisone or prednisolone) or tetracosactide (ACTH). The benzodiazepines clonazepam and nitrazepam are also approved for infantile spasms and may be used if there is an inadequate response to the drugs mentioned.
f. Due to its teratogenic potential, valproic acid is not a regular option for the adjunctive treatment of focal seizures in women of childbearing age. However, adjunctive treatment with valproic acid may be a possible option within the framework of an individualized therapy.

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

The company followed the G-BA's specification on the ACT. However, the company differs in part in the naming of individual drugs to be used under it. The company states that the majority of patients with tuberous sclerosis have a treatment-refractory course that does not allow further individualized improvement with the existing seizure-suppressant drugs.

Therefore, the company also considers placebo-controlled studies to be an adequate study design for representing the G-BA's ACT. The approach of the company is not appropriate. The benefit assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment is 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 the maintenance therapy of 12 weeks were used for deriving any added benefit. This departs from the inclusion criteria used by the company, which stated a 12-week treatment duration. The company did not take into account that, according to the Summary of Product Characteristics (SPC) for cannabidiol, maintenance therapy can be started no earlier than 1 week after the start of treatment. This deviation has no consequences for the present benefit assessment, as no relevant study was identified (see Chapter I 3 below).

I 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 list on cannabidiol (status: 5 September 2023)
- bibliographical literature search on cannabidiol (last search on 5 September 2023)
- search in trial registries/trial results databases for studies on cannabidiol (last search on 5 September 2023)
- search on the G-BA website for cannabidiol (last search on 6 September 2023)

To check the completeness of the study pool:

- search in trial registries for studies on cannabidiol (last search on 20 December 2023); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check. Deviating from this, the company identified the RCT GWEP1521 [3] and included it in its assessment. The study GWEP1521 is described below and it is explained why it is not suitable for deriving an added benefit in the present therapeutic indication.

GWEP1521 study

The GWEP1521 study is a double-blind, placebo-controlled RCT. It included patients aged 1 to 65 years with tuberous sclerosis whose epilepsy was not fully controlled by the seizure-suppressant therapy available at the time of inclusion in the study. A total of 224 patients were included in the study and allocated in a 2:2:1:1 ratio to treatment with cannabidiol 25 mg/kg/day, cannabidiol 50 mg/kg/day or a respective placebo equivalent. The study comprised a 4-week baseline phase in which, among other things, the patients' seizure frequency was recorded. Only patients who had at least 8 seizures during this period, including at least 1 seizure in the last week of the baseline phase, were allowed to start the 16-week treatment phase. This comprised a 9-day (for cannabidiol 25 mg/kg/day) or a 29-day (for cannabidiol 50 mg/kg/day) titration phase for dose escalation and a subsequent maintenance phase with stable dosing of either cannabidiol 25 mg/kg/day or cannabidiol 50 mg/kg/day in the intervention arms or placebo equivalent in the respective comparator arms. The administration of cannabidiol deviated in part from the specification of the SPC (Jazz Pharmaceuticals, 2023 #25}. A dosage of cannabidiol 50 mg/kg/day is not intended according to the approval. In the study's intervention arm with cannabidiol 25 mg/kg/day, titration to the next dose level took place every 2 days; the SPC specifies a weekly rhythm. Moreover, a maintenance dose of 25 mg/kg/day was planned for all patients in this study arm. According

to the SPC, a dose increase beyond 10 mg/kg/day up to the recommended maximum dose of 25 mg/kg/day should be performed by balancing the individual benefit and risk and in compliance with the full monitoring plan. Following the treatment phase, patients could either continue treatment in an open extension phase, or the dosage was reduced over 10 days, followed by a 4-week follow-up.

The primary outcome of the study was the change in the frequency of seizures associated with tuberous sclerosis.

Seizure-suppressant basic therapy

According to the inclusion criteria, patients should have been taking 1 or more antiepileptic drugs at the time of inclusion in the study, the dose of which had to have been stable for at least 4 weeks before screening. Adjustment of non-drug therapies such as vagus nerve stimulation or a ketogenic diet was also not allowed in the same period before the screening. During the entire duration of the study, the dose of the seizure-suppressant drugs already started before inclusion in the study had to be kept stable. The start of new seizure-suppressant therapies (drugs, ketogenic diet or vagus nerve stimulation) was also prohibited. The use of rescue medication was permitted. According to the inclusion criteria of the studies, patients should have had at least 8 convulsive seizures during the baseline phase of 28 days despite their previous seizure-suppressant therapy, including at least 1 seizure in the last week of the baseline phase.

ACT not implemented

The G-BA defined an individualized adjunctive antiepileptic therapy for the present therapeutic indication, choosing from various drugs (see also Table 4). In doing so, the therapy should be based on the type of seizure occurring, the basic and previous therapy (therapies) and any associated side effects. In its notes, the G-BA also states, among other things, that the unchanged continuation of an inadequate therapy does not correspond to the implementation of the ACT if there is still the option of optimization.

The study presented by the company compares cannabidiol as an adjunctive treatment to an ongoing seizure-suppressant therapy with an ongoing seizure-suppressive therapy combined with placebo. The ongoing seizure-suppressant therapies were not allowed to be adjusted during the study period and no new seizure-suppressant therapy was allowed to be started, although according to the inclusion criteria the seizures in the study population were not fully controlled by the ongoing seizure-suppressant therapy. Overall, therefore, the therapy was not optimized at any time during the study, and an individualized therapy as an ACT was thus not implemented.

Deviating from this, the company argues that the G-BA's ACT was implemented in the GWEP1521 study, as the included patients were a pharmacoresistant population and a further

adjustment of the ongoing seizure-suppressant therapy had not been not possible. The company explained that the patients received a median of 4 prior and 3 concomitant seizure-suppressant drugs, which exceeds the value of at least 2 failed therapies, which according to Kwan 2010 is specified as the threshold value for treatment-refractory patients [4]. In addition, the company assumes that there was no promising option for the patients to switch therapy, as the previous seizure-suppressant therapy had to be kept stable for at least 4 weeks before screening. In Module 4 C, the company provides information on the most common previous and concomitant seizure-suppressant drugs of the included patients. However, there is no information as to why the drugs of the ACT were no longer a treatment option for the patients included in the studies. It cannot be inferred from the available data that the patients included were no longer eligible for individualized adjunctive seizure-suppressant therapy or that an option for optimization was no longer existing.

According to the S2k guideline “First epileptic seizure and epilepsies in adulthood”, the goal of pharmacotherapy for epilepsies is seizure freedom or the best possible seizure control and no or at most minimal adverse effects of the substances used [5]. The guideline also states that even in cases of pharmacoresistance, the aim is to minimize the frequency of seizures while ensuring the best possible tolerability of the medication. In individual cases, pharmacoresistant patients can even become seizures-free. There is also a national interdisciplinary consensus that, given the large number of seizure-suppressant drugs available, there are only a few therapeutic situations in which optimization of therapy is not an option [6].

Conclusion

The placebo-controlled study GWEP1521 presented by the company is unsuitable to prove an added benefit in comparison with the ACT. The study design did not allow therapy adjustment in the comparator arm at any time, so that cannabidiol as an adjunctive therapy to a seizure-suppressant basic therapy was only compared with an ongoing seizure-suppressant therapy. The implementation of an individualized therapy as ACT is therefore not given.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of cannabidiol as adjunctive treatment in comparison with the ACT in patients aged 2 years and older with seizures associated with tuberous sclerosis. There is no hint of an added benefit of cannabidiol in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of cannabidiol as an adjunctive treatment in comparison with the ACT is summarized in Table 5.

Table 5: Cannabidiol – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adjunctive therapy in patients 2 years of age and older with seizures associated with tuberous sclerosis[b]	An individualized adjunctive antiepileptic therapyc taking into account the type of seizuresd occurring, the basic and previous therapy (therapies) and any associated side effects choosing from ▪ brivaracetam, carbamazepine, cenobamate, clonazepame, eslicarbazepine, everolimus, gabapentin, lacosamide, lamotrigine, levetiracetam, nitrazepame, oxcarbazepine, perampanel, pregabalin, topiramate, valproic acidf, vigabatrine,zonisamide, glucocorticoids (prednisone or prednisolone)[e], tetracosactide (ACTH)[e]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that for patients with tuberous sclerosis who are eligible for treatment with cannabidiol, epilepsy surgery is not indicated at the current time of treatment. The implementation of dietary measures can be considered as part of the treatment of the disease in question. Against this background, patients in both study arms should have the opportunity to take advantage of appropriate nutritional advice or to continue a diet already started before the start of the study during the study.
c. For the implementation of individualized therapy in a direct comparative study, according to the G-BA, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria (multicomparator study). A rationale must be provided for the choice and any limitation of treatment options. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). When implementing the ACT in the context of a clinical study, it must be ensured that the patient-specific choice of the adjunctive antiepileptic treatment is described as specifically as possible by criteria (e.g. by documenting the respective previous therapies, the reasons for a treatment discontinuation or a treatment switch). Usually, combination therapies are used in this therapeutic indication. If monotherapy is indicated in the comparator arm, this must be justified in the dossier. The unchanged continuation of an inadequate therapy does not correspond to the implementation of the ACT if there is still the option of optimization. Simply adjusting the dosage of a previously stable inadequate antiepileptic therapy does not regularly correspond to the ACT.
d. The disease profile of tuberous sclerosis typically includes focal or secondary generalised seizures and infantile spasms. Drugs that are explicitly approved for the treatment of these seizure types or for epilepsy in general can therefore also be considered as part of the ACT, provided there are no contraindications for tuberous sclerosis. As the approved therapeutic indication for cannabidiol is very general and not explicitly aimed at a "last-line" therapeutic situation, it is assumed that antiepileptic drugs for the treatment of focal seizures, which guidelines only recommend for the last line of therapy, such as phenytoin and phenobarbital, are only used in individual cases in the present therapeutic indication.
e. Vigabatrin is particularly recommended for the treatment of infantile spasms, possibly in combination with glucocorticoids (prednisone or prednisolone) or tetracosactide (ACTH). The benzodiazepines clonazepam and nitrazepam are also approved for infantile spasms and may be used if there is an inadequate response to the drugs mentioned.
f. Due to its teratogenic potential, valproic acid is not a regular option for the adjunctive treatment of focal seizures in women of childbearing age. However, adjunctive treatment with valproic acid may be a possible option within the framework of an individualized therapy.

ACT: appropriate comparator therapy; ACTH: adrenocorticotropic hormone; 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 on the basis of the data presented by it.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment departs from the results of the G-BA's assessment conducted as part of the extension of the therapeutic indication in 2021, where the G-BA had determined a non-quantifiable added benefit of cannabidiol. However, in this assessment, the added benefit had been regarded as proven by the approval irrespective of the underlying data because of the special situation for orphan drugs.

I 6 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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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-121.html.