Cannabidiol
(Lennox-Gastaut syndrome)

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

EXTRACT

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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.

Patient and family involvement

No patients or families were involved in the present dossier assessment.

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Keywords

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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)

I 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 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 in combination with clobazam (hereinafter referred to as cannabidiol + clobazam) as an adjunctive therapy compared with an individualized adjunctive therapy as appropriate comparator therapy (ACT) in patients aged 2 years and older with seizures associated with Lennox-Gastaut syndrome.

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

Table 2: Research question for the benefit assessment of cannabidiol + clobazam

Therapeutic indication	**ACT**[a]
Adjunctive therapy in patients aged 2 years and older with seizures associated with Lennox-Gastaut syndrome[b]	Individualized adjunctive antiepileptic therapy[c, d], if medically indicated and if no pharmacoresistance (in the sense of an inadequate response), intolerance or contraindication is known, choosing[e] from: ▪ clonazepam, rufinamide, topiramate, lamotrigine, felbamate, vigabatrin, clobazam, brivaracetam, eslicarbazepine, gabapentin, lacosamide, levetiracetam, oxcarbazepine, perampanel, pregabalin, valproic acide, zonisamide, primidone, phenytoin, phenobarbital, ethosuximide, mesuximide, cenobamate, bromide taking into account the types of seizures occurring, the basic and previous therapy (therapies) and any associated side effects

a. Presented is the ACT specified by the G-BA.
b. According to expert opinion, a ketogenic diet can also 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 ketogenic 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 the present 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. In addition to the drug cannabidiol, the drugs clonazepam, rufinamide, topiramate, lamotrigine, felbamate as well as fenfluramine are specifically approved for the therapeutic indication Lennox-Gastaut syndrome. Based on the generally recognized state of medical knowledge, fenfluramine is not determined as an ACT in the context of individualized adjunctive antiepileptic therapy. The disease profile of Lennox-Gastaut syndrome typically includes a variety of seizure types (including tonic, tonic-clonic, myoclonic and atonic seizures). Drugs that are approved for the various forms of seizures or for the treatment of epileptic seizures in general can therefore also be considered as part of the ACT, provided there is no contraindication for Lennox-Gastaut syndrome.
e. 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; G-BA: Federal Joint Committee

At first, the company followed the G-BA's specification on the ACT. In the following, however, it explains that a treatment-refractory course of the disease is typical for patients with Lennox-Gastaut syndrome, which does not allow further patient-specific 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 studies GWEP1414 und GWEP1423 and included them in its assessment. Both studies are blinded RCTs comparing cannabidiol with placebo, each in addition to the previous seizure-suppressant basic therapy. The studies included patients aged 2 to 55 years with a clinical diagnosis of Lennox-Gastaut syndrome whose seizures could not be fully controlled with their ongoing seizure-suppressant medication. These studies are 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 + clobazam as adjunctive therapy in comparison with the ACT in patients aged 2 years and older with seizures associated with Lennox-Gastaut syndrome. There is no hint of an added benefit of cannabidiol + clobazam 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 + clobazam.

[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 + clobazam – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adjunctive therapy in patients aged 2 years and older with seizures associated with Lennox-Gastaut syndrome[b]	Individualized adjunctive antiepileptic therapy[c, d], if medically indicated and if no pharmacoresistance (in the sense of an inadequate response), intolerance or contraindication is known, choosing[e] from: ▪ clonazepam, rufinamide, topiramate, lamotrigine, felbamate, vigabatrin, clobazam, brivaracetam, eslicarbazepine, gabapentin, lacosamide, levetiracetam, oxcarbazepine, perampanel, pregabalin, valproic acide, zonisamide, primidone, phenytoin, phenobarbital, ethosuximide, mesuximide, cenobamate, bromide taking into account the types of seizures occurring, the basic and previous therapy (therapies) and any associated side effects	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to expert opinion, a ketogenic diet can also 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 ketogenic 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 the present 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. In addition to the drug cannabidiol, the drugs clonazepam, rufinamide, topiramate, lamotrigine, felbamate as well as fenfluramine are specifically approved for the therapeutic indication Lennox-Gastaut syndrome. Based on the generally recognized state of medical knowledge, fenfluramine is not determined as an ACT in the context of individualized adjunctive antiepileptic therapy. The disease profile of Lennox-Gastaut syndrome typically includes a variety of seizure types (including tonic, tonic-clonic, myoclonic and atonic seizures). Drugs that are approved for the various forms of seizures or for the treatment of epileptic seizures in general can therefore also be considered as part of the ACT, provided there is no contraindication for Lennox-Gastaut syndrome.
e. 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; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of the market launch in 2021, where the G-BA determined a considerable 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 in combination with clobazam (hereinafter referred to as cannabidiol + clobazam) as an adjunctive therapy compared with an individualized adjunctive therapy as ACT in patients aged 2 years and older with seizures associated with Lennox-Gastaut syndrome.

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

Table 4: Research question for the benefit assessment of cannabidiol + clobazam

Therapeutic indication	**ACT**[a]
Adjunctive therapy in patients aged 2 years and older with seizures associated with Lennox-Gastaut syndrome[b]	Individualized antiepileptic adjunctive therapyc, d, if medically indicated and if no pharmacoresistance (in the sense of an inadequate response), intolerance or contraindication is known, choosing[e] from: ▪ clonazepam, rufinamide, topiramate, lamotrigine, felbamate, vigabatrin, clobazam, brivaracetam, eslicarbazepine, gabapentin, lacosamide, levetiracetam, oxcarbazepine, perampanel, pregabalin, valproic acid[e], zonisamide, primidone, phenytoin, phenobarbital, ethosuximide, mesuximide, cenobamate, bromide taking into account the types of seizures occurring, the basic and previous therapy (therapies) and any associated side effects

a. Presented is the ACT specified by the G-BA.
b. According to expert opinion, a ketogenic diet can also 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 ketogenic 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 the present 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. In addition to the drug cannabidiol, the drugs clonazepam, rufinamide, topiramate, lamotrigine, felbamate as well as fenfluramine are specifically approved for the therapeutic indication Lennox-Gastaut syndrome. Based on the generally recognized state of medical knowledge, fenfluramine is not determined as an ACT in the context of individualized adjunctive antiepileptic therapy. The disease profile of Lennox-Gastaut syndrome typically includes a variety of seizure types (including tonic, tonic-clonic, myoclonic and atonic seizures). Drugs that are approved for the various forms of seizures or for the treatment of epileptic seizures in general can therefore also be considered as part of the ACT, provided there is no contraindication for Lennox-Gastaut syndrome.
e. 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; G-BA: Federal Joint Committee

At first, the company followed the G-BA's specification on the ACT. In the following, however, it explains that a treatment-refractory course of the disease is typical for patients with Lennox-Gastaut syndrome, which does not allow further patient-specific 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 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

The check did not identify any additional relevant study.

Evidence provided by the company

The company included 2 RCTs in its assessment: GWEP1414 [3] and GWEP1423 [4]. These studies were the basis for the approval of cannabidiol in the present therapeutic indication. The data presented by the company are not suitable for deriving an added benefit of cannabidiol + clobazam, as the ACT was not implemented in both studies. This is justified below.

Studies GWEP1414 and GWEP1423

The studies GWEP1414 and GWEP1423 have an almost identical design and are summarized below. Both studies are blinded RCTs comparing cannabidiol with placebo, each in addition to the previous seizure-suppressant basic therapy. Both studies were conducted in the years 2015 - 2016 and are completed. The studies included patients aged 2 to 55 years with a clinical diagnosis of Lennox-Gastaut syndrome whose seizures could not be fully controlled with their ongoing seizure-suppressant medication. The GWEP1414 study included a total of 225 patients who were randomly assigned in a 2:2:1:1 ratio to treatment with either cannabidiol 10 mg/kg/day, 20 mg/kg/day or to one of two placebo groups. The study GWEP1423 included a total of 171 patients who were randomly assigned in a 1:1 ratio to treatment with either cannabidiol 20 mg/kg/day or placebo.

Both studies consisted of a 4-week baseline phase, in which, among other things, the patients' seizure frequency under their previous seizure-suppressant therapy was recorded. The double-blind treatment phase of the studies lasted 14 weeks, divided into a 2-week titration

phase and a 12-week maintenance phase with a subsequent 10-day phasing out period and a 4-week follow-up.

Primary outcome of the studies was the change in the number of drop seizures compared to baseline.

Patients with any concomitant seizure suppressant medication were included in the studies. According to the approval, cannabidiol may only be used in combination with clobazam. For the dossier, the company therefore presented a subpopulation of each of the studies whose seizure-suppressant therapy included clobazam (GWEP1414: N = 110; GWEP1423: N = 84).

Seizure-suppressant basic therapy in the studies

According to the inclusion criteria of both studies, the patients had to be refractory, i.e. more than 1 seizure-suppressant drug had led to treatment failure during the course of the disease. The current seizure-suppressant therapy had to consist of 1 to maximally 4 different drugs, the dosage of which had to have been stable for at least 4 weeks prior to screening and was not allowed to be changed during the 4-week baseline phase and during the entire duration of the study. Patient-specific dose adjustments, the addition or the discontinuation of drugs were not permitted 4 weeks before the start of the study and during the entire course of the study. The use of rescue medication was permitted. Non-drug measures such as a ketogenic diet or vagus nerve stimulation was also to be maintained in a stable regimen as early as 4 weeks prior to study inclusion and throughout the course of the study. Initiation of a ketogenic diet or vagus nerve stimulation was prohibited during the study. According to the inclusion criteria of the studies, patients should have had at least 2 drop seizures per week during the baseline phase despite their previous seizure-suppressant therapy.

ACT not implemented

The G-BA determined an individualized antiepileptic add-on therapy as ACT, if medically indicated and if no pharmacoresistance, intolerance or contraindications were known, choosing from 24 different seizure-suppressant drugs (see Table 4). Treatment was to be performed at the investigator's discretion depending on the basic and prior therapy/therapies under consideration of the occurring seizure types and accompanying side effects. The G-BA also pointed out that in the included studies, it must be ensured that the patient-specific choice of the adjunctive seizure-suppressant treatment takes place before randomization and is described as concretely as possible by criteria (e. g. by documenting the respective previous therapies, the reasons for treatment discontinuation or treatment switch). In addition, the G-BA did not consider the unchanged continuation of an inadequate therapy to be an implementation of the ACT if there was still the option of optimization.

Deviating from this, the studies GWEP1414 and GWEP1423 compared cannabidiol as an add-on therapy to an existing seizure-suppressant therapy with an existing seizure-suppressant

therapy that was not allowed to be changed. Although the patients' seizures were inadequately controlled by the current basic therapy according to the inclusion criteria of the studies, patients in the comparator group only received placebo as a control. Adjustment of the therapy according to individual criteria such as frequency of seizures, previous therapies, side effects and contraindications was prohibited. The ACT was thus not implemented in any of the studies presented by the company.

In the company's view, however, the G-BA's ACT was implemented in the studies GWEP1414 and GWEP1423, as the included patients were a pharmacoresistant population and a further adjustment of the existing seizure-suppressant therapy was not possible. The company explained that the patients received a median of 4.5 to 6 seizure-suppressant drugs to treat their Lennox-Gastaut syndrome (at least 0 and at most 19 seizure-suppressant drugs) during the course of the disease, 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 [5]. 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.

The company's reasoning is not appropriate. In Module 4 B, the company only provides information on the previous and concomitant seizure-suppressant drugs of the included patients. This information shows that a large proportion of patients had not yet received the drugs recommended in the first and second line of treatment according to the guidelines [6-9]. For example, only around 39% and 42% of patients in the studies GWEP1414 and GWEP1423, respectively, had received lamotrigine, 58% and 56% valproic acid, 38% and 33% rufinamide and 57% and 52% topiramate as prior seizure-suppressant medication. The company also provided information on the current therapy during the studies: lamotrigine in around 27% and 37% of patients in the studies GWEP1414 and GWEP1423, valproic acid in 26% and 29%, rufinamide in 26% and 29% and topiramate in 14% each. This does not indicate that the patients included were no longer eligible for individualized seizure-suppressant adjunctive therapy or that an option for optimization was no longer existing. However, in its dossier, the company provided no information as to why the drugs of the ACT were no longer a treatment option for the patients included in the studies.

According to current guidelines [6,8,9], individual optimization of the drug therapy is also possible and useful for patients who are not seizure-free despite seizure-suppressant therapy or whose seizures cannot be adequately controlled. This can be done, for example, by switching to another seizure-suppressant treatment or by adding another seizure-suppressant drug to the ongoing treatment. According to the guideline of the German Society of Neurology [6], 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. Likewise, the response or non-response to certain drugs is not permanent and rather fluctuates during the course of the disease [5]. A new treatment attempt is therefore useful and possible. 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 [10].

Conclusion

The placebo-controlled studies GWEP1414 und GWEP1423 presented by the company are unsuitable to prove 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.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of cannabidiol + clobazam in comparison with the ACT in patients aged 2 years and older with seizures associated with Lennox-Gastaut syndrome. There is no hint of an added benefit of cannabidiol + clobazam 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 + clobazam in comparison with the ACT is summarized in Table 5.

Table 5: Cannabidiol + clobazam – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adjunctive therapy in patients aged 2 years and older with seizures associated with Lennox-Gastaut syndrome[b]	Individualized adjunctive antiepileptic therapyc, d, if medically indicated and if no pharmacoresistance (in the sense of an inadequate response), intolerance or contraindication is known, choosing[e] from: ▪ clonazepam, rufinamide, topiramate, lamotrigine, felbamate, vigabatrin, clobazam, brivaracetam, eslicarbazepine, gabapentin, lacosamide, levetiracetam, oxcarbazepine, perampanel, pregabalin, valproic acide, zonisamide, primidone, phenytoin, phenobarbital, ethosuximide, mesuximide, cenobamate, bromide taking into account the types of seizures occurring, the basic and previous therapy (therapies) and any associated side effects	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to expert opinion, a ketogenic diet can also 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 ketogenic 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 the present 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. In addition to the drug cannabidiol, the drugs clonazepam, rufinamide, topiramate, lamotrigine, felbamate as well as fenfluramine are specifically approved for the therapeutic indication Lennox-Gastaut syndrome. Based on the generally recognized state of medical knowledge, fenfluramine is not determined as an ACT in the context of individualized adjunctive antiepileptic therapy. The disease profile of Lennox-Gastaut syndrome typically includes a variety of seizure types (including tonic, tonic-clonic, myoclonic and atonic seizures). Drugs that are approved for the various forms of seizures or for the treatment of epileptic seizures in general can therefore also be considered as part of the ACT, provided there is no contraindication for Lennox-Gastaut syndrome.
e. 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; G-BA: Federal Joint Committee

The assessment described above deviates from that of the company, which derived a hint of a considerable added benefit on the basis of the data provided by it.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of the market launch in 2021, where the G-BA determined a considerable 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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