Cannabidiol
(Dravet 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

Cannabidiol, Dravet Syndrome, Child, Adolescent, Adult, Benefit Assessment

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 therapy as appropriate comparator therapy (ACT) in patients aged 2 years and older with seizures associated with Dravet 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 Dravet 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 from: ▪ brivaracetam, bromide, clobazam, fenfluramine, levetiracetam, stiripentol, topiramate, valproic acid[e] 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 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. In addition to the drug cannabidiol, the drugs stiripentol, fenfluramine and bromide are specifically approved for the therapeutic indication Dravet syndrome. Guidelines also recommend the drugs valproic acid, clobazam, levetiracetam and topiramate for the present therapeutic indication, which are generally approved for the treatment of various epileptic seizures.
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 the patients included in the studies are a pharmacoresistant population for whom the best possible individualized therapy has already been used. 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 GWEP1424 und GWEP1332 (Part B) 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 18 years with a clinical diagnosis of Dravet 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 Dravet 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 Dravet 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 from: ▪ brivaracetam, bromide, clobazam, fenfluramine, levetiracetam, stiripentol, topiramate, valproic acid[e] 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 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. In addition to the drug cannabidiol, the drugs stiripentol, fenfluramine and bromide are specifically approved for the therapeutic indication Dravet syndrome. Guidelines also recommend the drugs valproic acid, clobazam, levetiracetam and topiramate for the present therapeutic indication, which are generally approved for the treatment of various epileptic seizures.
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 therapy as ACT in patients aged 2 years and older with seizures associated with Dravet 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 Dravet 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 from: ▪ brivaracetam, bromide, clobazam, fenfluramine, levetiracetam, stiripentol, topiramate, valproic acid[e] 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 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. In addition to the drug cannabidiol, the drugs stiripentol, fenfluramine and bromide are specifically approved for the therapeutic indication Dravet syndrome. Guidelines also recommend the drugs valproic acid, clobazam, levetiracetam and topiramate for the present therapeutic indication, which are generally approved for the treatment of various epileptic seizures.
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 the patients included in the studies are a pharmacoresistant population for whom the best possible individualized therapy has already been used. 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 2024); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check.

Evidence provided by the company

The company included the 2 RCTs GWEP1424 [3] and GWEP1332 (Part B) [4] in its assessment. 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 GWEP1424 and GWEP1332

The studies GWEP1424 and GWEP1332 (Part B) 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. The studies were conducted in the years 2014 - 2018 and are completed. The studies included patients aged 2 to 18 years with a clinical diagnosis of Dravet syndrome whose seizures could not be fully controlled with their ongoing seizure-suppressant medication. The GWEP1424 study included 199 patients who were randomly assigned in a 2:2:1:1 ratio to treatment with cannabidiol 10 mg/kg/day, 20 mg/kg/day or to one of the two placebo groups (10 mg/kg/day dose equivalent or 20 mg/kg/day dose equivalent). The study GWEP1332 (Part B) included a total of 120 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 convulsive seizures compared to the baseline phase.

Patients with any concomitant seizure suppressant medication were included in the studies. According to the SPC, cannabidiol may only be used in combination with clobazam in this therapeutic indication [5]. For the dossier, the company therefore presented a subpopulation of each of the studies whose seizure-suppressant therapy included clobazam (GWEP1424: N = 126; GWEP1332 [Part B]: N = 78).

Seizure-suppressant basic therapy in the studies

According to the inclusion criteria of both studies, the current seizure-suppressant therapy had to consist of ≥ 1 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 were 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 4 convulsive seizures during the baseline phase of 28 days despite their previous seizure-suppressant therapy.

ACT not implemented

The G-BA determined an individualized adjunctive antiepileptic therapy as ACT, if medically indicated and if no pharmacoresistance, intolerance or contraindications were known, choosing from 8 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 GWEP1424 and GWEP1332 (Part B) compared cannabidiol as an adjunctive therapy to an ongoing seizure-suppressant therapy with an ongoing 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 GWEP1424 and GWEP1332 (Part B), as the included patients were a pharmacoresistant population and a further adjustment of the existing seizure-suppressant therapy was not possible. It justified this by stating that, on the one hand, the majority of patients had already undergone therapy escalation, which - measured against the recommendations for last-line therapies of the current National Institute for Health and Care Excellence (NICE) guideline [6] - does not allows for any further optimization. On the other hand, the individual pharmacoresistance of the test subjects went far beyond the criteria of the International League Against Epilepsy (ILAE) for the existence of pharmacoresistance (failure of at least 2 seizure-suppressant drugs when used adequately) [7]. This assessment is not appropriate. In Module 4 A of its dossier, the company provides information on both seizure-suppressant therapies in the history and ongoing seizure-suppressant therapies 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. In relation to the company's argumentation with regard to last-line therapies, for example, potassium bromide is recommended in accordance with the NICE [6] guideline, if other therapies have not been successful. The information in Module 4 A shows that at the time of study enrolment, only a maximum of 2.4% of patients in study GWEP1424 and a maximum of 10.5% in study GWEP1332 (Part B) received bromide. Prior to inclusion in the study, a maximum of 4.5% of patients in the GWEP1424 study and 0% in the GWEP1332 study (Part B) received bromide. In each case, the data refer to the subpopulation presented by the company whose seizure-suppressant therapy included clobazam. The majority of patients had therefore not yet received therapy with (potassium) bromide without giving a reason. Furthermore, it cannot be inferred from the information on pretreatments and therapies at the time of study inclusion that recommended drugs from an earlier line of therapy - such as topiramate or levetiracetam - would not have been an option for individual patients.

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, chances of success to become seizure-free decrease after failure of the first

treatment [8]. 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 [7]. 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 GWEP1424 und GWEP1332 (Part B) 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 as adjunctive therapy in comparison with the ACT in patients aged 2 years and older with seizures associated with Dravet 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 2 years of age and older with seizures associated with Dravet 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 from: ▪ brivaracetam, bromide, clobazam, fenfluramine, levetiracetam, stiripentol, topiramate, valproic acid[e] 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 GB-A.
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 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. In addition to the drug cannabidiol, the drugs stiripentol, fenfluramine and bromide are specifically approved for the therapeutic indication Dravet syndrome. Guidelines also recommend the drugs valproic acid, clobazam, levetiracetam and topiramate for the present therapeutic indication, which are generally approved for the treatment of various epileptic seizures.
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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Miller I, Scheffer IE, Gunning B et al. Dose-Ranging Effect of Adjunctive Oral Cannabidiol vs Placebo on Convulsive Seizure Frequency in Dravet Syndrome: A Randomized Clinical Trial. JAMA Neurol 2020; 77(5): 613-621. https://doi.org/10.1001/jamaneurol.2020.0073.

4. Devinsky O, Cross JH, Laux L et al. Trial of Cannabidiol for Drug-Resistant Seizures in the Dravet Syndrome. N Engl J Med 2017; 376(21): 2011-2020. https://doi.org/10.1056/NEJMoa1611618.

5. Jazz Pharmaceuticals. Epidyolex 100 mg/ml Lösung zum Einnehmen [online]. 2023 [Accessed: 17.01.2024]. URL: https://www.fachinfo.de.

6. National Institute for Health and Care Excellence. Epilepsies in children, young people and adults [online]. 2022. URL: https://www.nice.org.uk/guidance/ng217/resources/epilepsies-in-children-young-people-and-adults-pdf-66143780239813.

7. Kwan P, Arzimanoglou A, Berg AT et al. Definition of drug resistant epilepsy: consensus proposal by the ad hoc Task Force of the ILAE Commission on Therapeutic Strategies. Epilepsia 2010; 51(6): 1069-1077. https://doi.org/10.1111/j.1528-1167.2009.02397.x.

8. Holtkamp M, May T, Berkenfeld R et al. S2k-Leitlinie Erster epileptischer Anfall und Epilepsien im Erwachsenenalter [online]. 2023. URL: https://register.awmf.org/assets/guidelines/030-041l_S2k_Erster-epileptischer-Anfall-Epilepsien-Erwachsenenalter_2023-09.pdf.

9. Scottish Intercollegiate Guidelines Network. SIGN 159, Epilepsies in children and young people: investigative procedures and management; A national clinical guideline [online]. 2021. URL: https://www.sign.ac.uk/media/1844/sign-159-epilepsy-in-children-final.pdf.

10. Hamer HM, Holtkamp M, Kaiser T et al. Position paper of a German interdisciplinary round table on future designs of trials on adjunctive treatment with antiseizure drugs. Seizure 2020; 78: 53-56. https://doi.org/10.1016/j.seizure.2020.03.004.

The full report (German version) is published under https://www.iqwig.de/en/projects/a23-119.html.