IQWiG Reports – Commission No. A18-27

Extract from Cannabis sativa (spasticity due to multiple sclerosis) –

Benefit assessment according to §35a Social Code Book V[1] (expiry of the decision)

Extract

[1] Translation of the executive summary of the dossier assessment *Extrakt aus Cannabis sativa (Spastik aufgrund von multipler Sklerose) – Nutzenbewertung gemäß § 35a SGB V (Ablauf Befristung)* (Version 1.0; Status: 26 July 2018). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 extract from *Cannabis sativa*. 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 26 April 2018.

Research question

The aim of this report is to assess the added benefit of a *Cannabis sativa* extract as an add-on to optimized standard therapy in comparison with optimized standard therapy as the appropriate comparator therapy (ACT) in patients with moderate to severe spasticity due to multiple sclerosis (MS) who failed to respond adequately to other anti-spasticity medication and who demonstrate considerable clinical improvement in spasticity-related symptoms during a 4-week initial trial of therapy.

The *Cannabis sativa* extract contains the drug combination delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Hereinafter, *Cannabis sativa* extract is referred to as THC/CBD.

Table 2 presents the research question of the benefit assessment of THC/CBD.

Table 2[2]: Research question of the benefit assessment of THC/CBD

Research question	Indication	ACT[a]
1	Adult patients with moderate to severe MS-related spasticity who failed to respond adequately to other anti-spasticity medication and who demonstrate considerable clinical improvement in spasticity-related symptoms during a 4-week initial trial of therapy.	Optimized standard therapy with baclofen (oral) or tizanidine or dantrolene in consideration of approved dosages. At least 2 previous therapies were to have taken place, each of which using different optimized oral spasmolytics – at least one of which had to be a product containing baclofen or tizanidine.
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The company deviates from the ACTs specified by the G-BA, while following the specifications regarding optimized standard therapy with baclofen (oral) or tizanidine or dantrolene in consideration of the approved dosages. The deviation concerns the G-BA's specification that at least 2 previous therapies were to have taken place, each of which using different optimized oral spasmolytics – at least 1 of which had to be a product containing baclofen or tizanidine. The company stated that it did not want to generally exclude from its assessment any studies in which patients had received only 1 previous therapy. This criterion

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

does not, however, lead to the exclusion of studies which meet the G-BA criterion; on the contrary, it potentially results in too many studies being included.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 12 weeks were used for deriving an added benefit.

Results

The benefit assessment of THC/CBD as an add-on to optimized standard therapy in comparison with optimized standard therapy in patients with moderate to severe MS-related spasticity included the studies SAVANT and GWSP0604.

Study design

SAVANT study

The SAVANT study included adult patients with moderate to severe MS-related spasticity, defined as a score ≥ 4 on an 11-point numerical rating scale (NRS). Spasticity symptoms and MS were to have been present for at least 12 months. Patients were to have received at least 2 previous oral treatment attempts (at least 1 of them with baclofen or tizanidine) and have been receiving stable, optimized anti-spasticity treatment with baclofen, tizanidine, or dantrolene for at least 3 months without adequate relief of symptoms despite optimization.

The SAVANT study was conducted in 3 phases. In the single-blind, 1-arm Phase A, all patients received THC/CBD as an add-on to optimized standard anti-spasticity treatment for 4 weeks. Phase A is the initial trial of therapy required by the Summary of Product Characteristics (SPC) for selecting responders to THC/CBD therapy. Response was defined as improvement of spasticity on the NRS by at least 20%. Only responders remained in the study and entered the subsequent wash-out phase.

In the wash-out phase (1 to 4 weeks), THC/CBD was discontinued, but the optimized standard anti-spasticity therapy was continued. Only patients whose improvement in the initial trial of therapy was reduced by at least 80% within at most 4 weeks in the wash-out phase were included in the subsequent randomized, double-blind, placebo-controlled Phase B. This is the phase relevant for the benefit assessment.

On the basis of the 80% criterion, 16.4% of THC/CBD treatment responders in Phase A were excluded from the study because they did not experience a sufficient deterioration during the wash-out phase. Patients randomized in Phase B are therefore a selected subpopulation of the actual target population of patients who responded to the initial trial of therapy. It remains unclear how much the effect size observed in the SAVANT study would change if these patients were randomized as well. Patients with the greatest potential improvement under THC/CBD therapy were specifically selected. This considerable difference in study design compared to study GWSP0604 (described below) casts doubt on the transferability of results to routine healthcare. Resulting consequences are described under “Implementation of the ACT”.

A total of 106 patients were randomized to treatment with THC/CBD as an add-on to optimized standard therapy (N = 53) or optimized standard therapy (N = 53). Blinding was achieved by add-on placebo doses in the comparator arm.

Patients were treated in accordance with the specifications in the SPC. Treatment was administered for 12 weeks. The optimized standard anti-spasticity therapy with baclofen and/or tizanidine and/or dantrolene was adjustable according to the patient's needs and as permitted by the respective marketing authorization. During Phase B, standard anti-spasticity therapy was adjusted in 7.5% of patients in the placebo arm and 5.7% of patients in the THC/CBD arm.

The primary outcome of the SAVANT study was improvement of spasticity in the NRS. Secondary outcomes were outcomes on morbidity, health-related quality of life and adverse events.

Study GWSP0604

The study GWSP0604 included adult patients with moderate to severe MS-related spasticity, defined as a score ≥ 4 on the NRS. Spasticity symptoms were to have been present for at least 3 months and MS was to have been diagnosed for at least 6 months. Patients were to either be unable to achieve full symptom relief on their current anti-spasticity drugs or have been unable to tolerate and discontinued a previous treatment attempt.

The GWSP0604 study was conducted in 2 phases. Like in the above-described SAVANT study, Phase A represents the 4-week initial trial of therapy as per the SPC to identify the patients who responded to THC/CBD therapy. Response was again defined as improvement of spasticity by at least 20% on the NRS. The randomized, double-blind, placebo-controlled Phase B is again the phase relevant for the benefit assessment.

A total of 241 patients were randomized to treatment with THC/CBD as an add-on to optimized standard therapy (N = 124) or to optimized standard therapy (N = 117). Blinding was achieved by add-on placebo doses in the comparator arm.

Patients were treated as per the SPC specifications. The treatment duration was 12 weeks. Unlike in the SAVANT study, in the GWSP0604 study, the optimized standard anti-spasticity therapy with baclofen and/or tizanidine and/or dantrolene was supposed to remain as stable as possible and be adjusted only if the medical situation required. In Phase B, the standard anti-spasticity treatment was adjusted in 2.6% of patients in the placebo arm and in 2.4% of patients in the THC/CBD arm.

Subpopulation relevant for the benefit assessment

For answering the research question, only a subpopulation of the GWSP0604 study is relevant, namely patients from the randomized ITT population with at least 2 documented previous therapies with baclofen and/or tizanidine and/or dantrolene.

The relevant subpopulation used for the assessment equals 24.3% of the total population, with n = 28 patients in the intervention arm and n = 29 patients in the comparator arm.

Implementation of the ACT

Number of previous therapies

THC/CBD is approved for patients with moderate to severe MS-related spasticity who failed to respond adequately to other anti-spasticity drug therapy. According to the G-BA, the term drug therapy implies that the prior therapy is to be considered a treatment regimen consisting of multiple drugs rather than the application of a single drug. This interpretation is the basis for the G-BA's specification of at least 2 prior trials of therapy, each using different optimized oral spasmolytics – at least 1 of which contained baclofen or tizanidine.

The information presented by the company does not clearly show for either study whether the current optimized standard anti-spasticity therapy at the time of patient inclusion in the study corresponds to the 2nd trial of therapy or whether it represents a 3rd adjustment. In addition to THC/CBD, baclofen, tizanidine, and dantrolene are approved for treating spasticity in MS. But due to high hepatotoxicity, dantrolene is of very limited practical relevance. In accordance with Annex VI of the Pharmaceutical Guidelines, off-label use of gabapentin is permitted in case of failure of all approved therapies; therefore, it does not represent a further therapeutic optimization option in the current situation. In accordance with treatment recommendations, MS-related spasticity should initially be treated with baclofen or tizanidine monotherapy, and combination therapies can be used if the patient fails to respond. Under the assumption that this has been done and due to limited treatment optimization options, the above-described uncertainty regarding the number of prior trials of therapy is not considered to be in conflict with treatment which had been optimized before the start of the study.

Optimization of prior therapies

The SAVANT study's inclusion criteria specify that patients are to have received optimized standard therapy before the start of the study. Optimization was defined as having reached the most efficacious and best tolerated dose according to the relevant approval. Both the investigator and the patient had to confirm that the treatment at the start of the study had been optimized. This was not required in the GWSP0604 study. To show that the patients of the GWSP0604 study nevertheless received optimized standard anti-spasticity therapy before the start of the study, the company presented analyses on the optimization of standard anti-spasticity therapy within 36 months before the start of the study. Despite these analyses, it is not completely clear whether all patients of the relevant subpopulation received optimized prior therapy at the start of the study.

Treatment optimization in the studies' comparator arm

The ACT specified by the G-BA is optimized standard therapy with baclofen and/or tizanidine and/or dantrolene. This means that there should be an option for further optimizing standard anti-spasticity therapy during the study as well. The SAVANT study explicitly allowed an

adjustment of the optimized standard anti-spasticity therapy during the study in both treatment arms. Nevertheless, treatment was further optimized in only 7.5% of patients in the placebo arm and 5.7% in the THC/CBD arm.

The GWSP0604 study provided for an adjustment of the standard anti-spasticity therapy during the study only if the medical situation required. In the overall population, the standard anti-spasticity therapy was adjusted in 2.6% of patients in the placebo arm and 2.4% of patients in the THC/CBD arm. For the relevant subpopulation, the adjustment rate was similar. Given the low adjustment rate in the SAVANT study, it can be assumed that further treatment optimization was usually not possible with the available therapeutic options; therefore, the GWSP0604 study can be included in the benefit assessment despite the restrictive adjustment options. It is assumed that, as described above, patients received optimized therapy at the start of the study and further optimization during the study was possible only to a very limited extent. Nevertheless, it ultimately remains unclear whether more optimization would have taken place if more liberal options had been available.

Meta-analytical summary of study results makes little sense

An essential difference in the design of the two studies was the inclusion of a wash-out phase only in the SAVANT study. Due to the selection of patients whose improvement in the initial trial of therapy was reduced again by at least 80% on the NRS in the wash-out phase, which lasted at most 4 weeks, the randomized patients of the SAVANT study – unlike the randomized patients of the GWSP0604 study – represent only a subpopulation of the actual target population of THC/CBD responders. It remains unclear how the effect size in the SAVANT study would change if the patients in whom the symptoms did not sufficiently deteriorate again were randomized as well. Discontinuation of THC/CBD in the wash-out phase and the additional introduction of the 80% criterion potentially lead to effect maximization. Thus, the selected subpopulation shows the potentially greatest treatment effect of THC/CBD.

Due to these differences between studies, results can be assumed to be inherently heterogeneous. Therefore, it is not appropriate to calculate a pooled estimator in a meta-analysis. Instead, the studies were qualitatively summarized. This included checking the studies for parallel effects.

Risk of bias and summary assessment of reliability

The risk of bias on the study level is assessed as low for both studies. For all included outcomes, the risk of bias is also considered low. No usable data are available for the specific adverse event (AE) dizziness.

The studies SAVANT and GWSP0604 entail various uncertainties regarding the optimization of prior therapies, treatment optimization during the studies, as well as patient selection after the wash-out phase in the SAVANT study. Due to these uncertainties, at most indications, for example of an added benefit, can be inferred from the qualitative summary of the SAVANT and GWSP0604 studies. For specific outcomes, this assessment may differ.

For outcomes used only in the SAVANT study, at most a hint, for example of an added benefit, can be inferred due to the described uncertainty regarding the effect size.

Mortality

All-cause mortality

For the outcome all-cause mortality, no events occurred in the SAVANT study.

In the GWSP0604 study, 2 events occurred in the THC/CBD arm. No statistically significant difference between treatment groups was found.

Overall, no hint of added benefit of THC/CBD in comparison with optimized standard therapy was derived; therefore, an added benefit is not proven.

Morbidity

Spasticity

In the SAVANT study, a statistically significant difference in favour of THC/CBD was found.

In the GWSP0604 study, a statistically significant difference in favour of THC/CBD was found as well. Here, however, the extent for this outcome from the category non-serious/non-severe symptoms/late complications is not more than marginal.

Since a statistically significant effect was found in both studies, the qualitative summary of the studies assumes parallel effects, but reliability has been downgraded due to the marginal effect in the GWSP0604 study. Overall, this results in a hint of an added benefit of THC/CBD in comparison with optimized standard therapy.

Sleep disruption due to spasticity (NRS)

For the outcome sleep disruption due to spasticity, as measured by an NRS, the SAVANT study shows a statistically significant difference in favour of THC/CBD. The respective confidence interval of the standardized mean difference (Hedges' g) is fully outside the irrelevance range [−0.2; 0.2]. This has been interpreted as a relevant effect. Furthermore, the SAVANT study showed an effect modification by the subgroup attribute of sex, albeit without having any effect on the overall assessment of added benefit for this outcome.

In the GWSP0604 study, no statistically significant difference between treatment groups was found. Subgroup analyses for the relevant subpopulation are not available.

Overall, the studies show divergent results. Consequently, there is no hint of added benefit of THC/CBD in comparison with optimized standard therapy; therefore, an added benefit is not proven.

Pain due to spasticity (NRS)

The outcome pain due to spasticity was measured only in the SAVANT study.

In the SAVANT study, a statistically significant difference in favour of THC/CBD was found. The respective confidence interval of the standardized mean difference (Hedges' g) is fully outside the irrelevance range [−0.2; 0.2]. This has been interpreted as a relevant effect. Furthermore, an effect modification by the subgroup attribute of sex was found for this outcome.

For women, this results in a hint of added benefit of THC/CBD in comparison with optimized standard therapy. For men, this does not result in a hint of added benefit of THC/CBD in comparison with optimized standard therapy; therefore, an added benefit is not proven.

Activities of daily living (Barthel index)

No statistically significant difference between treatment groups was found in either the SAVANT study or the GWSP0604 study.

Consequently, there is a hint of added benefit of THC/CBD in comparison with optimized standard therapy; therefore, an added benefit is not proven.

Gait speed (10 m walk test)

In the SAVANT study, no statistically significant difference between treatment groups was found for the responder analysis or the mean difference. For the GWSP0604 study, no statistically significant difference between treatment groups was found for mean difference either.

This does not result in a hint of added benefit of THC/CBD in comparison with optimized standard therapy; therefore, an added benefit is not proven.

Health status

Measured by the Subject Global Impression of Change (SGIC)

In the SAVANT study, no statistically significant difference between treatment groups was found for this outcome.

In the GSWP0604 study, a statistically significant difference was found in favour of THC/CBD.

Overall, the studies show divergent results. Consequently, there is no hint of added benefit of THC/CBD in comparison with optimized standard therapy; therefore, an added benefit is not proven

Measured by the Visual Analogue Scale (VAS) of the European Quality of Life Questionnaire (EQ-5D VAS)

In the SAVANT study, health status was not measured by the VAS of EQ-5D. In the GWSP0604 study, no statistically significant difference between treatment groups was found.

Consequently, there is no hint of added benefit of THC/CBD in comparison with optimized standard therapy; therefore, an added benefit is not proven.

Health-related quality of life

36-Item Short Form Health Survey (SF-36)

For the sections physical functioning, physical role functioning, general health perceptions, vitality, social role functioning, emotional role functioning, emotional role functioning, and mental health, neither the SAVANT study nor the GWSP0604 study show a statistically significant difference between treatment groups.

For the section bodily pain, the SAVANT study shows a statistically significant difference in favour of THC/CBD. The respective confidence interval of the standardized mean difference (Hedges' g) is not fully outside the irrelevance range [−0.2; 0.2], however. Hence, it is not possible to conclude that the effect is relevant.

The GWSP0604 study did not find a statistically significant difference between treatment groups for the bodily pain section either.

Overall, for the SF-36, no hint of added benefit of THC/CBD in comparison with optimized standard therapy was derived; therefore, an added benefit is not proven.

Adverse events

Serious adverse events (SAEs)

For SAEs, no statistically significant difference between treatment groups was found in the SAVANT or GWSP0604 study.

Overall, no hint of greater or lesser harm of THC/CBD in comparison with optimized standard therapy was derived; therefore, greater or lesser harm is not proven.

Discontinuation due to adverse events (AEs)

For the outcome discontinuation due to AEs, no statistically significant difference between treatment groups was found in the SAVANT or GWSP0604 study.

Overall, no hint of greater or lesser harm of THC/CBD in comparison with optimized standard therapy was derived; therefore, greater or lesser harm is not proven.

Specific AEs

Psychiatric disorders

For the outcome psychiatric disorders, no events occurred in the SAVANT study. In the GWSP0604 study, no statistically significant difference between treatment groups was found.

Overall, no hint of greater or lesser harm of THC/CBD in comparison with optimized standard therapy was derived; therefore, greater or lesser harm is not proven.

Dizziness

Since no suitable operationalization is available, neither study supplies usable data on the outcome dizziness.

Overall, no hint of greater or lesser harm of THC/CBD in comparison with optimized standard therapy was derived; therefore, greater or lesser harm is not proven.

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

On the basis of the presented results, the probability and extent of added benefit of the drug THC/CBD in comparison with the ACT is assessed as follows:

Overall, there are 2 positive effects in the outcome category morbidity, 1 of which in the subgroup of women, and no negative effects for THC/CBD compared to optimized standard anti-spasticity therapy.

In summary, for patients with moderate to severe MS-related spasticity who failed to respond adequately to different anti-spasticity drug therapy and exhibited clinically important improvement of spasticity-related symptoms during an initial trial of therapy, there is a hint of non-quantifiable added benefit of THC/CBD as an add-on to optimized standard therapy in comparison with optimized standard therapy. The extent was classified as at most considerable.

Table 3 presents a summary of the probability and extent of the added benefit of THC/CBD.

[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: THC/CBD – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with moderate to severe MS-related spasticity who failed to respond adequately to other anti-spasticity medication and who demonstrate considerable clinical improvement in spasticity-related symptoms during a 4-week initial trial of therapy.	Optimized standard therapy with baclofen (oral) or tizanidine or dantrolene in consideration of approved dosages. At least 2 previous therapies were to have taken place, each of which using different optimized oral spasmolytics – at least one of which had to be a product containing baclofen or tizanidine.	Hint of added benefit; extent: not quantifiable, at most considerable
a: Presentation of the ACT specified by the G-BA ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

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2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-27-extract-from-cannabis-sativa-spasticity-due-to-multiple-sclerosis-benefit-assessment-according-to-35a-social-code-book-v-expiry-of-the-decision.9646.html.