IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

Extract from Cannabis sativa – Benefit assessment according to § 35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment ("Extrakt aus Cannabis Sativa – Nutzenbewertung gemäß § 35a SGB V" (Version 1.0; Status: 29.03.2012). Please note: This translation 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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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. Individual sections and conclusions in the dossier assessment therefore do not necessarily reflect his opinion.

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[2] Due to legal data protection regulations, employees have the right not to be named.

Table of contents

List of tables

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
CBD	cannabidiol
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MS	multiple sclerosis
SGB	Sozialgesetzbuch (Social Code Book)
THC	delta-9-tetrahydrocannabinol
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

On 02.01.2012, 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 extract from *Cannabis sativa* containing the active substance combination delta-9-tetrahydrocannabinol/cannabidiol (THC/CBD). The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 02.01.2012.

In the following, "extract from *Cannabis sativa*" will be referred to by "THC/CBD".

Research question

The present benefit assessment of THC/CBD was carried out for the approved therapeutic indication: "...symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy" (Summary of Product Characteristics, SPC [1]). According to the SPC, THC/CBD is intended to be used as add-on treatment to the patient's previous anti-spasticity medication.

The benefit assessment was carried out in comparison with the appropriate comparator therapy (ACT) specified by the G-BA. This is the optimized standard therapy with baclofen or tizanidine, or drugs approved for the treatment of spasticity in underlying neurological disease, taking into account the approved dosages. At least 2 previous trials of therapy were to have taken place, in each of which different oral spasmolytics - at least one of which had to be a product containing baclofen or tizanidine - were used in an optimum way.

The aim of this report is therefore to assess the added benefit of THC/CBD in comparison with an optimized standard therapy (as specified by the G-BA) in patients with spasticity due to MS (as described in the approval status).

The company deviated from the ACT specified by the G-BA. At first it designated the continuation of the individual previous medication as the ACT. In justifying its choice of the ACT, the company widened its definition of the ACT on the basis of the assumption that an optimized therapy could be presumed in chronically pre-treated patients. It designated the continuation of the previous optimized anti-spasticity medication as the ACT. According to the company, the previous therapy results from the sum of the percentage proportions of all the drugs approved for the indication of THC/CBD that were administered to patients.

With both definitions, the company deviated from the G-BA's specification of the ACT. However, these deviations are not adequately justified.

Results

In its dossier, the company did not carry out any assessment of the above-named research question as it chose a different comparator therapy.

Additional examination of the presented studies showed that in none of them was an optimization of the previous anti-spasticity medication planned. The studies were therefore not suitable for drawing conclusions about the added benefit of THC/CBD in comparison with an optimized standard therapy (as specified by the G-BA). Accordingly, the company presented no studies relevant for the benefit assessment. Therefore, the assessment presented by the company in its dossier provides no proof of an added benefit of THC/CBD in comparison with the ACT specified by the G-BA.

Extent and probability of the added benefit, patient groups with therapeutically important added benefit

On the basis of the results presented, the extent and probability of the added benefit of the active ingredient THC/CBD is assessed as follows:

- There is no proof of an added benefit of THC/CBD.

The result for patient groups with therapeutically important added benefit is as follows:

- There are no patient groups for whom a therapeutically important added benefit is proven.

The decision regarding added benefit is made by the G-BA.

2.2 Research question

The present benefit assessment of THC/CBD was carried out for the approved therapeutic indication: "…symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS) who have not responded adequately to other anti-spasticity medication and who demonstrate clinically significant improvement in spasticity related symptoms during an initial trial of therapy" [1]. According to the SPC, THC/CBD is intended to be used as add-on treatment to the patient's previous anti-spasticity medication.

The company designated continuation of the individual previous therapy of the patient as the ACT. Accordingly, in its dossier the company formulated as a research question for the assessment the comparison of an add-on therapy with THC/CBD with continuation of the previous anti-spasticity medication. In addition, in justifying its ACT, the company postulated that optimized therapy could be presumed in chronically pre-treated patients and, as a result, it described the ACT as the continuation of the previous optimized anti-spasticity medication.

With regard to the two definitions of the ACT and the research question, the company deviated from the G-BA's specification, which specified an optimized standard therapy as the ACT. Table 2 shows the G-BA's ACT and the company's definitions of the ACT.

Table 2: Comparison of the specification of the ACT by the G-BA and the definitions of the ACT by the company[3]

ACT of the G-BA	ACT of the company
The ACT in the therapeutic indication "Spasticity due to multiple sclerosis" is the optimized standard therapy with baclofen or tizanidine, or drugs that are approved for the treatment of spasticity in underlying neurological disease, taking into account the approved dosages. At least 2 previous trials of therapy were to have taken place, in each of which different oral spasmolytics - at least one of which had to be a product containing baclofen or tizanidine - were used in an optimum way.	Definition 1: Continuation of the individual previous anti-spasticity medication of the patient Definition 2: The ACT is therefore appropriately tailored and defined as the continuation of the previous optimized anti-spasticity medication. The previous therapy is the sum of the percentage proportions of all the drugs approved for the current indication that were administered to patients.
ACT: appropriate comparator therapy; G-BA: Gemeinsamer Bundesausschuss (Federal Joint Committee)	

In the Institute's view, the deviation of the company from the G-BA's ACT is not adequately justified. A detailed explanation of this view is provided in Section 2.7.1 of the full dossier assessment. The present report on the assessment of added benefit of THC/CBD is therefore based on the ACT specified by the G-BA.

The aim of the present report is therefore to assess the added benefit of THC/CBD in comparison with an optimized standard therapy (as specified by the G-BA) in patients with spasticity due to MS (as described in the approval status).

The assessment was to be carried out with respect to patient-relevant outcomes and on the basis of randomized controlled trials.

Further information about the research question can be found in Module 3, Section 3.1 and Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

- Studies on THC/CBD completed by the company up to 01.11.2011 (study list of the company)
- Results of a bibliographical literature search and a search in trial registries for studies on THC/CBD (last search in bibliographical databases on 03.11.2011, in trial registries on 04.10.2011, searches by the company)
- The Institute's own search in bibliographical databases and trial registries for studies on THC/CBD to check the company's search results up to 13.01.2012. The check on

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

information retrieval identified no studies in addition to those shown in the company's dossier.

The identified studies corresponded to the study pool of the company.

These studies were examined to see if they are suitable for drawing conclusions concerning the added benefit of THC/CBD in comparison with an optimized standard therapy (as specified by the G-BA) (see Section 2.7.2.4.1 of the full dossier assessment). Since no optimization of the anti-spasticity medication was planned in any of the studies, they could not be used for the comparison of THC/CBD with the ACT of the G-BA. There is therefore no study relevant to the benefit assessment in the identified study pool.

Further information about the inclusion criteria for studies in the present benefit assessment and the methods of information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.4 Results concerning added benefit

In its dossier, the company presented no assessment of the research question on the basis of the ACT of the G-BA because it chose a different ACT. No study in the company's study pool was suitable for assessing THC/CBD in comparison with the ACT specified by the G-BA.

Since no study relevant to the benefit assessment was presented, there is no proof of an added benefit of THC/CBD in comparison with the ACT specified by the G-BA.

This result deviates from that of the company which, on the basis of the studies it presented on the comparison of THC/CBD and its chosen ACT, in total derived an added benefit of THC/CBD.

Further information about the results concerning added benefit can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier and in Section 2.7.2.4 of the full dossier assessment.

2.5 Extent and probability of the added benefit

On the basis of the data available, there is no proof of an added benefit of THC/CBD in comparison with the ACT specified by the G-BA. For this reason, there are also no patient groups for whom a therapeutically important added benefit can be derived.

The assessment of the Institute deviates from that of the company, which states a considerable added benefit of THC/CBD over its chosen ACT.

Further information about the results on extent and probability of the added benefit and on patients groups with a therapeutically important added benefit can be found in Module 4 (Section 4.4) of the dossiers and in Section 2.7.2.8 of the full dossier assessment.

2.6 List of included studies

No information is provided in this section as no relevant study to determine the added benefit of THC/CBD in comparison with the ACT specified by the G-BA was included by the company in its assessment.

References for English extract

Please see full dossier assessment for full reference list.

1. Electronic Medicines Compendium (eMC). Sativex Oromucosal Spray. Summary of Product Characteristics [online]. Date of revision: 07/2011 [Accessed: 07.09.2012]. URL: http://www.medicines.org.uk/EMC/medicine/23262/SPC/Sativex+Oromucosal+Spray/

The full report (German version) is published under www.iqwig.de.