IQWiG Reports – Commission No. A20-44

Apremilast (Behçet's disease) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Apremilast (Behçet-Syndrom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 August 2020). 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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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.

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

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)

2 Benefit assessment

2.1 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 apremilast. 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 6 May 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of this report is to assess the added benefit of apremilast in comparison with therapy upon the physician's discretion as the appropriate comparator therapy (ACT) in adult patients with oral ulcers associated with Behçet's disease who are candidates for systemic therapy.

Table 2: Research question of the benefit assessment of apremilast

Therapeutic indication	**ACT**[a]
Adult patients with oral ulcers associated with Behçet's disease who are candidates for systemic therapy	Therapy upon the physician's discretion[b]
a. Presented is the respective ACT specified by the G-BA. b. In the context of a clinical trial, the following drugs can be used as comparators: dapsone, azathioprine, cyclosporine, interferon alpha, TNF alpha inhibitors and thalidomide. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor	

The company followed the G-BA's specification of the ACT.

The assessment was 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 24 weeks were used for the derivation of the added benefit.

Results

Concurring with the company's findings, the check of the study pool did not identify any relevant RCT for the direct comparison of apremilast with the ACT.

The company explored the possibility of an adjusted indirect comparison, but did not conduct one for deriving an added benefit, since the studies it identified are insufficiently similar. This is an apt evaluation.

In its dossier for assessing the added benefit of apremilast in adult patients with oral ulcers associated with Behçet's disease who are candidates for systemic therapy, the company does not present any suitable data for a comparison with the ACT. Consequently, there is no hint of added benefit of apremilast 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]

Based on the results presented, the probability and extent of added benefit of the drug apremilast in comparison with the ACT are assessed as follows:

Table 3 presents a summary of the probability and extent of added benefit of apremilast.

Table 3: Apremilast – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with oral ulcers associated with Behçet's disease who are candidates for systemic therapy	Therapy upon the physician's discretion[b]	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. In the context of a clinical trial, the following drugs can be used as comparators: dapsone, azathioprine, cyclosporine, interferon alpha, TNF alpha inhibitors and thalidomide. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor		

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of apremilast in comparison with therapy upon the physician's discretion as the ACT in adult patients with oral ulcers associated with Behçet's disease who are candidates for systemic therapy. Table 4 shows the research question of the benefit assessment.

[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 4: Research question of the benefit assessment of apremilast

Therapeutic indication	**ACT[a]**
Adult patients with oral ulcers associated with Behçet's disease who are candidates for systemic therapy	Therapy upon the physician's discretion[b]
a. Presented is the respective ACT specified by the G-BA. b. In the context of a clinical trial, the following drugs can be used as comparators: dapsone, azathioprine, cyclosporine, interferon alpha, TNF alpha inhibitors and thalidomide. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor	

The company identifies therapy upon the physician's discretion as the ACT and thereby follows the G-BA's specification.

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 24 weeks were used for the derivation of added benefit. This departs from the inclusion criteria used by the company, which applied no limit with regard to study duration.

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on apremilast (as of 30 March 2020)
- Bibliographic literature search on apremilast (most recent search on 20 March 2020)
- Search in trial registries / study results databases on apremilast (most recent search on 20 March 2020)
- Search on the G-BA website on apremilast (most recent search on 30 March 2020)
- Bibliographic literature search on the ACT (most recent search on 20 March 2020)
- Search in trial registries or results databases on the ACT (most recent search on 15 April 2020)
- Search on the G-BA website on the ACT (most recent search on 30 March 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on apremilast (most recent search on 15 May 2020)

Concurring with the company, the check of the study pool did not identify any RCTs permitting a direct comparison with the ACT.

In the absence of any directly comparative data, the company explored the possibility of conducting an adjusted indirect comparison through the common comparator of placebo. For

this purpose, the company first included the placebo-controlled approval study RELIEF [3] on the intervention side and 2 placebo-controlled studies with the drugs of etanercept [4] or thalidomide [5] on the comparator side. The company did not calculate an indirect comparison; this is because different study inclusion and exclusion criteria as well as different patient characteristics at baseline dissuaded the company from assuming sufficient similarity to the patient population of the RELIEF study. The company's approach is appropriate and is discussed below.

Data presented by the company

RELIEF study on apremilast

For the intervention to be assessed, the company presents the RELIEF double-blind, parallel-group RCT [3]. The study was conducted from 2014 through 2018 in 53 study centres worldwide; it compared apremilast (30 mg orally, twice daily) treatment of oral ulcers associated with Behçet's disease versus placebo. The study included adult patients with diagnosed Behçet's disease who had 3 occurrences of oral ulcers within the 12 months before the study start. At the start of the study, patients had to have at least 2 oral ulcers for which topical treatment alone was deemed insufficient by the physician. In addition, patients had to have prior treatment with at least 1 non-biologic Behçet's disease therapy.

The actively controlled study duration was 12 weeks. Primary outcome of the study was the area under the curve for the number of oral ulcers during the 12-week placebo-controlled treatment phase. Further outcomes were the number, response rate, and painfulness of oral ulcers, time to complete remission or recurrence as well as outcomes to measure disease activity, health-related quality of life, and safety.

The study included a total of 207 patients, who were randomized in a 1:1 ratio. The mean patient age was 40 years, and patients suffered from Behçet's disease for almost 7 years on average. At baseline, patients had an average of 4 oral ulcers each.

Melikoglu 2005 and Hamuryudan 1998 studies on the comparator therapy

Melikoglu 2005

Melikoglu 2005 [4] is a double-blind, parallel-group RCT comparing treatment of Behçet disease using etanercept (25 mg, twice weekly as a subcutaneous injection) versus placebo. Due to its controlled duration of only 4 weeks, however, this study is far too short to be included in the benefit assessment for a chronic therapeutic indication; therefore, it is not further analysed below.

Hamuryudan 1998

The Hamuryudan 1998 study [5] is a double-blind, parallel-group RCT as well. The study compared the treatment of genital and oral ulcers associated with Behçet's disease using thalidomide (300 mg/day orally or 100 mg/day orally) versus placebo. The study included male patients 18 to 35 years of age with diagnosed Behçet's disease and at least 2 episodes of oral or

genital ulcers within the 3 months before study start. Neither the presence of oral ulcers at baseline nor a need for systemic ulcer therapy were required by the inclusion criteria. In addition, the study excluded patients who suffered from moderate to severe manifestation of Behçet's disease of the eye or who had previously received immunosuppressant therapy.

The study consisted of a 24-week controlled double-blind phase and a 4-week follow-up phase after discontinuation of the study drug. The primary outcome was complete response defined as the complete absence of oral or genital ulcers. Secondary outcomes were a change in the number of mucocutaneous lesions and either the absence of uveitis or reduced visual acuity.

In total, 95 patients were randomized in a 1:1:1 ratio. The mean patient age was 28 years; patients suffered from Behçet disease for an average of almost 3 years and had a mean of about 2 oral ulcers at baseline.

Insufficient study duration

For chronic diseases such as Behçet's disease, a study duration of 24 weeks is generally considered necessary. The RELIEF study's actively controlled duration of 12 weeks for apremilast is therefore insufficient for assessing the benefit of the new intervention. Hence, on the intervention side, no relevant study for a direct comparison is available.

This departs from the company's assessment, which did not apply any limit with regard to the study duration.

Unclear suitability of the Hamuryudan 1998 study for the research question

In accordance with the Summary of Product Characteristics of apremilast [6], patients of the RELIEF study were candidates for systemic therapy. No data on prior treatment is available for the patients of the Hamuryudan 1988 study, and – as discussed by the company – it remains unclear whether systemic therapy was indicated for these patients and whether they consequently fit the present research question.

Studies insufficiently similar for an indirect comparison

Irrespective of the described limitations with regard to the research question, the RELIEF and Hamuryudan 1998 studies are insufficiently similar, as discussed by the company.

The RELIEF study included both men (38.5%) and women (61.5%). Hamuryudan 1998, in contrast, included only men. A comparison of the two studies' patient characteristics shows that the mean patient age is more than 10 years lower in Hamuryudan 1998 (28 years) than in RELIEF (40 years). The studies also differ with regard to disease duration (approx. 7 years in RELIEF versus approx. 3 years in Hamuryudan 1998). At baseline, the patients in the RELIEF study exhibited a higher disease burden than patients in the Hamuryudan 1998 study: The patients in the RELIEF study exhibited approximately 4 oral and 3 genital ulcers at baseline. In the Hamuryudan 1998 study, they had about 2 oral and 1 genital ulcers. Additionally, the study

results are not comparable due to different operationalizations of the treatment response outcomes.

Concurring with the company, the RELIEF and Hamuryudan 1998 studies are deemed unsuitable for an indirect comparison for the above reasons.

Comparison with placebo unsuitable for deriving an added benefit

The company states that, as the best available evidence regarding the therapeutic indication, the RELIEF study is suitable for investigating the medical benefit and added benefit, and it bases its derivation of added benefit exclusively on the results of this study comparing apremilast versus placebo. The company's approach of deriving an added benefit exclusively on the basis of the placebo-controlled RELIEF study is inappropriate. Relying solely on the results of the RELIEF study means that the intervention to be assessed can be compared merely to placebo, but not to the ACT specified by the G-BA. In addition, as discussed above, the controlled study duration is too short to be included in the benefit assessment.

2.4 Results on added benefit

In its dossier, the company does not present any suitable data for assessing the added benefit of apremilast in comparison with the ACT. Consequently, there is no hint of added benefit of apremilast in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The company did not present any suitable data for the assessment of the added benefit of apremilast. Consequently, there is no proof of added benefit of apremilast in comparison with the ACT.

Table 5 presents a summary of the result of the benefit assessment of apremilast in comparison with the ACT.

Table 5: Apremilast – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with oral ulcers associated with Behçet's disease who are candidates for systemic therapy	Therapy upon the physician's discretion[b]	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. In the context of a clinical trial, the following drugs can be used as comparators: dapsone, azathioprine, cyclosporine, interferon alpha, TNF alpha inhibitors and thalidomide. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor		

The above assessment deviates from that of the company, which derived an indication of considerable added benefit.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a20-44-apremilast-behcet-s-disease-benefit-assessment-according-to-35a-social-code-book-v.13163.html.