Justification

Gemeinsamer Bundesausschuss

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Apremilast (New Therapeutic Indication: Behçet's Disease)

of 5 November 2020

Contents

1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient apremilast (Otezla®) was listed for the first time on 15 February 2015 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 8 April 2020, apremilast received marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 5 May 2020, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient apremilast with the new therapeutic indication “Otezla is indicated for the treatment of adult patients with oral ulcers associated with Behçet’s disease (BD) who are candidates for systemic therapy”.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 17 August 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of apremilast compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of apremilast.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of apremilast (Otezla®) in accordance with the product information

Otezla is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with oral ulcers associated with Behçet's disease who are candidates for systemic therapy.

Appropriate comparator therapy:

- Therapy according to the doctor's instructions

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal applications or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.

[1] General methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care), Cologne.

4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. The glucocorticoids prednisone and prednisolone and the active ingredient azathioprine have been approved in the present therapeutic indication. Azathioprine has been approved in patients with Behçet's disease if they are intolerant to glucocorticoids or if high doses of glucocorticoids do not elicit an adequate therapeutic effect.

On 2. There are no non-medicinal treatments for treatment of oral ulcers associated with Behçet's disease.

On 3. No resolutions of the G-BA have been made in the therapeutic indication considered here.

On 4. The general accepted state of medical knowledge on which the decision of the G-BA are based was illustrated by systematic research for guidelines and reviews of clinical studies in this indication.

There are currently no curative treatment options for Behçet's disease. Hence, treatment aims to alleviate symptoms, reduce inflammation, limit tissue damage and prevent life-threatening complications. Treatment choice depends on the combination of clinical symptoms and the severity of involvement of organs. Treatment focuses primarily on eye symptoms, the gastrointestinal tract, the CNS and cardiovascular symptoms. Oral ulcers are a frequent symptom associated with this disease.

In the present therapeutic indication, only the active ingredient azathioprine and the glucocorticoids prednisone and prednisolone are approved in treatment of Behçet's disease. Apremilast is to be used as an element of long-term therapy in patients with oral ulcers associated with Behçet's disease. Systemic glucocorticoids are used to treat exacerbations but solely on a short-term basis due to their side effects, so they cannot be considered as an appropriate comparative therapy in the indication at hand.

The European League Against Rheumatism (EULAR) guideline recommends as an element of systemic therapy the use of colchicine as first-line treatment of oral lesions in Behçet's disease. If patients gain insufficient relief of their symptoms, the use of immunomodulatory or immunosuppressive agents (azathioprine; thalidomide, interferon alpha or TNF alpha inhibitors) is recommended. An S2k guideline of the Association of Scientific Medical Societies in Germany (AWMF) on treatment of ulcers and ulcerated lesions of the oral and pharyngeal mucosa recommends the active ingredients azathioprine, cyclosporine and interferon alpha in patients with Behçet's disease. Thus, despite insufficient clinical data and the lack of approved treatment options, both guidelines agree in their recommendation of systemic therapy to treat oral ulcers associated with Behçet's disease. In contrast, the active ingredient dapsone is not mentioned in the EULAR guideline to treat oral lesions in Behçet's disease, while it represents only one possible treatment option for refractory and severe ulcers in the AWMF S2k guideline. Therefore, the active ingredient dapsone will receive no further consideration in determining the appropriate comparator therapy for the indication at hand.

In summary, the active ingredients azathioprine, cyclosporine, colchicine, interferon alpha, thalidomide and TNF alpha inhibitors can be considered in treatment of oral ulcers associated with Behçet's disease. It should be borne in mind that cyclosporine, colchicine, interferon alpha, thalidomide and TNF alpha inhibitors are not approved for the present indication. There is, thus, a discrepancy between medicinal products approved in the indication and those recommended in guidelines.

For adult patients with oral ulcers associated with Behçet's disease who are candidates for systemic therapy, treatment according to the doctor's instructions represents the

appropriate comparator therapy due to the limited body of evidence and in the absence of approved treatment options. In the context of treatment according to the doctor's instructions and in accordance with recommendations provided by the guidelines, the active ingredients azathioprine, cyclosporine, colchicine, interferon alpha, thalidomide and TNF alpha inhibitors can be considered. However, the fact that in a clinical study the above-mentioned active ingredients may be used in non-compliance with authorisation in no way serves as evidence of their usefulness in off-label use in standard care of SHI patients. Such an assessment would be reserved for a decision as per Section 35c SGB V. Off-label prescription in individual cases according to the established case law of the German Federal Social Court regarding off-label use not covered by the Pharmaceuticals Directive has no bearing on such a decision.

It is assumed that only those patients for whom topical therapy alone is not adequate will be treated.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of apremilast is assessed as follows:

For adult patients with oral ulcers associated with Behçet's disease who are candidates for systemic therapy an additional benefit for apremilast compared to the appropriate comparator therapy has not been proven.

Justification:

RELIEF study (apremilast vs placebo)

The pharmaceutical company presented the pivotal RELIEF study for the patient population under evaluation, in which apremilast (30 mg, oral, twice daily) was compared to placebo over a period of 12 weeks. The study included adult patients who had been diagnosed with Behçet's disease and who had developed at least three oral ulcers in the 12 months prior to the start of the study. Only patients who had experienced at least two oral ulcers and for whom topical treatment alone was considered inadequate by their doctor were included in the study. The patients were also required to have received non-biological therapy for Behçet's disease at least once. Patients with serious organ involvement (i.e. pulmonary, vascular, gastrointestinal or central nervous symptoms and ocular lesions requiring immunosuppressive therapy) were excluded from the study.

A total of 207 patients were included in the study and randomised at a 1:1 ratio. The patients were a mean 40 years of age and had been suffering from Behçet's disease for a mean of almost 7 years. At the start of the study, each patient had a mean 4 oral ulcers.

The primary endpoint of the study was the area under the curve for the number of oral ulcers. Further endpoints were the number, response rate and painfulness of oral ulcers, the time to complete remission or recurrence, as well as endpoints assessing disease activity, health-related quality of life and safety.

RELIEF, a placebo-controlled study, provides no data that would permit a comparison of apremilast with the appropriate comparator therapy. Comparison with a pure placebo is not consistent with the appropriate comparator therapy defined by the G-BA: treatment according to the doctor's instructions incorporating various systemic therapeutics. In addition, the directly comparative study duration of 12 weeks is considered too short to infer an additional benefit. Since Behçet's disease is a chronic disease in which oral ulcers recur, and apremilast is intended to be used as a component of long-term therapy, a minimum study period of 24 weeks is considered necessary to establish an additional benefit.

Indirect comparison

In line with the pharmaceutical company's assessment, the RELIEF study is not suitable to derive an additional benefit, and hence the pharmaceutical company examines the possibility of an adjusted indirect comparison via the bridge comparator, placebo. To this end, the pharmaceutical company draws on the RELIEF placebo-controlled pivotal study for the intervention and two placebo-controlled studies with the active ingredients etanercept and thalidomide to serve as comparator therapy.

Studies serving as comparator therapy

Melikoglu 2005 (etanercept vs placebo)

This trial is a double-blind, parallel RCT comparing treatment of Behçet's disease with etanercept (25 mg, injected twice weekly subcutaneously) versus placebo. However, the duration of this study is only 4 weeks and, thus, far too short to be drawn on to derive a benefit assessment for a chronic therapeutic indication.

Hamuryudan 1998 (thalidomide vs placebo)

This study is a double-blind, parallel RCT comparing treatment of genital and oral ulcers associated with Behçet's disease with thalidomide (300 mg/day orally or 100 mg/day orally) versus placebo. The study included adult male patients aged 18 to 35 years who had been diagnosed with Behçet's disease and who had experienced at least two episodes of oral or genital ulcers within the last three months prior to the start of the study. The presence of oral ulcers at the start of the study or the requirement for systemic therapy to treat ulcers was not an inclusion criterion in the study. Furthermore, patients with moderate to severe Behçet's disease symptoms in the eye and patients who had previously received immunosuppressive therapy were excluded.

The study comprised a 24-week controlled double-blind phase and a 4-week follow-up phase. The primary endpoint was a complete response, defined as complete freedom from oral or genital ulcers. Secondary endpoints were changes in the number of mucocutaneous lesions, the absence of uveitis or a decrease in visual acuity.

A total of 95 patients were enrolled in the study, randomised at a ratio of 1:1:1. The patients were a mean 28 years of age, had been suffering from Behçet's disease for a mean of almost 3 years and a mean 2 oral ulcers at the start of the study.

Suitability of the RELIEF and Hamuryudan 1998 studies to enable an indirect comparison

According to product information, apremilast is to be used in patients who are candidates for systemic therapy. However, no information is available on pre-treatment of the patients in the Hamuryudan 1998 study, and it is unclear whether systemic therapy was indicated for these patients and, hence, whether they meet the criteria to be of value for the issue under consideration.

Moreover, the baseline characteristics of the two studies are insufficiently similar. RELIEF included both men (38.5%) and women (61.5%). In contrast, only men were included in Hamuryudan 1998. Comparing the patient characteristics of the two studies also reveals that the mean age in Hamuryudan 1998 was a good 10 years younger (28 years) than in RELIEF (40 years). The studies also differ in terms of the duration of the disease (approximately 7 years in RELIEF vs approximately 3 years in Hamuryudan 1998). Patients in RELIEF had a higher disease burden at the start of the study than patients in Hamuryudan 1998: patients in RELIEF were suffering from approximately 4 oral ulcers and approximately 3 genital ulcers at the start of the study, while patients in Hamuryudan 1998 were suffering from approximately 2 oral ulcers and approximately 1 genital ulcer at the start of the study. Furthermore, a comparison of the findings of the studies is not possible due to differing operationalisations of the endpoints assessing the response to the therapy.

For the aforementioned reasons, the RELIEF and Hamuryudan 1998 studies are and are not suitable for indirect comparison, in line with the assessment of the pharmaceutical company.

Overall assessment

The pharmaceutical company has presented the pivotal study RELIEF for the benefit assessment, in which apremilast is compared over a period of 12 weeks with placebo. Consequently, the findings do not permit a comparison of the intervention with the appropriate comparator therapy. In addition, for a chronic disease such as Behçet's disease, a study period of 24 weeks is generally considered necessary. At 12 weeks, the actively controlled study duration is therefore too short to derive an additional benefit.

In addition, the pharmaceutical company examines whether it would be possible to perform an adjusted indirect comparison via the bridge comparator, placebo. To achieve this, in addition to the placebo-controlled study RELIEF for the intervention, the company presents two further placebo-controlled studies with the active ingredients etanercept and thalidomide to serve as comparator therapy. The Melikoglu 2005 study with the active ingredient etanercept is not suitable to be used for indirect comparison as the controlled duration of the study is only 4 weeks. The patient population of the Hamuryudan 1998 study with the active ingredient thalidomide is insufficiently similar to that of the apremilast study with regards to inclusion and exclusion criteria and patient characteristics at the start of the study, and, hence, this study is also not appropriate for indirect comparison. Therefore, an indirect comparison to derive an additional benefit is not conceivable.

In the overall view, the G-BA concludes that an additional benefit of apremilast compared with the appropriate comparator therapy is not proven.

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of a new therapeutic indication for the active ingredient apremilast. The therapeutic indication assessed here is as follows: Otezla is indicated for the treatment of adult patients with oral ulcers associated with Behçet's disease (BD) who are candidates for systemic therapy.

The G-BA defined the appropriate comparator therapy to be "treatment according to the doctor's instructions".

The pharmaceutical company has presented the pivotal study RELIEF for the benefit assessment, in which apremilast is compared over a period of 12 weeks with placebo. As the findings allow no comparison to be made with the appropriate comparator therapy and as the duration of the study, at only 12 weeks, is not deemed sufficiently long for a chronic condition such as Behçet's disease, the study cannot be drawn on to derive an additional benefit.

Furthermore, consideration is made as to whether an adjusted indirect comparison via the bridge comparator, placebo, might be possible. However, the selected studies are not well suited to form an indirect comparison, either because they are very short, lasting 4 weeks, or because of heterogeneous inclusion and exclusion criteria and differing patient characteristics at the start of the study.

In the overall view, the G-BA concludes that an additional benefit of apremilast compared with the appropriate comparator therapy is not proven.

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The G-BA bases the resolution on the estimate of the patient numbers derived by the pharmaceutical company in the dossier. This estimate is based both on data from the German register "Morbus Adamantiades-Behçet e.V." and on SHI routine data analysis. Despite existing uncertainties, the size of the target population specified by the pharmaceutical company generally appears plausible.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Otezla® (active ingredient: apremilast) at the following publicly accessible link (last access: 3 September 2020):

https://www.ema.europa.eu/documents/product-information/otezla-epar-product-information_en.pdf

Treatment with apremilast should only be initiated and monitored by specialists who are experienced in the treatment of patients with Behçet's disease.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 October 2020).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is different for each individual patient and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, the time between individual treatments, and the maximum treatment duration if specified in the product information.

For the calculation of the dosages as a function of body weight, the average body measurements from the official representative statistics “Microcensus 2017 – body measurements of the population” were used as a basis (average body weight): 77.0 kg).[2]

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Apremilast	continuously, 2 × daily	365	1	365
Appropriate comparator therapy				
Therapy according to the doctor’s instructions				
- Azathioprine[a]	continuously, 1 × daily	365	1	365

[a] Costs are only shown for the active ingredient azathioprine. In addition to azathioprine, the medicinal products cyclosporine, colchicine, interferon-alpha, thalidomide and TNF alpha inhibitors also represent suitable comparators for the present benefit assessment in the context of a therapy according to the doctor’s instructions. However, these medicinal products are not approved in the present therapeutic indication and therefore no costs are shown for them.

[2] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Apremilast	30 mg	60 mg	2 × 30 mg	365	730 × 30 mg
Appropriate comparator therapy					
Therapy according to the doctor's instructions					
- Azathioprine[a]	< 1 mg/kg - 3 mg/kg BW	25 mg – 231 mg	1 × 25 mg – 2 x 100 mg + 1 x 25 mg	365	365 × 25 mg – 730 x 100 mg + 365 x 25 mg

[a] Costs are only shown for the active ingredient azathioprine. In addition to azathioprine, the medicinal products cyclosporine, colchicine, interferon-alpha, thalidomide and TNF alpha inhibitors also represent suitable comparators for the present benefit assessment in the context of a therapy according to the doctor's instructions. However, these medicinal products are not approved in the present therapeutic indication and therefore no costs are shown for them.

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Apremilast	168 FCT	€ 3,193.22	€ 1.77	€ 0.00	€ 3,191.45
Appropriate comparator therapy					
Therapy according to the doctor's instructions					
- Azathioprine 25 mg[3]	100 FCT	€ 28.76	€ 1.77	€ 1.46	€ 25.53
- Azathioprine 100 mg[3]	100 FCT	€ 56.28	€ 1.77	€ 3.69	€ 50.82
Abbreviations: FCT = film-coated tablets					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 October 2020

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 6 August 2019, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

[3] Fixed reimbursement rate

On 5 May 2020, the pharmaceutical company submitted a dossier for the benefit assessment of apremilast to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 6 May 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient apremilast.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 August 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 17 August 2020. The deadline for submitting written statements was 7 September 2020.

The oral hearing was held on 21 September 2020.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 27 October 2020, and the proposed resolution was approved.

On 5 November 2020, the G-BA resolved by written statement to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	6 August 2019	Determination of the appropriate comparator therapy
Working group Section 35a	16 September 2020	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	21 September 2020	Conduct of the oral hearing
Working group Section 35a	30 September 2020 14 October 2020 21 October 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee on Medicinal Products	27 October 2020	Concluding discussion of the draft resolution
Plenum	5 November 2020	Written resolution on the amendment of Annex XII of the AM-RL

Berlin, 5 November 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken