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Baricitinib (atopic dermatitis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Baricitinib (atopische Dermatitis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 February 2021). 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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[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)
PDE	phosphodiesterase type 4
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
TCS	topical corticosteroids

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 baricitinib. 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 16 November 2020.

Research question

The aim of the present report is the assessment of the added benefit of baricitinib in comparison with the appropriate comparator therapy (ACT) in adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy.

In accordance with the G-BA's specification of the ACT, 2 research questions resulted for the benefit assessment. These are presented in Table 2.

Table 2: Research questions of the benefit assessment of baricitinib

Research question	Subindication	ACT[a]
Adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy		
A	Patients for whom long-term/continued systemic therapy is not indicated	An individually optimized treatment regimen consisting of topical and systemic therapy depending on the severity of the disease and under consideration of the prior therapy, choosing from the following therapies: ▪ topical class 2 to 4 glucocorticoids ▪ tacrolimus (topical) ▪ UV therapy (UVA/NB-UVB/balneo-phototherapy) ▪ systemic glucocorticoids (only short-term within the framework of a relapse treatment) ▪ ciclosporin
B	Patients for whom long-term/continued systemic therapy is indicated	Dupilumab (possibly in combination with TCS and/or TCI)

a. Presentation of the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); TCI: topical calcineurin inhibitors; TCS: topical corticosteroids; UVA: ultraviolet A light

The company did not consider research question A to be relevant and did not name an ACT for it. In research question B, the company followed the ACT specified by the G-BA.

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

Research question A: patients for whom long-term/continued systemic therapy is not indicated

The company did not present any data for the assessment of the added benefit of baricitinib in comparison with the ACT in the treatment of adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy and for whom long-term/continued systemic therapy is not indicated. This resulted in no hint of an added benefit of baricitinib in comparison with the ACT; an added benefit is therefore not proven.

Research question B: patients for whom long-term/continued systemic therapy is indicated

Due to the lack of a study of direct comparison, the company presented an adjusted indirect comparison of baricitinib versus dupilumab via the common comparator placebo for research question B. However, this adjusted indirect comparison is not suitable for drawing conclusions on the added benefit of baricitinib, as, with a treatment duration of 16 weeks, the study included on the comparator side for dupilumab (study CAFE) is too short. This concurs with the assessment of the company, which also did not use the adjusted indirect comparison for the derivation of an added benefit. Thus, no suitable data are available for the assessment of the added benefit of baricitinib in comparison with the ACT in the treatment of adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy and for whom long-term/continued systemic therapy is indicated. This resulted in no hint of an added benefit of baricitinib 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 presents a summary of the probability and extent of the added benefit of baricitinib.

[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: Baricitinib – probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy			
A	Patients for whom long-term/continued systemic therapy is not indicated	An individually optimized treatment regimen consisting of topical and systemic therapy depending on the severity of the disease and under consideration of the prior therapy, choosing from the following therapies: ▪ topical class 2 to 4 glucocorticoids ▪ tacrolimus (topical) ▪ UV therapy (UVA/NB-UVB/balneo-phototherapy) ▪ systemic glucocorticoids (only short-term within the framework of a relapse treatment) ▪ ciclosporin	Added benefit not proven
B	Patients for whom long-term/continued systemic therapy is indicated	Dupilumab (possibly in combination with TCS and/or TCI)	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); TCI: topical calcineurin inhibitors; TCS: topical corticosteroids; UVA: ultraviolet A light

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of baricitinib in comparison with the ACT in adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy.

In accordance with the G-BA's specification of the ACT, 2 research questions resulted for the benefit assessment. These are presented in Table 4.

Table 4: Research questions of the benefit assessment of baricitinib

Research question	**Subindication**	**ACT[a]**
Adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy		
A	Patients for whom long-term/continued systemic therapy is not indicated	An individually optimized treatment regimen consisting of topical and systemic therapy depending on the severity of the disease and under consideration of the prior therapy, choosing from the following therapies: ▪ topical class 2 to 4 glucocorticoids ▪ tacrolimus (topical) ▪ UV therapy (UVA/NB-UVB/balneo-phototherapy) ▪ systemic glucocorticoids (only short-term within the framework of a relapse treatment) ▪ ciclosporin
B	Patients for whom long-term/continued systemic therapy is indicated	Dupilumab (possibly in combination with TCS and/or TCI)
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); TCI: topical calcineurin inhibitors; TCS: topical corticosteroids; UVA: ultraviolet A light		

The company did not consider research question A to be relevant (see Section 2.3.1) and did not name an ACT for it. In research question B, the company followed the ACT specified by the G-BA.

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 the added benefit. This concurs with the company's inclusion criteria.

2.3 Research question A: patients for whom long-term/continued systemic therapy is not indicated

2.3.1 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 baricitinib (status: 17 August 2020)
- bibliographical literature search on baricitinib (last search on 17 August 2020)
- search in trial registries/trial results databases for studies on baricitinib (last search on 19 August 2020)
- search on the G-BA website for baricitinib (last search on 17 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on baricitinib (last search on 25 November 2020)

No relevant study was identified from the check of the completeness of the study pool for research question A.

The company did not consider research question A to be relevant, as the therapeutic concept of baricitinib according to the approval is based on long-term/continued systemic use. In order to fulfil the "formal completeness", the company nonetheless conducted an information retrieval for research question A. It included no study for a direct comparison in research question A.

The studies excluded by the company include the I4V-MC-JAIN study (hereinafter referred to as "JAIN"), which compared baricitinib with placebo + topical glucocorticoids (topical corticosteroids [TCS]). The company justified the exclusion of the study by stating that both the study population and the study intervention do not correspond to research question A. Rather, the included patients were to be assigned to subpopulation B due to their prior therapies, the high burden of symptoms, a very long duration of disease of about 25 years and the chronic nature of the disease.

The reasoning of the company for excluding the JAIN study for research question A is comprehensible. In the present assessment, the JAIN study was assigned to research question B due to its patient population and intervention.

2.3.2 Results on added benefit

The company did not present any data for the assessment of the added benefit of baricitinib in comparison with the ACT in the treatment of adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy and for whom long-term/continued systemic

therapy is not indicated. This resulted in no hint of an added benefit of baricitinib in comparison with the ACT; an added benefit is therefore not proven.

2.3.3 Probability and extent of added benefit

As there are no data available to assess the added benefit of baricitinib in comparison with the ACT for adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy and for whom long-term/continued systemic therapy is not indicated, an added benefit of baricitinib in this research question is not proven.

The company did not assess the extent and probability of an added benefit of baricitinib in the present research question A.

2.4 Research question B: patients for whom long-term/continued systemic therapy is indicated

2.4.1 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 baricitinib (status: 17 August 2020)
- bibliographical literature search on baricitinib (last search on 17 August 2020)
- search in trial registries/trial results databases for studies on baricitinib (last search on 19 August 2020)
- search on the G-BA website for baricitinib (last search on 17 August 2020)
- bibliographical literature search for the ACT (last search on 17 August 2020)
- search in trial registries/trial results databases for the ACT (last search on 19 August 2020)
- search on the G-BA website for the ACT (last search on 17 August 2020)

To check the completeness of the study pool:

- search in trial registries for studies on baricitinib (last search on 25 November 2020)

Concurring with the company, the check of the completeness of the study pool did not produce any RCTs of direct comparison of baricitinib versus dupilumab for research question B.

Adjusted indirect comparison presented by the company

Due to the lack of a study of direct comparison, the company presented an adjusted indirect comparison of baricitinib versus dupilumab via the common comparator placebo for research question B. It included the JAIN study for baricitinib and the R668-AD-1424 study (hereinafter referred to as “CAFE”) for dupilumab. The adjusted indirect comparison presented by the

company is not suitable for drawing conclusions on the added benefit of baricitinib versus the ACT, however. This is justified below.

The JAIN study [3] is a randomized, double-blind, 4-arm study comparing baricitinib (in 3 different dosages, including the approval-compliant dosage of 4 mg peroral [4]) versus placebo + TCS. All patients also received standardized background therapy with emollients and, in the case of active lesions, additional moderate-potency TCS or – depending on the skin region – tacrolimus, another topical calcineurin inhibitor or a topical phosphodiesterase type 4 (PDE4) inhibitor. The background therapy could be adapted or escalated, and administration of rescue therapy was also possible. Only patients with severe atopic dermatitis for whom therapy with ciclosporin was unsuitable were included. Reasons why ciclosporin was not an option for the included patients were, for example, a medical contraindication to ciclosporin (e.g. due to an accompanying disease or hypersensitivity to ciclosporin) or a history of insufficient response to ciclosporin. The double-blind treatment phase lasted 52 weeks; the company used the data cut-off at week 16 for the adjusted indirect comparison. It additionally presented data on week 24, but did not use them for its benefit assessment.

The CAFE study [5] is a randomized, double-blind, 3-arm study on the comparison of dupilumab (in 2 different dosages) with placebo. In one of the dupilumab arms, dupilumab was administered in compliance with the approval [6] as a subcutaneous injection with a starting dose of 600 mg and a biweekly maintenance dose of 300 mg. Moreover, all patients received a standardized background therapy with emollients and – depending on the skin region – moderate-potency or low-potency TCS. The background therapy could be adapted or escalated every 4 weeks, and administration of rescue therapy was also possible. Only patients with severe atopic dermatitis for whom therapy with ciclosporin was unsuitable for several reasons (e.g. due to an accompanying disease or hypersensitivity to ciclosporin) were included. The double-blind treatment phase was 16 weeks.

The adjusted indirect comparison presented by the company is not suitable for the assessment of research question B. Although the populations investigated in the studies JAIN and CAFE correspond to research question B, the treatment duration in the CAFE study, and thus also the presented adjusted indirect comparison at week 16, is too short for drawing conclusions on the added benefit of a long-term treatment of chronic atopic dermatitis (see also [7,8]). This assessment concurs with the rationale of the company, which also did not use the adjusted indirect comparison for the derivation of an added benefit.

2.4.2 Results on added benefit

The company did not provide any suitable data for the assessment of the added benefit of baricitinib in comparison with the ACT in the treatment of adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy and for whom long-term/continued systemic therapy is indicated. This resulted in no hint of an added benefit of baricitinib in comparison with the ACT; an added benefit is therefore not proven.

2.4.3 Probability and extent of added benefit

As there are no suitable data available to assess the added benefit of baricitinib in comparison with the ACT for adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy and for whom long-term/continued systemic therapy is indicated, an added benefit of baricitinib in this research question is not proven.

This concurs with the company's assessment.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of baricitinib in comparison with the ACT is summarized in Table 5.

Table 5: Baricitinib – probability and extent of added benefit

Research question	**Subindication**	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with moderate to severe atopic dermatitis who are candidates for systemic therapy			
A	Patients for whom long-term/continued systemic therapy is not indicated	An individually optimized treatment regimen consisting of topical and systemic therapy depending on the severity of the disease and under consideration of the prior therapy, choosing from the following therapies: ▪ topical class 2 to 4 glucocorticoids ▪ tacrolimus (topical) ▪ UV therapy (UVA/NB-UVB/balneo-phototherapy) ▪ systemic glucocorticoids (only short-term within the framework of a relapse treatment) ▪ ciclosporin	Added benefit not proven
B	Patients for whom long-term/continued systemic therapy is indicated	Dupilumab (possibly in combination with TCS and/or TCI)	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); TCI: topical calcineurin inhibitors; TCS: topical corticosteroids; UVA: ultraviolet A light

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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