Gemeinsamer Bundesausschuss

Justification

on 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 Baricitinib (new therapeutic indication: moderate to severe atopic dermatitis)

of 6 May 2021

Contents

1. Legal basis

According to Section 35a (1) 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 submission 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:

1st Approved therapeutic indications,

2nd Medical benefit,

3rd Additional medical benefit in relation to the appropriate comparator therapy,

4th Number of patients and patient groups for whom there is a therapeutically significant additional benefit,

5th Treatment costs for statutory health insurance funds,

6th 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 (3) SGB V, the G-BA decides on the benefit assessment within three months of its publication. The decision is to be published online and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient baricitinib (Olumiant) was listed for the first time in the Great German Specialties Tax (Lauer Tax) on 1 April 2017.

On 19 October 2020, baricitinib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2a to Commission Regulation (EC) No 1234/2008 of 24 November 2008 concerning the examination of amendments to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 16 November 2020, i.e. at the latest within four weeks after the pharmaceutical company was informed of the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in accordance with Section 4 (3) number 2 of the Ordinance on the Benefit Assessment of Pharmaceutical Products (AM-NutzenV) in conjunction with Chapter 5, Section 8 (1) number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient baricitinib with the new indication (treatment of adult patients with moderate to severe

atopic dermatitis who are eligible for systemic therapy). The G-BA commissioned IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 February 2021 on the website of the G-BA (www.g-ba.de), 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 baricitinib 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 IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of baricitinib.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has come to 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 baricitinib (Olumiant) in accordance with product information

Olumiant is indicated for the treatment of moderate to severe atopic dermatitis in adult patients eligible for systemic therapy.

Therapeutic indication of the resolution (resolution of 6/5/2021):

see new therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adult patients with moderate to severe atopic dermatitis who are eligible for continuous systemic therapy

Appropriate comparator therapy:

Dupilumab (in combination with TCS and/or TCI if required)

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 in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven

1 General Methods, version 6.0 of 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
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. Medicinal products with the following active ingredients are approved for the present therapeutic indication:

- topical glucocorticoids of classes 2 to 4
- Pimecrolimus (moderate atopic eczema) and Tacrolimus (moderate to severe atopic eczema)
- systemic glucocorticoids (severe eczema)
- Ciclosporin (severe atopic dermatitis)
- Antihistamines
- Dupilumab

on 2. UV treatments (UVA/NB-UVB/balneophototherapy) are eligible as non-medicinal treatments, but UVA1 is not eligible as it is not a reimbursable treatment.

on 3. In the therapeutic indication under consideration here, the following decisions of the G-BA are available:

- Therapeutic information on Tacrolimus (resolution of 4 September 2003) and Pimecrolimus (resolution of 4 September 2003)
- Resolution on the benefit assessment according to Section 35a SGB V for the active ingredient dupilumab dated 17 May 2018 and 20 February 2020
- Resolution on the amendment of the Directive of Prescription of Medicinal Products in SHI-accredited Medical Care (MVV-RL): "Balneophototherapy for atopic eczema," 20 March 2020

on 4. The generally recognised state of medical knowledge on which the resolution of the G-BA is based, was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication.

According to the marketing authorisation, those patients are included in the therapeutic indication who are eligible for a systemic therapy.

For the present benefit assessment, adult patients with moderate to severe atopic dermatitis for whom continuous systemic therapy is indicated are considered.

For the present patient population of adults with moderate to severe atopical dermatitis eligible for continuous systemic therapy, the active ingredient dupilumab is available as further therapy option. Based on the benefit assessment resolution of 17 May 2018, dupilumab was able to show evidence of considerable additional benefit compared with the appropriate comparator therapy in adults. In the context of the available evidence, dupilumab represents an adequate therapeutic option for patients with moderate to severe atopic dermatitis who are eligible for continuous systemic therapy. Therefore, there is beneficial evidence for an active ingredient that has now also proven itself in practical application.

Even with permanent or continuous systemic therapy, topical glucocorticoids (TCS) in classes 2 to 4 and the calcineurin inhibitor (TCI) tacrolimus may also be indicated as topical therapy options for individual lesions or in a limited period of time.

For patients for whom continuous systemic therapy is indicated, dupilumab (possibly in combination with TCS and/or TCI) is the appropriate comparator therapy.

Change of the appropriate comparator therapy:

To date, two separate patient populations have been identified for adult patients with moderate to severe atopic dermatitis who are eligible for systemic therapy, including split appropriate comparator therapy.

Patient group a) included adult patients with moderate to severe atopic dermatitis for whom continuous systemic therapy is not indicated. Patient group b) included adult patients with moderate to severe atopic dermatitis for whom continuous systemic therapy is indicated.

This division was made because the wording of the approved therapeutic indication includes the treatment of moderate to severe atopic dermatitis without further specification/restriction. Depending on the severity of the disease and the patient's pre-treatment, both topical therapies and systemic therapies may also be used according to the topical and systemic therapy recommendations. Particularly as atopic dermatitis is a disease with fluctuating symptomatology - including seasonal - the treatment has to be individually adapted. Not all patients require a permanent and continuous systemic therapy, but are also adequately treated with a patient-individual therapy consisting of TCS/TCI as well as a short-term flare therapy with systemic glucocorticoids. A temporary therapy with ciclosporine can also be considered. Based on this medical rationale, two patient groups were identified.

However, in the context of the comments on the benefit assessment of baricitinib, it became clear that patients who are eligible for therapy with baricitinib do not correspond to the patient group that can be adequately treated with a therapy regime consisting of topical and systemic therapy that is optimised for the individual patient. This results from the different therapy concept of baricitinib (and also dupilumab), as both active ingredients are exclusively used as continuous therapy.

Overall, taking into account the clinical treatment situation and the findings from the statement procedure, the G-BA therefore considers it appropriate to adjust the patient population and to conduct the benefit assessment for those patients for whom continuous systemic therapy is indicated.

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

2.1.3 Extent and probability of the additional benefit

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

Adult patients with moderate to severe atopic dermatitis who are eligible for continuous systemic therapy

For adult patients with moderate to severe atopic dermatitis who are eligible for continuous systemic therapy, the additional benefit for baricitinib compared to the appropriate comparator therapy is not proven.

Justification:

In the assessment of the additional benefit of baricitinib, the pharmaceutical company does not present any suitable direct-comparative studies with a sufficiently long study duration compared to the appropriate comparator therapy in his dossier.

Due to the lack of a direct comparative study, the pharmaceutical company presents an adjusted indirect comparison of baricitinib versus dupilumab via the bridge comparator placebo for adult patients eligible for continuous systemic therapy.

For the indirect comparison, the JAIN study will be included for baricitinib, and the R668-AD-1424 (CAFE) study will be included for dupilumab. The JAIN study is a randomised, double-blind, 4-arm study comparing baricitinib (at 3 different doses, including the 4 mg peroral dose compliant with the marketing authorisation) versus placebo + TCS. All patients also received standardised background therapy with emollients and, in the case of active lesions, additional medium-strength TCS or - depending on the skin region - tacrolimus, another topical calcineurin inhibitor or a topical PDE-4 inhibitor. The background therapy could be adjusted or titrated, and the administration of rescue therapy was also possible. Only patients with severe atopical dermatitis for whom a therapy with ciclosporin was not suitable were included. The double-blind treatment phase lasted 52 weeks, and the data cut-off at week 16 is used for the adjusted indirect comparison.

The CAFE study is a randomised, double-blind, 3-arm study comparing dupilumab (at 2 different doses) with placebo. All patients also received a standardised background therapy with emollients and - depending on the skin region - moderately or weakly effective TCS. The background therapy could be adjusted or escalated every 4 weeks, and the administration of rescue therapy was also possible. Only patients with severe atopic dermatitis for whom a therapy with ciclosporin was not suitable for various reasons (e.g. due to a concomitant disease or hypersensitivity to ciclosporin) were included. The double-blind treatment phase lasted 16 weeks.

However, the adjusted indirect comparison presented by the company is not suitable for the assessment of the additional benefit. Although the groups examined in the studies JAIN and CAFE correspond to patients for whom a continuous systemic therapy is indicated, the duration of treatment in the CAFE study and thus also the presented adjusted indirect comparison to week 16 is too short to make statements on the additional benefit of a permanent treatment of the chronic atopical dermatitis.

This adjusted indirect comparison is therefore not suitable for making statements on the additional benefit of baricitinib, as the study included on the comparison page for dupilumab (CAFE study) with a treatment duration of 16 weeks is too short. Therefore, no suitable data

are available for the assessment of the additional benefit of baricitinib compared to the appropriate comparator therapy in the treatment of adult patients with moderate to severe atopic dermatitis for whom systemic therapy is an option and for whom continuous systemic therapy is indicated. This does not provide any hint for an additional benefit of baricitinib compared with the appropriate comparator therapy; an additional benefit is therefore not proven.

2.1.4 Summary of the assessment

The present assessment is a benefit assessment of a new therapeutic indication for the active ingredient baricitinib. The therapeutic indication assessed here is as follows: "Olumiant is indicated for the treatment of moderate to severe atopic dermatitis in adult patients who are eligible for systemic therapy."

Dupilumab (in combination with TCS and/or TCI if required) was determined by the G-BA as an appropriate comparator therapy.

Due to the lack of a direct comparative study, the pharmaceutical company presents an adjusted indirect comparison of baricitinib versus dupilumab via the bridge comparator placebo for adult patients eligible for continuous systemic therapy.

This adjusted indirect comparison is not suitable for making statements on the additional benefit of baricitinib, as the study included on the comparison page for dupilumab (CAFE study) is too short with a treatment duration of 16 weeks. Therefore, no suitable data are available for the assessment of the additional benefit of baricitinib compared to the appropriate comparator therapy in the treatment of adult patients with moderate to severe atopic dermatitis for whom systemic therapy is an option and for whom continuous systemic therapy is indicated. This does not provide any hint for an additional benefit of baricitinib compared with the appropriate comparator therapy; an additional benefit is therefore 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 information is based on the data from the resolution of the G-BA on dupilumab[2] in the therapeutic indication area of moderate to severe atopic dermatitis in adults who are eligible for systemic therapy and information from the written statement procedure.

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) has published the contents of the product information (Summary of Product Characteristics, SmPC) for Olumiant (active ingredient: baricitinib) is freely available at the following link (last accessed: 14 April 2021):

[2] Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V of 17 May 2018

https://www.ema.europa.eu/documents/product-information/olumiant-epar-product-information_de.pdf

In patients in whom no therapeutic benefit can be demonstrated after 8 weeks of treatment, discontinuation of treatment should be considered.

In accordance with the requirements for risk minimisation activities in the EPAR (European Public Assessment Report), the following information material on baricitinib must be provided by the pharmaceutical company:

- Training and information material for the doctor/medical staff
- Training and information material for the patient

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 April 2021).

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 patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments / patient / year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Baricitinib is approved for use alone or in combination with topical glucocorticoids (TCS) or topical calcineurin inhibitors (TCI) for the treatment of adult patients with moderate to severe atopic dermatitis. A therapy with TCS or TCI can be considered in combination with baricitinib as well as in combination with dupilumab. As a result, the corresponding costs for TCS or TCI, if applicable, are incurred both for the medicinal product to be assessed and for the appropriate comparator therapy and are therefore not listed separately.

Treatment duration:

Name of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Days of treatment/patient/ Year
Medicinal product to be assessed				
Baricitinib	continuously, once a day	365	1	365
Appropriate comparator therapy				
Dupilumab	once every 14 days	26.1	1	26.1

Consumption:

Name of the therapy	Dosage/ application	Dosage/ patient/ days of treatment	Consumption according to potency/ treatment day	Days of treatment/ Patient/ Year	Annual average consumption by potency
Medicinal product to be assessed					
Baricitinib	4 mg	4 mg	1 x 4 mg	365	365 x 4 mg
Appropriate comparator therapy					
Dupilumab	300 mg	300 mg	1 x 300 mg	26.1	26.1 x 300 mg

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:

Name of the therapy	Package size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate § 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Baricitinib	98 FCT	€ 4,078.46	€ 1.77	€ 229.65	€ 3,847.04
Appropriate comparator therapy					
Dupilumab	6 ILO	€4,337.01	€ 1.77	€244.41	€4,090.83

LAUER-TAXE® last revised: 15 April 2021

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 evaluated 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 the standard expenditure in the course of the treatment are not shown.

Prior to treatment with baricitinib, patients should be tested for tuberculosis infection. The costs presented are a blood test (quantitative determination of an in vitro interferon-gamma release after ex vivo stimulation with antigens specific for Mycobacterium tuberculosis-complex (except BCG)) and a chest radiograph. The tuberculin skin test is not mapped due to lack of sensitivity and specificity as well as the possibility of "sensitisation".

In addition, patients should be screened for the presence of HBV infection before starting treatment with baricitinib. For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required[3]. A serological step-by-step diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If HBs antigen is positive, an active HBV infection is detected.

These tests are not required when using dupilumab.

Overall, additional necessary SHI services are required for the diagnosis of suspected chronic hepatitis B as well as for the examinations for tuberculosis infections, which usually differ between the drug to be evaluated and the appropriate comparative therapy and are therefore considered as additionally required SHI services in the resolution.

[3] "Update of the S3 guideline on prophylaxis, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011" https://www.awmf.org/uploads/tx_szleitlinien/021-011l_S3_Hepatitis_B_Virusinfektionen_Prophylaxe_Diagnostik_Therapie_2011-abgelaufen.pdf

Name of the therapy	Name of the service	Number/	Costs/unit	Costs/patient/year
Medicinal product to be assessed: Baricitinib				
Baricitinib	Quantitative determination of an in vitro interferon-gamma release after ex vivo stimulation with antigens (at least ESAT-6 and CFP-10) specific for Mycobacterium tuberculosis-complex (except BCG) (GOP 32670)	1	€ 58.00	€ 58.00
Baricitinib	X-ray thorax (GOP 34241)	1	€ 16.24	€ 16.24
Baricitinib	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	anti-HBs antibody (GOP 32617)[4]	1	€ 5.50	€ 5.50
	anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)[5]	1	€ 89.50	€ 89.50
Appropriate comparator therapy: Dupilumab				
not applicable				

3. Bureaucratic cost calculation

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 meeting on 28 July 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

[4] Only if HBs antigen negative and anti-HBc antibody positive
[5] Invoicing for GOP 32823 possible before or during antiviral therapy with interferon and/or nucleic acid analogues.

On 16 November 2020, the pharmaceutical company submitted a dossier for the benefit assessment of baricitinib to the G-BA in due time in accordance with Chapter 5, Section 8(1)(2) of the VerfO.

By letter dated 16 November 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 baricitinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 February 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 March 2021. The deadline for submitting the written statement procedure was 9 March 2021.

The oral hearing was held on 23 March 2021.

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 meetings.

The evaluation of the written statements received and the oral hearing were discussed at the meeting of the subcommittee on 27 April 2021, and the draft resolution was approved.

At its meeting on 6 May 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Meeting	Date	Subject of consultation
Subcommittee Medicinal products	28 July 2020	Determination of the appropriate comparator therapy
Working group Section 35a	17 March 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	23 March 2021	Conduct of the oral hearing
Working group Section 35a	30 March 2021 14 April 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	27 April 2021	Concluding consultation of the draft resolution
Plenum	6 May 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 6 May 2021

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

Prof. Hecken