

Justification

of the Resolution of the Federal Joint Committee (G-BA) on
an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with
New Active Ingredients according to Section 35a (SGB V)
Baricitinib (new therapeutic indication: enthesitis-related
arthritis, ≥ 2 years)

of 2 May 2024

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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 the 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 is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient baricitinib was listed for the first time on 2 April 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 5 May 2023, the pharmaceutical company submitted an application to postpone the start date of the benefit assessment procedure for baricitinib in the therapeutic indication "active juvenile idiopathic arthritis (JIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs" according to Section 35a paragraph 5b SGB V.

At its session on 15 June 2023, the G-BA approved the application pursuant to Section 35a paragraph 5b SGB V and postponed the relevant date for the start of the benefit assessment and the submission of a dossier for the benefit assessment for the therapeutic indication in question to four weeks after the marketing authorisation of the other therapeutic indication of the therapeutic indication covered by the application, at the latest six months after the first relevant date. The marketing authorisation for the other therapeutic indication covered by

the application according to Section 35a paragraph 5b SGB V were granted within the 6-month period.

On 15 September 2023, baricitinib received the extension of the marketing authorisation for the therapeutic indication "active juvenile idiopathic arthritis (JIA) in patients 2 years of age and older who have had an inadequate response or intolerance to one or more conventional synthetic or biological DMARDs". The extension of the marketing authorisation for the therapeutic indication "paediatric patients (2 years of age and older) with moderate to severe atopic dermatitis who are candidates for systemic therapy" was granted on 18 October 2023. Both extensions of the marketing authorisation are classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 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, 12.12.2008, sentence 7).

On 13 November 2023, the pharmaceutical company has 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 baricitinib with the new therapeutic indication:

"Baricitinib is indicated for the treatment of active juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic DMARDs:

- Enthesitis-related arthritis.

Baricitinib may be used as monotherapy or in combination with methotrexate."

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 February 2024 on the G-BA website (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:

¹ General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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

2.1.1 Approved therapeutic indication of Baricitinib (Olmiant) in accordance with product information

Baricitinib is indicated for the treatment of active juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic DMARDs:

- Enthesitis-related arthritis.

Baricitinib may be used as monotherapy or in combination with methotrexate.

Therapeutic indication of the resolution (resolution of 2 May 2024):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

- a) Children aged 2 to 5 years with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

Appropriate comparator therapy for baricitinib, alone or in combination with MTX:

- Adalimumab or etanercept

- b) Children and adolescents 6 years of age and older with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

Appropriate comparator therapy for baricitinib, alone or in combination with MTX:

- Adalimumab or etanercept (≥ 12 years) or secukinumab

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 para. 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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 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 G-BA 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

- on 1. Besides baricitinib, glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying antirheumatic drugs (csDMARDs; including MTX, sulfasalazine and hydroxychloroquine) and biologic DMARDs (bDMARDs; here etanercept, adalimumab and secukinumab) are approved for the treatment of enthesitis-associated arthritis (EAA) in the therapeutic indication. For the approved therapeutic indications of csDMARDs and bDMARDs, some specifications on the approved age have to be additionally considered.
- on 2. Non-medicinal measures at the expense of the SHI are not considered as sole appropriate comparator therapy in the present therapeutic indication.
- on 3. In the therapeutic indication to be considered here, there is a G-BA resolution from 5 January 2023 on the benefit assessment of medicinal products with new active ingredients for the active ingredient secukinumab.
- on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication.

The scientific-medical societies and the Drugs Commission of the German Medical Association (AkDÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

For the treatment of patients 2 years of age and older with EAA, it can first be stated that different diseases are distinguished within the juvenile idiopathic arthritis (JIA) indication; EAA represents one of these subtypes, usually without a polyarticular course.

Due to the age restriction of the dosage instructions in the product information for baricitinib to patients 2 to under 18 years of age and taking into account the statement of the competent national regulatory authority (BfArM) on this matter, the G-BA assumes that patients 18 years of age and older are not covered by the marketing authorisation. The marketing authorisation of baricitinib in the therapeutic indication of juvenile idiopathic arthritis therefore relates exclusively to children and adolescents between 2 and 17 years of age.

The German guideline on juvenile idiopathic arthritis (S2k guideline of the DGKJ and GKJR from 2020) also takes enthesitis-related arthritis into account in parts, but references are mainly made to evidence from the polyarticular juvenile idiopathic arthritis (pJIA). In the overall assessment, the guideline recommends the use of csDMARDs for the treatment of EAA after failure of (symptomatic) NSAIDs and, if necessary, short-term use of glucocorticoids, especially in the presence of peripheral EAA. If there is an inadequate response or intolerance to csDMARDs, the guideline advocates the use of TNF α inhibitors². The specific value of MTX in combination with a TNF α inhibitor in cases of inadequate response or intolerance to csDMARDs within enthesitis-related arthritis cannot be assessed at present.

The American College of Rheumatology/Arthritis Foundation guideline from 2019 also recommends the use of TNF α inhibitors for children with active enthesitis-related arthritis³.

The TNF-alpha inhibitor adalimumab is approved for the treatment of active enthesitis-related arthritis in patients 6 years of age and older who have had an inadequate response or intolerance to a conventional therapy. The TNF-alpha inhibitor etanercept is approved for the treatment of enthesitis-related arthritis in adolescents 12 years of age and older who have had an inadequate response or intolerance to a conventional therapy. The IL-17 inhibitor secukinumab is approved for the treatment of active enthesitis-related arthritis in patients 6 years of age and older whose disease had an inadequate response or intolerance to a conventional therapy. Accordingly, no approved therapy options are available in this therapeutic indication for children 2 to 5 years of age (patient population a).

² Society for Paediatric and Adolescent Rheumatology (GKJR) and German Society for Paediatrics (DGKJ), 2020 (S2k guideline "Therapy of Juvenile Idiopathic Arthritis", AWMF Registry No. 027/020):

- Recommendation 6: "If there is an insufficient response or intolerance to csDMARD therapy (e.g. MTX), TNF-alpha inhibition should be used for non-systemic JIA and can be used for systemic JIA. The choice of TNF blocker should take into account the presence of extra-articular symptoms. (Consensus strength: 100%)"

³ Ringold S et al., 2019 (American College of Rheumatology/Arthritis Foundation Guideline for the Treatment of Juvenile Idiopathic Arthritis: Therapeutic Approaches for Non-Systemic Polyarthritis, Sacroiliitis, and Enthesitis):

- Recommendations for the initial and subsequent treatment of children and adolescents with JIA and enthesitis: "In children and adolescents with active enthesitis despite treatment with NSAIDs: Using a TNFi is conditionally recommended over methotrexate or sulfasalazine. (Level of evidence: Low)"

The use of TNF α inhibitors is recommended for children and adolescents with active EAA who have had an inadequate response or intolerance to a conventional or biological therapy (see above). Secukinumab is a new therapeutic alternative in this therapeutic indication that is not yet explicitly mentioned in the guidelines. The evidence base for the existing guideline recommendations must be categorised as limited in each case. There are no major, randomised studies in this therapeutic indication that would be necessary to derive stronger evidence. According to the above guideline recommendations, TNF α inhibitors for children and adolescents 2 years of age and older are to be regarded as the therapy standard in the therapeutic indication under consideration here. In the definable patient population of children 2 to 5 years of age with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs (patient population a), the use of etanercept and adalimumab as unapproved therapy options is medically necessary in the absence of approved alternatives. In the overall assessment, it is therefore appropriate according to Section 6, paragraph 2, no. 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) to determine the off-label use of the active ingredients adalimumab or etanercept as appropriate comparator therapy for patient population a.

The appropriate comparator therapy determined here for patient population a includes several therapy options. These therapeutic alternatives are equally appropriate for the comparator therapy.

In the overall assessment, the use of TNF α inhibitors is also considered appropriate for children and adolescents 6 years of age and older (patient population b). In addition, the IL-17 inhibitor secukinumab is also an approved therapy option for these patients. Taking into account the comments of the clinical experts at the oral hearing and the specifications on the approved age, a therapy with adalimumab or etanercept (≥ 12 years) or secukinumab is determined as the appropriate comparator therapy for children and adolescents 6 years of age and older with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs.

The appropriate comparator therapy determined here includes several therapy options for patient population b. In this context, individual therapy options only represent a comparator therapy for the part of the patient population that has the patient characteristics specified in brackets. The therapeutic alternatives are only to be considered equally appropriate in the therapeutic indication, where the patient populations have the same characteristics.

It is assumed that the patients covered by the therapeutic indication are not (or no longer) eligible for (symptomatic) therapy with NSAIDs and/or glucocorticoids alone. Irrespective of this, the use of glucocorticoids (systemic and/or intra-articular) should always be possible in the context of flare therapy.

Change of the appropriate comparator therapy

To date, the TNF α inhibitors adalimumab or etanercept (≥ 12 years) have been considered appropriate comparator therapy for children and adolescents 6 years of age and older with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs (patient population b). In the opinion of the clinicians involved in the written statement procedure, this no longer corresponds to the current medical treatment situation. Accordingly, all approved bDMARDs have a comparable significance in the treatment of active EAA. The options mentioned are to be regarded as equivalent; a differential

therapy recommendation or criteria for the selection of one of these treatment options are not available. Adalimumab, etanercept (≥ 12 years) and secukinumab can therefore be considered equally appropriate therapy options in the overall assessment.

For this reason, the G-BA considers it appropriate to change the appropriate comparator therapy for patient population b and to specify therapy with adalimumab or etanercept (≥ 12 years) or secukinumab as the appropriate comparator therapy for patient population b.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

- a) Children aged 2 to 5 years with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

For children 2 to 5 years of age with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs, the additional benefit is not proven.

- b) Children and adolescents 6 years of age and older with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

For children and adolescents 6 years of age and older with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs, the additional benefit is not proven.

Justification for patient populations a) and b):

The pharmaceutical company does not present any data for both patient populations on the assessment of the additional benefit of baricitinib compared to the appropriate comparator therapy.

In accordance with the pharmaceutical company, no suitable studies for a comparison of baricitinib with the appropriate comparator therapy could be identified. In the label-enabling I4V-MC-JAHV study (JUVE-BASIS), all patients initially received baricitinib for 12 weeks, followed by a double-blind treatment phase lasting up to 32 weeks, during which patients with a response were randomised to further treatment with baricitinib or placebo. In accordance with the pharmaceutical company's approach in the dossier, this study is not considered for the present benefit assessment due to the lack of comparison with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient baricitinib.

The therapeutic indication assessed here is as follows: "Baricitinib is indicated for the treatment of active juvenile idiopathic arthritis in patients 2 years of age and older who have had an inadequate response or intolerance to one or more prior conventional synthetic or biologic DMARDs: enthesitis-related arthritis. Baricitinib may be used as monotherapy or in combination with methotrexate."

In the therapeutic indication under consideration, two patient groups were differentiated according to age with regard to the availability of approved therapy options.

Patient group a)

Children aged 2 to 5 years with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

The G-BA determined a therapy with adalimumab or etanercept or as the appropriate comparator therapy.

In accordance with the pharmaceutical company's approach, no studies could be identified in the dossier for this patient group that would allow a comparison of baricitinib with the appropriate comparator therapy.

An additional benefit of baricitinib compared to the appropriate comparator therapy is therefore not proven.

Patient group b)

Children and adolescents 6 years of age and older with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

The G-BA determined a therapy with adalimumab or etanercept (≥ 12 years) or secukinumab as the appropriate comparator therapy.

In accordance with the pharmaceutical company's approach, no studies could be identified in the dossier for this patient group that would allow a comparison of baricitinib with the appropriate comparator therapy.

An additional benefit of baricitinib compared to the appropriate comparator therapy 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 provided by the pharmaceutical company in the dossier. The calculation of the size of the target population was based on a routine data analysis from the dossier for the benefit assessment of the active ingredient secukinumab⁴ and is subject to uncertainties in the overall assessment. These result, among other things, from prevalence

⁴ Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V for secukinumab dated 5 January 2023.

data that refer to different age groups, as well as uncertainties regarding the operationalisation of an active disease or an inadequate response and intolerance.

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 Olumiant (active ingredient: baricitinib) at the following publicly accessible link (last access: 10 January 2024):

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

Treatment with baricitinib should only be initiated and monitored by doctors experienced in the therapy of enthesitis-related arthritis.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (incl. patient identification card).

In particular, the training material contains information and warnings on the risk of serious and opportunistic infections including tuberculosis and herpes zoster. It also points out the need for an effective contraceptive method.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 15 April 2024).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

Treatment period:

- a) Children aged 2 to 5 years with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Baricitinib	Continuously,	365.0	1	365.0

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x daily			
Methotrexate, if necessary	Continuously, 1 x every 7 days	52.1	1	52.1
Appropriate comparator therapy				
Adalimumab or etanercept				
Adalimumab	Continuously, 1 x every 14 days	26.1	1	26.1
Etanercept	Continuously, 2 x in 7 days	104.3	1	104.3
	or Continuously, 1 x in 7 days	or 52.1	or 1	or 52.1

- b) Children and adolescents 6 years of age and older with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Baricitinib	Continuously, 1 x daily	365.0	1	365.0
Methotrexate, if necessary	Continuously, 1 x every 7 days	52.1	1	52.1
Appropriate comparator therapy				
Adalimumab or etanercept or secukinumab				
Adalimumab	Continuously, 1 x every 14 days	26.1	1	26.1
Etanercept	Continuously, 2 x in 7 days	104.3	1	104.3
	or Continuously, 1 x in 7 days	or 52.1	or 1	or 52.1

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Secukinumab	Continuously, 1 x monthly	12.0	1	12.0
Methotrexate, if necessary	Continuously, 1 x every 7 days	52.1	1	52.1

Consumption:

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 varies from patient to patient 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.

Methotrexate is available on the market in both oral and parenteral dosage forms. For cost representation, it is assumed that patients 6 years of age and older generally receive the more economical option (tablets). Conversely, the parenteral dosage form is used to calculate the annual treatment costs for the lower limit of the range (children ≥ 2 years of age), as it is often not possible to administer tablets to children 2-5 years of age.

- a) Children aged 2 to 5 years with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

The active ingredients adalimumab and etanercept are not approved for enthesitis-related arthritis in the age group considered here. Against this background, the information on dosage for juvenile idiopathic arthritis from the respective product information was used for the cost representation. Methotrexate is approved for children 3 years of age and older. For cost representation, the dosage was calculated here as a function of body surface area for children 2 years of age and older.

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population⁵" (average body weight of two-year-olds at 14.1 kg and 5-year-olds at 20.8 kg, as well as body height of two-year-olds at 0.93 m and 5-year-olds at 1.15 m). This results in a body surface area of 0.59 m² for two-year-olds, 0.81 m² for 5-year-olds (calculated according to Du Bois 1916).

⁵ Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

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					
Baricitinib	2 mg	2 mg	1 x 2 mg	365.0	365.0 x 2 mg
Methotrexate	$\frac{10-15 \text{ mg/m}^2}{\text{BSA}}$ 5.9 mg – 12.15 mg	5.9 mg – 12.15 mg	1 x 7.5 mg – 1 x 12.5 mg	52.1	52.1 x 7.5 mg – 52.1 x 12.5 mg
Appropriate comparator therapy					
Adalimumab or etanercept					
Adalimumab	20 mg	20 mg	1 x 20 mg	26.1	26.1 x 20 mg
Etanercept	$\frac{0.4-0.8 \text{ mg/kg BW}}{\text{BSA}}$ 5.64 mg – 16.64 mg	5.64 mg – 16.64 mg	1 x 10 mg – 2 x 10 mg	104.3 – 52.1	104.3 x 10 mg – 104.2 x 10 mg

- b) Children and adolescents 6 years of age and older with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

For dosages depending on body weight (BW) or body surface area (BSA), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population⁵" (average body weight of 6-year-olds at 23.6 kg and 12-year-olds at 47.1 kg, as well as body height of 6-year-olds at 1.22 m). This results in a body surface area of 0.9 m² for 6-year-olds (calculated according to Du Bois 1916). The "Microcensus 2021 – body measurements of the population⁶" was applied for the 17-year-olds (average body weight: 67.2 kg, average body height: 1.74 m). This results in a body surface area of 1.81 m² (calculated according to Du Bois 1916).

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					
Baricitinib	2 mg – 4 mg	2 mg – 4 mg	1 x 2 mg – 1 x 4 mg	365.0	365.0 x 2 mg – 365.0 x 4 mg
Methotrexate, if necessary	$\frac{10-15 \text{ mg/m}^2}{\text{BSA}}$ 9.0 mg –	9.0 mg – 27.15 mg	1 x 10 mg – 2 x 10 mg + 1 x 7.5 mg	52.1	52.1 x 10 mg – 104.2 x 10 mg + 52.1 x 7.5 mg

⁶ Federal Health Reporting. Average body measurements of the population (2021, both sexes, 15 years and older), www.gbe-bund.de

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	27.15 mg				
Appropriate comparator therapy					
Adalimumab or etanercept ⁷ or secukinumab ⁸					
Adalimumab	20 mg – 40 mg	20 mg – 40 mg	1 x 20 mg – 1 x 40 mg	26.1	26.1 x 20 mg – 26.1 x 40 mg
Etanercept	<u>0.4-0.8 mg/kg BW</u>	18.84 mg –	2 x 10 mg –	104.3	208.6 x 10 mg –
	18.84 mg – 50.00 mg ⁹	50.00 mg	1 x 50 mg	52.1	52.1 x 50 mg
Secukinumab	75 mg – 150 mg	75 mg – 150 mg	1 x 75 mg – 1 x 150 mg	12.0	12.0 x 75 mg – 12.0 x 150.0 mg
Methotrexate, if necessary	<u>10-15 mg/m² BSA</u> 9.0 mg – 27.15 mg	9.0 mg – 27.15 mg	1 x 10 mg – 2 x 10 mg + 1 x 7.5 mg	52.1	52.1 x 10 mg – 104.2 x 10 mg + 52.1 x 7.5 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 Section 130 and Section 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. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

a) Children aged 2 to 5 years with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

and

b) Children and adolescents 6 years of age and older with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

⁷ 12 years of age and older according to the marketing authorisation

⁸ 6 years of age and older according to the marketing authorisation

⁹ The maximum daily dose of etanercept is 50 mg when administered once a week and 25 mg when administered twice a week.

Designation of the therapy	Packaging 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					
Baricitinib 2 mg	98 FCT	€ 4,043.77	€ 2.00	€ 227.65	€ 3,814.12
Baricitinib 4 mg	98 FCT	€ 4,043.77	€ 2.00	€ 227.65	€ 3,814.12
Methotrexate 7.5 mg ¹⁰	30 TAB	€ 33.75	€ 2.00	€ 1.77	€ 29.98
Methotrexate 7.5 mg ¹⁰	SFIP 12 FS	€ 153.99	€ 2.00	€ 11.28	€ 140.71
Methotrexate 10 mg ¹⁰	30 TAB	€ 41.63	€ 2.00	€ 2.40	€ 37.23
Methotrexate 12.5 mg ¹⁰	SFIP 12 FS	€ 206.20	€ 2.00	€ 15.41	€ 188.79
Appropriate comparator therapy					
Adalimumab 20 mg	1 SFI	€ 256.22	€ 2.00	€ 13.56	€ 240.66
Adalimumab 40 mg ¹⁰	6 SFI	€ 2,859.20	€ 2.00	€ 0.00	€ 2,857.20
Etanercept 10 mg	4 DSS	€ 207.07	€ 2.00	€ 10.84	€ 194.23
Etanercept 50 mg ¹⁰	12 SFI	€ 2,859.20	€ 2.00	€ 0.00	€ 2,857.20
Secukinumab 75 mg	1 SFI	€ 406.41	€ 2.00	€ 0.00	€ 404.41
Secukinumab 150 mg	6 SFI	€ 4,654.03	€ 2.00	€ 0.00	€ 4,652.03
Abbreviations: FCT = film-coated tablets; SFIPFS = solution for injection in a pre-filled syringe; SFI = solution for injection; PEN = solution for injection in a pre-filled pen; TAB = tablets; DSS = dry substance with solvent					

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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.

Because there are no 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, no costs for additionally required SHI services need to be taken into account.

The additionally required SHI services for screening for HBV infection and tuberculosis infection are incurred equally for the medicinal product to be assessed and the appropriate comparator therapy, so that they are not presented.

¹⁰ Fixed reimbursement rate

2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designates all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA has decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA has decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding information in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA has decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

- a) Children aged 2 to 5 years with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

No medicinal product with new active ingredients that can be used in a combination therapy and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for baricitinib (Olumiant); Olumiant 1 mg/2 mg/4 mg film-coated tablets; last revised: October 2023

- b) Children and adolescents 6 years of age and older with active enthesitis-related arthritis who have had an inadequate response or intolerance to one or more conventional synthetic or biologic DMARDs

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for baricitinib (Olumiant); Olumiant 1 mg/2 mg/4 mg film-coated tablets; last revised: October 2023

3. Bureaucratic costs 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 session on 06 September 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy defined by the G-BA took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 26 September 2023.

On 13 November 2023, 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, paragraph 2 VerfO.

By letter dated 15 November 2023 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 13 February 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 February 2024. The deadline for submitting statements was 7 March 2024.

The oral hearing was held on 25 March 2024.

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 was discussed at the session of the subcommittee on 23 April 2024, and the proposed resolution was approved.

At its session on 2 May 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	6 September 2022	Implementation of the appropriate comparator therapy
Subcommittee Medicinal products	26 September 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	19 March 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	25 March 2024	Conduct of the oral hearing
Working group Section 35a	3 April 2024 16 April 2024	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee Medicinal products	23 April 2024	Concluding discussion of the draft resolution
Plenum	2 May 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 2 May 2024

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken