Gemeinsamer Bundesausschuss

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)
Bimekizumab
(new therapeutic indication: ankylosing spondylitis)

of 21 December 2023

Contents

1. Legal basis

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

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for 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 bimekizumab (Bimzelx) was listed for the first time on 15 September 2021 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 5 June 2023, bimekizumab received marketing authorisation for a new therapeutic indication to be 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 29 June 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 3 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 bimekizumab with the new therapeutic indication

“Bimzelx is indicated for the treatment of adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy.”

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The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 2 October 2023 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 bimekizumab compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of bimekizumab.

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 Bimekizumab (Bimzelx) according to product information

Bimzelx is indicated for the treatment of adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy.

Therapeutic indication of the resolution (resolution of 21 December 2023):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy

Appropriate comparator therapy for bimekizumab:

- a TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL17 inhibitor (secukinumab or ixekizumab)

b) Adults with active ankylosing spondylitis who have had an inadequate response or who have been intolerant to a prior biological disease-modifying antirheumatic drug (bDMARD) therapy

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

Appropriate comparator therapy for bimekizumab:

- Switching to a different biological disease-modifying antirheumatic drug: TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL17 inhibitor (secukinumab or ixekizumab)

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. In addition to bimekizumab, nonsteroidal anti-inflammatory drugs (NSAIDs) for the symptomatic treatment of pain and inflammation, glucocorticoids, biologic agents and JAK inhibitors are also approved in this therapeutic indication. The marketing authorisation covers biologic agents and JAK inhibitors in the therapeutic indication following a failure to respond to conventional therapies (or in the case of intolerance/contraindication to NSAIDs). In the present therapeutic indication, these are the TNF-α inhibitors adalimumab, golimumab, certolizumab pegol, etanercept and infliximab, the IL-17 inhibitors secukinumab and ixekizumab as well as the JAK inhibitors upadacitinib and tofacitinib.

on 2. A non-medicinal treatment paid by the SHI is not considered as an appropriate comparator therapy in the therapeutic indication.

on 3. For the treatment of ankylosing spondylitis, there are resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient secukinumab dated 2 June 2016, for the active ingredient ixekizumab dated 21 January 2021, for the active ingredient upadacitinib dated 15 July 2021 and for the active ingredient tofacitinib dated 16 June 2022.

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.

The active ankylosing spondylitis (AS) is the radiographic form of active axial spondyloarthritis (radiographic axSpA, r-axSpA); both terms are used synonymously. For the therapeutic indication, it is assumed that for patients after failure of a conventional therapy or NSAIDs, a continuation of the sole conventional therapy with NSAIDs or glucocorticoids is not (any longer) indicated according to medical assessment.

The ASAS-EULAR guideline[2] does not explicitly differentiate between the radiographic and non-radiographic forms of axSpA in its therapy recommendations, as patients had been found to be largely similar in terms of clinical presentation, disease burden, including comorbidities, treatment received and response. According to the German S3 guideline[3], r-axSpA (ankylosing spondylitis) and nr-axSpA are also one clinical picture. A distinction by the severity grade of axSpA apparent in the underlying evidence is also not noticeable: Neither the German S3 guideline nor the ASAS-EULAR/ EMA guidelines[4]

[2] ASAS-EULAR recommendations: Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis 2023;82(1):19-34.

[3] German Society for Rheumatology (DGRh). Axial spondyloarthritis including ankylosing spondylitis and early forms; S3 guideline [online]. AWMF register number 060-003. Version 2019. Berlin (GER): Association of the Scientific Medical Societies (AWMF); 2019.

[4] EMA Guideline on the clinical investigation of medicinal products for the treatment of Axial Spondyloarthritis - Adopted guideline (CPMP/EWP/4891/03 Rev.1) 12 October 2017; EMA Draft Guideline on the clinical

distinguish between severity grade in their recommendations for axSpA. Rather, a treatment decision is made in everyday care depending on the disease manifestation (e.g. axial, peripheral), the failure to respond to previous therapies and the disease activity.

Both the German S3 guideline and the European ASAS-EULAR guideline provide for the evidence-based use of NSAIDs in conventional (first-line) therapy of axSpA (symptomatic or continuous use). After the failure of therapy with NSAIDs or conventional therapy, the use of biologic agents (bDMARDs) is recommended on the basis of the available evidence. Conventional, classical DMARDs (e.g. MTX, sulphasalazine, leflunomide) are neither approved for the therapeutic indication axSpA nor is their use supported by the available evidence. The guidelines describe the use of both the older TNF-α inhibitors and the newer bDMARDs (IL-17 inhibitors).

Within the product class of TNF-α inhibitors, no distinction is made in the therapy recommendation so that there is accordingly no prioritisation within the TNF-α inhibitors approved in Germany. Furthermore, no head-to-head comparisons of the active ingredients would allow prioritisation; the evidence is mainly based on RCTs with placebo comparisons.

In addition to the TNF-α inhibitors, the IL-17 inhibitors secukinumab and ixekizumab are equally recommended. The G-BA did not determine an additional benefit of both active ingredients because no suitable data were available for a comparison with the appropriate comparator therapy. In medical treatment practice, the IL-17 inhibitors secukinumab and ixekizumab have established themselves as equal-ranking therapy options alongside TNF-α inhibitors for the treatment of ankolysing spondylitis after therapy failure on NSAIDs since their marketing authorisation in the therapeutic indication in November 2015 and June 2020, respectively. In the ASAS-EULAR guideline, TNF-α inhibitors and IL-17 inhibitors are considered equal, even in the absence of head-to-head comparisons of the active ingredients.

No additional benefit was derived for the JAK inhibitors upadacitinib and tofacitinib in the early benefit assessment. The ASAS-EULAR guideline also emphasises that there is less clinical experience, a smaller evidence base and less information on drug safety for JAK inhibitors. JAK inhibitors are associated with an increased risk of serious side effects.[5] According to the clinical experts involved in the written statement procedure, JAK inhibitors are therefore of secondary importance in the treatment of axial spondyloarthritis. Based on the generally recognised state of medical knowledge and taking into account the German standard of care, upadacitinib and tofacitinib are not determined to be an appropriate comparator therapy for the present procedure.

Since the therapy recommendations in the ASAS-EULAR guideline in the therapeutic indication of axSpA - including ankylosing spondylitis - are based in particular on the criterion of failure on prior therapies, the present therapeutic indication includes both patients who have responded inadequately to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) (so-called "second-line therapy") and patients who have responded inadequately to prior therapy with biologic antirheumatic drugs (so-called "third-line therapy"). As these two patient populations differ in the clinical course to date as well as in terms of therapy recommendations, a subdivision into two patient populations is made.

investigation of medicinal products for the treatment of Axial Spondyloarthritis - Draft (CPMP/EWP/4891/03 Rev.1) 2016.

[5] see product information of Xeljanz (tofacitinib) and Rinvoq (upadacitinib)

In the overall assessment, according to the current state of medical knowledge, the approved TNF-α inhibitors (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) and the IL-17 inhibitors secukinumab and ixekizumab can be considered as equally appropriate therapy options for the "second-line therapy" (failure to respond to conventional therapies) of ankylosing spondylitis. For the "third-line therapy" of ankylosing spondylitis after the failure of a first TNF-α inhibitor or IL-17 inhibitor, the evidence is overall weaker compared to "second-line therapy". Regardless of this, even after failure of a bDMARD, the available evidence does not allow prioritisation within the active ingredients of TNF-α inhibitors or IL-17 inhibitors considered for "third-line therapy". Instead, it depends on comorbidities and patient-individual criteria as well as on the previous therapy to which further bDMARD is switched after the failure of a first therapy with a bDMARD. Against this background, in this line of therapy of active ankylosing spondylitis, a switch to another approved bDMARD that is established in use is currently considered appropriate. Further differentiation of the patient population (e.g. also with regard to failure to respond to one versus more than one bDMARD) is not made at this time due to the lack of uniform therapy recommendations.

Taking into account the respective authorisation status of the medicinal products in conjunction with the clinical course and against the background of the available body of evidence, a TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (secukinumab or ixekizumab) is determined as appropriate comparator therapy for the treatment of adults with active ankylosing spondylitis who have responded inadequately to conventional therapy (patient group a). These therapeutic alternatives are equally appropriate for the comparator therapy.

For adults with active ankylosing spondylitis who have had an inadequate response or intolerance to previous therapy with biological disease-modifying antirheumatic drugs (bDMARD) (patient group b), a switch to another biological disease-modifying antirheumatic drug is determined to be an appropriate comparator therapy: explicitly switching to another TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL-17 inhibitor (secukinumab or ixekizumab). These therapeutic alternatives are equally appropriate for the comparator therapy.

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 bimekizumab is assessed as follows:

a) <u>Adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy</u>

The additional benefit is not proven for adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy.

b) Adults with active ankylosing spondylitis who have had an inadequate response or who have been intolerant to a prior biological disease-modifying antirheumatic drug (bDMARD) therapy

The additional benefit is not proven for adults with active ankylosing spondylitis who have had an inadequate response or who have been intolerant to a prior biological disease-modifying antirheumatic drug (bDMARD) therapy.

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 bimekizumab compared to the appropriate comparator therapy.

The BE MOBILE 2 study presented in the dossier is a randomised controlled trial comparing bimekizumab with placebo in the treatment of adult patients with active ankylosing spondylitis. 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 bimekizumab.

The therapeutic indication assessed here is as follows: “Bimzelx is indicated for the treatment of adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy.”

In the therapeutic indication to be considered, two patient groups were distinguished:

a) Adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy

and

b) Adults with active ankylosing spondylitis who have had an inadequate response or who have been intolerant to a prior biological disease-modifying antirheumatic drug (bDMARD) therapy

On patient group a)

The G-BA determined a therapy with a TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (secukinumab or ixekizumab) as an appropriate comparator therapy.

For the assessment of the additional benefit, the pharmaceutical company presents the BE MOBILE 2 RCT, in which bimekizumab was compared to 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.

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

On patient group b)

The G-BA determined switching to another bDMARD (TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL-17 inhibitor (secukinumab or ixekizumab)) as an appropriate comparator therapy.

For the assessment of the additional benefit, the pharmaceutical company presents the BE MOBILE 2 RCT, in which bimekizumab was compared to 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.

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

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

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 on the benefit assessment procedure of the active ingredient tofacitinib[6]. These figures are based on prevalence and incidence data from diagnosed patients. In the overall assessment, the number of patients in the tofacitinib procedure tends to be underestimated and is fraught with uncertainties. This results in the same number of patients that also formed the basis in the early benefit assessment of ixekizumab and upadacitinib[7] respectively. Despite the uncertainties, the figures from the tofacitinib procedure are considered to be lesser underestimated than those from the pharmaceutical company in the present 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) provides the contents of the product information (summary of product characteristics, SmPC) for Bimzelx (active ingredient: bimekizumab) at the following publicly accessible link (last access: 28 September 2023):

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

Treatment with bimekizumab should only be initiated and monitored by doctors experienced in treating ankylosing spondylitis.

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: 1 December 2023.

[6] Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V for tofacitinib dated 16 June 2022.
[7] Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for ixekizumab dated 21 January 2021 as well as for upadacitinib dated 15 July 2021.

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.

a) Adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy

and

b) Adults with active ankylosing spondylitis who have had an inadequate response or who have been intolerant to a prior biological disease-modifying antirheumatic drug (bDMARD) therapy

Treatment period:

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 the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Bimekizumab	Continuously, 1 x every 28 days	13.0	1	13.0
Appropriate comparator therapy				
TNF-α inhibitor				
Adalimumab	Continuously, 1 x every 14 days	26.1	1	26.1
Certolizumab pegol	Continuously, 1 x every 14 days or Continuously, 1 x every 28 days	26.1 or 13.0	1 1	26.1 or 13.0
Etanercept	Continuously, 2 x within 7 days or Continuously,	52.1 or 52.1	2 1	104.2 or 52.1

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x every 7 days			
Golimumab	Continuously, 1 x monthly	12.0	1	12.0
Infliximab	Continuously, 1 x every 14 days	26.1	1	26.1
IL-17 inhibitor				
Ixekizumab	Continuously, 1 x every 28 days	13.0	1	13.0
Secukinumab	Continuously, 1 x monthly	12.0	1	12.0

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Bimekizumab	160 mg	160 mg	1 x 160 mg	13.0	13.0 x 160 mg
Appropriate comparator therapy					
TNF-α inhibitor					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Certolizumab pegol	200 mg or 400 mg	200 mg or 400 mg	1 x 200 mg or 2 x 200 mg	26.1 or 13.0	26.1 x 200 mg or 26.0 x 200 mg
Etanercept	25 mg or 50 mg	25 mg or 50 mg	1 x 25 mg or 1 x 50 mg	104.2 or 52.1	104.2 x 25 mg or 52.1 x 50 mg
Golimumab	50 mg	50 mg	1 x 50 mg	12.0	12.0 x 50 mg
Infliximab	120 mg	120 mg	1 x 120 mg	26.1	26.1 x 120 mg
IL-17 inhibitor					
Ixekizumab	80 mg	80 mg	1 x 80 mg	13.0	13.0 x 80 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Secukinumab	150 mg – 300 mg	150 mg – 300 mg	1 x 150 mg – 1 x 300 mg	12.0	12.0 x 150 mg – 12.0 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 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:

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					
Bimekizumab 160 mg	4 SFI	€ 5,998.30	€ 2.00	€ 242.34	€ 5,753.96
Appropriate comparator therapy					
Adalimumab 40 mg[8]	6 SFI	€ 2,859.20	€ 2.00	€ 228.57	€ 2,628.63
Certolizumab pegol 200 mg[8]	6 SFI	€ 2,859.20	€ 2.00	€ 0.00	€ 2,857.20
Etanercept 25 mg[8]	24 SFI	€ 2,859.20	€ 2.00	€ 228.57	€ 2,628.63
Etanercept 50 mg[8]	12 SFI	€ 2,859.20	€ 2.00	€ 228.57	€ 2,628.63
Golimumab 50 mg[8]	3 SFI	€ 2,605.96	€ 2.00	€ 0.00	€ 2,603.96
Infliximab 120 mg	6 IFE	€ 4,118.45	€ 2.00	€ 397.56	€ 3,718.89
Ixekizumab 80 mg	3 PEN	€ 3,989.32	€ 2.00	€ 160.38	€ 3,826.94
Secukinumab 150 mg	6 PEN	€ 4,654.03	€ 2.00	€ 187.50	€ 4,464.53
Secukinumab 300 mg	3 PEN	€ 4,654.03	€ 2.00	€ 187.50	€ 4,464.53
Abbreviations: IFE = solution for injection in a pre-filled syringe; SFI = solution for injection; PEN = solution for injection in a pre-filled pen					

LAUER-TAXE® last revised: 1 December 2023

[8] Fixed reimbursement rate

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 the use of upadacitinib or the TNF-α inhibitor of the appropriate comparator therapy (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the patients must be examined for active and inactive ("latent") tuberculosis infections. In addition, patients must be tested for the presence of HBV infection before starting therapy with the TNF-α inhibitors of the appropriate comparator therapy (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab).

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Bimekizumab Adalimumab Certolizumab pegol Etanercept Golimumab Infliximab	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
	Chest radiograph (GOP 34241)	1	€ 16.78	€ 16.78
Adalimumab Certolizumab pegol Etanercept Golimumab Infliximab	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)[9]	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32817)[10]	1	€ 89.50	€ 89.50

2.5 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 Bimekizumab

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

[9] Only if HBs antigen negative and anti-HBc antibody positive.
[10] Settlement of GOP 32817 for diagnosis of HBV reactivation or before, during, at the end of or after discontinuation of specific antiviral therapy.

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) Adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy

   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 bimekizumab (Bimzelx); Bimzelx 160 mg solution for injection in a prefilled syringe/prefilled pen; last revised: June 2023

b) Adults with active ankylosing spondylitis who have had an inadequate response or who have been intolerant to a prior biological disease-modifying antirheumatic drug (bDMARD) therapy

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 bimekizumab (Bimzelx); Bimzelx 160 mg solution for injection in a prefilled syringe/prefilled pen; last revised: June 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 23 January 2018, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place once the positive opinion was granted. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 23 May 2023.

On 29 June 2023 the pharmaceutical company submitted a dossier for the benefit assessment of bimekizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 3 July 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 bimekizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 September 2023, and the written statement procedure was initiated with publication on the G-BA website on 2 October 2023. The deadline for submitting statements was 23 October 2023.

The oral hearing was held on 6 November 2023.

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 12 December 2023, and the proposed resolution was approved.

At its session on 21 December 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	23 January 2018	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	23 May 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	31 October 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	6 November 2023	Conduct of the oral hearing
Working group Section 35a	14 November 2023 5 December 2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 December 2023	Concluding discussion of the draft resolution
Plenum	21 December 2023	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 21 December 2023

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

Prof. Hecken