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: psoriatic arthritis, monotherapy or in combination with methotrexate)

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, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs)."

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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 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, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. 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, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).

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 psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy

Appropriate comparator therapy:

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

– a TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if necessary in combination with methotrexate

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

Appropriate comparator therapy:

– switching to another biological disease-modifying antirheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or ustekinumab), if necessary in combination with methotrexate

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 the therapeutic indication for psoriatic arthritis, the following active ingredients of different product classes are approved:

- Steroidal antirheumatic drugs: prednisolone, prednisone, triamcinolone
- non-steroidal anti-inflammatory drugs (NSAIDs): e.g. acemetacin
- Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs): methotrexate, leflunomide
- Biologic disease-modifying antirheumatic drugs (bDMARDs):
  - TNF-alpha inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab
  - Interleukin inhibitors: guselkumab, ixekizumab, secukinumab, ustekinumab, risankizumab
  - Inhibitor of T-cell activation: abatacept
- Targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs):
  - JAK inhibitors: tofacitinib, upadacitinib
  - Phosphodiesterase-4 inhibitor: apremilast

on 2. Non-medicinal measures as sole appropriate comparator therapy are not considered in the present therapeutic indication.

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

- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient apremilast dated 6 August 2015.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient ixekizumab dated 16 August 2018.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient tofacitinib from the 21 February 2019.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient secukinumab dated 18 February 2021.

- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient guselkumab dated 20 May 2021.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient upadacitinib dated 15 July 2021.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient risankizumab dated 19 May 2022.

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

Bimekizumab is approved for patients who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drugs. Mere treatment of these patients with non-steroidal anti-inflammatory drugs or glucocorticoids is no longer adequate. Even if the local injection of glucocorticoids in particular may be used as add-on therapy in some patients, non-steroidal anti-inflammatory drugs and glucocorticoids do not represent an appropriate treatment option in the present therapeutic indication, which is why both product classes are not considered further in the determination of the appropriate comparator therapy.

The inhibitor of T-cell activation abatacept and the phosphodiesterase-4 inhibitor apremilast are not relevant in the treatment of active psoriatic arthritis and are only considered as a secondary treatment option in the current therapy recommendations of the European League Against Rheumatism (EULAR 2020)[2]. Against the background of the diverse treatment options, both active ingredients are therefore not seen as part of the appropriate comparator therapy.

JAK inhibitors are associated with an increased risk of serious side effects.[3] According to the clinical experts involved in the written statement procedure, JAK inhibitors are therefore of secondary importance in the treatment of psoriatic arthritis.

The significance of the selective IL-23 inhibitors guselkumab and risankizumab cannot be conclusively assessed against the background of the unproven additional benefit and the lack of guideline recommendations. Based on the generally recognised state of medical knowledge and taking into account the German standard of care, tofacitinib, upadacitinib, guselkumab and risankizumab are not determined as appropriate comparator therapy for the present procedure.

On a) <u>Adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.</u>

For patients who have had an inadequate response or intolerance to previous conventional disease-modifying antirheumatic (csDMARD) therapy, initial treatment with a bDMARD is indicated. For these patients, therapy with a TNF-alpha inhibitor

2 Gossec L, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020;79:700-712.
3 See the product information for Xeljanz (tofacitinib) and Rinvoq (upadacitinib) respectively.

(adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), an interleukin-17 inhibitor (ixekizumab and secukinumab) or an interleukin-12/23 inhibitor (ustekinumab) is recommended according to the current therapy recommendations of the European League Against Rheumatism (EULAR 2020)[2].

For adults who have had an inadequate response or have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy, the TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the interleukin-17 inhibitors ixekizumab and secukinumab and the interleukin-12/23 inhibitor ustekinumab, if necessary in combination with methotrexate, are therefore determined to be equally appropriate therapeutic options.

On b) Adults with active psoriatic arthritis who have had an inadequate response or have been intolerant to a prior biologic disease-modifying antirheumatic drug (bDMARD) therapy.

For adults who have responded inadequately to, or who are intolerant to a biologic disease-modifying antirheumatic drug treatment (bDMARDs), switching to another bDMARD (TNF-alpha inhibitor, interleukin inhibitor) is recommended.

For adults who have responded inadequately to, or who are intolerant to a biologic disease-modifying antirheumatic drug treatment (bDMARDs), TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the interleukin-17 inhibitors ixekizumab and secukinumab and the interleukin-12/23 inhibitor ustekinumab, if necessary in combination with methotrexate, were determined to be equally appropriate treatment options in case of change of therapy. Continuation of an inadequate therapy does not correspond to the implementation of the appropriate 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) Adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy

The additional benefit has not been proven for adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.

Justification for patient population a):

For the benefit assessment, the pharmaceutical company submits the randomised controlled trial BE OPTIMAL, in which bimekizumab is compared with adalimumab or placebo, each in monotherapy or in combination therapy. The placebo arm is not considered in the benefit assessment as it does not allow a comparison with the appropriate comparator therapy.

The treatment duration with the study medication was 52 weeks. The study population comprises adult patients with at least 6 months of active psoriatic arthritis defined according to the Classification Criteria for the Diagnosis of Psoriatic Arthritis (CASPAR criteria). Patients had to have ≥ 3 swollen and ≥ 3 pressure pain sensitive joints and active plaque psoriasis or a documented history. In addition, the patients were not allowed to have received prior bDMARD treatment. Pretreatment with csDMARDs was possible. Only patients whose psoriatic arthritis had begun in adulthood were enrolled.

Under defined conditions, therapies with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), nonsteroidal anti-inflammatory drugs (NSAIDs), COX-2 inhibitors, analgesics and oral corticosteroids started before the start of study could be continued during treatment with the study medication. The following active ingredients were defined as csDMARDs in the study: Methotrexate, sulphasalazine, leflunomide, methotrexate sodium, apremilast, ciclosporin, tofacitinib, hydroxychloroquine sulphate, azathioprine. Bimekizumab and adalimumab are used as monotherapy or in combination with methotrexate in accordance with the marketing authorisation. The use of csDMARDs as a concomitant therapy to bimekizumab or adalimumab was therefore not compliant with the marketing authorisation for all study participants. If there was an inadequate response to therapy by week 16, the concomitant therapy could be adjusted. The initiation of biologic therapy led to study discontinuation.

For the benefit assessment, the pharmaceutical company submits results for the sub-population with at least one previous csDMARD therapy for which it states that they have had an inadequate response or intolerance to csDMARD therapy. The sub-population includes 339 patients in the bimekizumab arm and 108 in the adalimumab arm. Based on the information subsequently submitted during the written statement procedure, the pharmaceutical company was able to verify the plausibility of the fact that a total of at least 80% of the submitted sub-population had both responded inadequately to a previous csDMARD therapy or had not tolerated it and had been treated in monotherapy or in combination with csDMARDs in accordance with the marketing authorisation. The sub-population is therefore used for the benefit assessment.

Extent and probability of the additional benefit

Mortality

There were no deaths in the BE OPTIMAL study.

Morbidity

Minimal disease activity (MDA)

For the MDA endpoint, there is no statistically significant difference between bimekizumab and adalimumab.

Remission (DAPSA ≤ 4)

For the remission endpoint (DAPSA ≤ 4), there is no statistically significant difference between bimekizumab and adalimumab.

Pressure pain sensitive joints (TJC68 ≤ 1)

For the TJC68 endpoint, there is no statistically significant difference between the treatment groups.

Swollen joints (SJC66 ≤ 1)

For the SJC66 endpoint, there is no statistically significant difference between the treatment groups.

Enthesitis

Enthesitis is operationalised via the LEI and SPARCC enthesitis index. The assessment is primarily based on the LEI.

For enthesitis, measured using LEI, the mean change at week 52 is used. There is no statistically significant difference between bimekizumab and adalimumab. No suitable data are available for enthesitis measured using the SPARCC enthesitis index as the responder analyses only include patients with SPARCC > 0 at baseline, thus excluding 65.3% of the relevant sub-population.

Axial involvement (BASDAI)

For the endpoint of axial involvement (BASDAI), there is no statistically significant difference between bimekizumab and adalimumab.

Arthritic pain (PtAAP VAS)

For the endpoint of arthritic pain (PtAAP VAS), there is no statistically significant difference between bimekizumab and adalimumab.

Patient-reported global disease activity (PGA-PsA VAS)

For the endpoint of patient-reported global disease activity (PGA-PsA VAS), there is no statistically significant difference between bimekizumab and adalimumab.

Impairment due to the disease (PsAID-12)

For the endpoint of impairment due to the disease (PsAID-12), there is no statistically significant difference between bimekizumab and adalimumab.

Health status (EQ-5D VAS)

For the endpoint of health status (EQ-5D VAS), there is no statistically significant difference between bimekizumab and adalimumab.

Physical functional status (HAQ-DI)

The mean change at week 52 is used for the endpoint of physical functional status (HAQ-DI). There is no statistically significant difference between bimekizumab and adalimumab.

Fatigue (FACIT-Fatigue)

For the endpoint of fatigue (FACIT-Fatigue), there is no statistically significant difference between bimekizumab and adalimumab.

Skin symptomatology (Psoriasis Area and Severity Index (PASI))

In the German health care context, the PASI represents a standard instrument for the classification of severity by doctors and is considerably relevant for the diagnosis and monitoring of disease severity in health care. The PASI is used in conjunction with other instruments to determine the severity grade of psoriasis disease. The symptoms redness, lichenification and scaling of the skin are assessed by the physician for each of the body regions head, trunk, upper limbs and lower limbs with a score between 0 (absent) and 4 (very severe). The proportion of the body surface area affected is estimated by the principal investigator as a percentage of the total body surface area. Based on the evaluation of the symptoms and the assessment of the affected body surface area, an overall score is obtained. The PASI score can range from 0 (no evidence of psoriasis) to 72.

In the course of the study, the endpoint was only collected in patients with psoriasis on ≥ 3% of the body surface area at baseline. Only 49% of the relevant sub-population was included in the evaluations of the PASI (PASI100, PASI90 and PASI75). This approach of the pharmaceutical company is inappropriate. Even patients who have no or only mild skin symptomatology at the start of study can develop these symptoms during further disease progression. Due to the selected operationalisation of the pharmaceutical company, it is not possible to derive statements for the entire target population. In addition, the PASI is the standard instrument for categorising severity and monitoring disease severity, so that for half of the patients no information is available on this central instrument for assessing symptomatology and disease severity in psoriasis. The clinical experts involved in the written statement procedure also confirmed that it would have been preferable to analyse the entire patient population at baseline. Taken together, it would therefore have been necessary to include all patients in the evaluation of the PASI. The responder analyses on these endpoints are therefore unsuitable for the benefit assessment.

modified Nail Psoriasis Severity Index (mNAPSI)

The endpoint was only assessed during the study in patients with a value > 0 at the start of study. The evaluations of the mNAPSI did not include 44.7% of the relevant sub-population. The responder analyses for this endpoint are therefore - as with the PASI - unsuitable for the benefit assessment.

Dactylitis (LDI)

For the dactylitis endpoint, responder analyses are available for the entire sub-population, although only a few patients were included with their actual observed values. At week 52, the percentage of patients whose values were replaced by non-responder imputation (NRI) was around 60%. It is unclear in how many patients the missing values are due to a change in the protocol for collecting the LDI depending on the symptomatology. The evaluations of the LDI are therefore unsuitable for the benefit assessment.

Quality of life

SF-36

For the health-related quality of life as collected using the SF-36, there is no statistically significant difference between bimekizumab and adalimumab neither for the mental nor for the physical component sum score.

PsAQoL

For the health-related quality of life as collected using the PsAQoL, there is no statistically significant difference between bimekizumab and adalimumab.

Side effects

Overall rates of SAEs and discontinuation due to AEs

There is no statistically significant difference between the treatment groups for the endpoints of SAEs and discontinuation due to AEs.

Infections and infestations (SOC, AE)

For the endpoint of infections and infestations (SOC, AE), there is a statistically significant difference between the treatment groups. However, this difference is no more than minor.

Fungal infections (HLGT, AE)

For the endpoint of fungal infections (HLGT, AE), there is a statistically significant disadvantage of bimekizumab versus adalimumab.

Overall assessment/ conclusion

For adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy, the results of a sub-population of the BE OPTIMAL study were submitted. Bimekizumab is compared with adalimumab.

In the endpoint categories of morbidity and health-related quality of life, there was neither an advantage nor a disadvantage of bimekizumab versus adalimumab. In the endpoint category of side effects, there is no statistically significant difference between the treatment groups for the endpoints of SAEs and discontinuation due to AEs. In detail, there is a statistically significant disadvantage of bimekizumab compared to adalimumab for the endpoint of fungal infections. For the endpoint of infections and infestations, there is a statistically significant difference between the treatment groups but this is no more than a minor one.

In the overall conclusion, no results are available to justify an additional benefit. In the endpoint category of side effects, in contrast, there are disadvantages in detail for the non-serious side effects (fungal infections).

Against this background, the G-BA states that an additional benefit of bimekizumab compared to the appropriate comparator therapy is not proven.

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

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

Justification for patient population b):

The pharmaceutical company does not present any data for the assessment of the additional benefit of bimekizumab compared with the appropriate comparator therapy for patient population b), as no relevant study could be identified.

The approval study BE COMPLETE is a randomised controlled trial comparing bimekizumab versus placebo in the treatment of adult patients with psoriatic arthritis who have had an inadequate response or who have been intolerant to treatment with one or two TNF-alpha antagonists. 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, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs)."

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

a) Adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy

and

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

On patient group a)

The G-BA determined a therapy with a TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if necessary in combination with methotrexate, as an appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the results of a sub-population of the RCT BE OPTIMAL, in which bimekizumab was compared with adalimumab (as monotherapy or with csDMARD concomitant therapy respectively). The comparison presented represents a suitable implementation of the comparator therapy.

In the endpoint categories of mortality, morbidity and health-related quality of life, there was neither an advantage nor a disadvantage of bimekizumab versus adalimumab. In the endpoint category of side effects, there is no relevant difference between the treatment arms for the benefit assessment; in detail, there was a disadvantage of bimekizumab compared to adalimumab in the endpoint of fungal infections.

In the overall assessment, an additional benefit of bimekizumab compared to the appropriate comparator therapy is not proven.

On patient group b)

The G-BA determined the change to another biologic disease-modifying antirheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or ustekinumab), possibly in combination with methotrexate, as an appropriate comparator therapy.

For this patient group, the pharmaceutical company does not submit any data on the assessment of the additional benefit of bimekizumab compared to the appropriate comparator therapy, as no relevant study could be identified.

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 data provided by the pharmaceutical company in the dossier. The derivation is analogous to the resolution of the G-BA on ixekizumab from 20184 and the resolutions on secukinumab, guselkumab and upadacitinib from 2021[5], [6], [7] and the resolution on risankizumab from 2022[8]. The estimate is therefore subject to the same uncertainties. The deviating patient numbers are due to the updated higher population figures used in the baseline and a slightly higher SHI share. Overall, an underestimate can be assumed further.

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 psoriatic arthritis.

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.

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.

Bimekizumab is approved alone or in combination with methotrexate for the treatment of adults with
active psoriatic arthritis. The active ingredients of the appropriate comparator therapy

4 Benefit assessment resolution of the G-BA on ixekizumab dated 16 August 2018.
5 Benefit assessment resolution of the G-BA on secukinumab dated 18 February 2021.
6 Benefit assessment resolution of the G-BA on guselkumab dated 20 May 2021.
7 Benefit assessment resolution of the G-BA on upadacitinib dated 15 July 2021.
8 Benefit assessment resolution of the G-BA on risankizumab dated 19 May 2022.

in the patient groups can also be used both in the context of monotherapy and in combination with methotrexate. Thus, the corresponding costs for methotrexate may be incurred for both the medicinal product to be assessed and the appropriate comparator therapy and are therefore not listed separately.

a) Adults with active psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) therapy.

b) Adults with active psoriatic arthritis who have had an inadequate response or have been intolerant to a prior biologic 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 for 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-alpha antagonist				
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	26.1 or 13.0
Etanercept	Continuously, 2 x in 7 days or Continuously, 1 x in 7 days	52.1 or 52.1	2 or 1	104.2 or 52.1
Golimumab	1 x monthly	12.0	1	12.0
Infliximab	Continuously, 1 x every 14 days	26.1	1	26.1

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Interleukin inhibitor				
Ixekizumab	Continuously, 1 x every 28 days	13.0	1	13.0
Secukinumab	Continuously, 1 x monthly	12.0	1	12.0
Ustekinumab	Continuously, 1 x every 84 days	4.3	1	4.3

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-alpha antagonist					
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
Interleukin 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 or 300 mg	150 mg or 300 mg	1 x 150 mg or 1 x 300 mg	12.0	12.0 x 150 mg or 12.0 x 300 mg
Ustekinumab	45 mg	45 mg	1 x 45 mg	4.3	4.3 x 45 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[9]	6 SFI	€ 2,859.20	€ 2.00	€ 228.57	€ 2,628.63
Certolizumab pegol 200 mg[9]	6 SFI	€ 2,859.20	€ 2.00	€ 0.00	€ 2,857.20
Etanercept 25 mg[9]	24 SFI	€ 2,859.20	€ 2.00	€ 228.57	€ 2,628.63
Etanercept 50 mg[9]	12 SFI	€ 2,859.20	€ 2.00	€ 228.57	€ 2,628.63
Golimumab 50 mg[9]	3 SFIPFS	€ 2,605.96	€ 2.00	€ 0.00	€ 2,603.96
Infliximab 120 mg	6 SFI	€ 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
Ustekinumab 45 mg	1 PEN	€ 5,818.60	€ 2.00	€ 564.02	€ 5,252.58
Abbreviations: SFIPFS = solution for injection in a pre-filled syringe; SFI = solution for injection; PEN = solution for injection in a pre-filled pen					

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[9] 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 bimekizumab or the TNF-α inhibitors of the appropriate comparator therapy (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab) as well as the interleukin inhibitor ustekinumab, 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 and 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 Ustekinumab	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)[10]	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32817)[11]	1	€ 89.50	€ 89.50

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

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 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 psoriatic arthritis who have had an inadequate response or who have been intolerant to a prior disease-modifying antirheumatic drug (DMARD) 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 psoriatic arthritis who have had an inadequate response or have been intolerant to a prior biologic disease-modifying antirheumatic drug (bDMARD) therapy

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 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 11 July 2017, 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 1, sentence 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 27 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.

By letter dated 7 November 2023, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 1 December 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	11 July 2017	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, Commissioning of the IQWiG with the supplementary assessment of documents
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 Annex XII AM-RL

Berlin, 21 December 2023

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

Prof. Hecken