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)
Mirikizumab (ulcerative colitis, pretreated)

of 18 January 2024

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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient mirikizumab on 15 July 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 14 July 2023.

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 16 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 mirikizumab 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 mirikizumab.

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 mirikizumab (Omvoh) in accordance with the product information

Omvoh is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.

Therapeutic indication of the resolution (resolution of 18.01.2024):

See the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy

Appropriate comparator therapy for mirikizumab:

- A TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or ustekinumab or ozanimod

b) Adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

Appropriate comparator therapy for mirikizumab:

- Vedolizumab or ustekinumab or tofacitinib or filgotinib or ozanimod or a TNF-α antagonist (adalimumab or infliximab or golimumab)

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

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. For the treatment of ulcerative colitis (UC), the medicinal products approved in the therapeutic indication are 5-aminosalicylates (mesalazine, sulfasalazine, olsalazine), glucocorticoids, azathioprine, TNF-α antagonists (infliximab, adalimumab, golimumab),

the interleukin inhibitor ustekinumab, the integrin inhibitor vedolizumab, the JAK inhibitors (tofacitinib, upadacitinib, filgotinib) as well as the sphingosine-1-phosphate receptor modulator ozanimod.

on 2. A non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication. Surgical resection is a patient-individual decision made on a case-by-case basis, which does not represent the standard case and is not to be taken into account for the determination of the appropriate comparator therapy.

on 3. There is a resolution of the G-BA on the prescribability of Escherichia coli for ulcerative colitis. Escherichia coli was taken off from the exclusion from prescriptions according to AM-RL Annex III No. 22. The prescription of Escherichia coli strain Nissle 1917 is only permitted for the treatment of ulcerative colitis in the remission phase when mesalazine is not tolerated.

Furthermore, in the therapeutic indication, there are resolutions of the G-BA on the benefit assessment of active ingredients according to Section 35a SGB V for the treatment of ulcerative colitis. For the active ingredient vedolizumab, the resolution of 8 January 2015, for the active ingredient tofacitinib, the resolution of 21 February 2019, for the active ingredient filgotinib, the resolution of 19 May 2022, for the active ingredient ozanimod, the resolution of 16 June 2022 and for the active ingredient upadacitinib, the resolution of 16.02.2023.

In addition, there is a resolution on the amendment to the Pharmaceuticals Directive (AM-RL): Annex VI (off-label use) - 6-mercaptopurine for immunosuppression in the therapy of chronic inflammatory bowel diseases (resolution of 21.10.2021).

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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 indication according to Section 35a paragraph 7 SGB V.

On the basis of the established therapy algorithms and approved medicinal products in the present therapeutic indication, the G-BA divided the patient groups as follows:

a) Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response or were intolerant to conventional therapy.
b) Adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor).

A further differentiation of the patient population, in the sense of subjects who have failed any biological therapy, is not undertaken at this time due to a lack of delimiting criteria as well as a lack of uniform therapy recommendations.

Extensive published data as well as guidelines are available for determining the appropriate comparator therapy for patients with moderate-to-severe ulcerative colitis.

Conventional treatment of ulcerative colitis includes 5-aminosalicylates and - in line with the approved therapeutic indications for TNF-α-antagonists - glucocorticoids and azathioprine or 6-mercaptopurine. These active ingredients or product classes are therefore no longer considered as appropriate comparator therapy for the present treatment setting.

Accordingly, TNF-α antagonists (infliximab, adalimumab, golimumab), the interleukin inhibitor ustekinumab, the integrin inhibitor vedolizumab, JAK inhibitors (tofacitinib, upadacitinib, filgotinib) and the sphingosine-1-phosphate receptor modulator ozanimod as appropriate comparator therapy can still be considered as approved medicinal treatment options.

The current German S3 guideline[2] equally recommend these active ingredients for patients with moderately to severely active ulcerative colitis who have had an inadequate response or lost response to conventional therapy or therapy with TNF-α antagonists, with the exception of the recently for this therapeutic indication approved active ingredient upadacitinib. Individual active ingredients or product classes were not prioritised due to missing or inadequate comparator data.

However, in view of the fact that the use of JAK inhibitors is associated with an increased risk of serious side effects[3], the G-BA believes that tofacitinib and filgotinib do not have the same significance in medical practice as the other active ingredients recommended in the guidelines in the earlier treatment setting, i.e. after failure of or intolerance to conventional therapy. Filgotinib and tofacitinib are therefore not determined as appropriate comparator therapy for patient group a).

However, for patients who require further therapy escalation and thus a broader spectrum of therapy options in this difficultly adjustable treatment setting, as they have already responded inadequately to biologics or have not tolerated them (patient group b), the JAK inhibitors tofacitinib and filgotinib represent another equally suitable therapy option, taking into account the authorisation status and previous therapy (therapies), and are therefore considered as appropriate comparator therapy in this patient group.

After failure of a previous therapy with a biologic agent, especially for active ingredients that do not belong to the product class of TNF-α antagonists, the body of evidence is weak. The S3 guideline only contains specific recommendations on how to proceed in the event of failure on TNF-α antagonists. In the event of primary or secondary failure of therapy with TNF-α antagonists, a switch to ustekinumab, vedolizumab, tofacitinib, filgotinib, ozanimod or calcineurin inhibitors should be made after a possible intensification of therapy. Switching to an alternative TNF antibody is only recommended as one of the therapy options in the event of secondary failure. Calcineurin inhibitors are not approved in the present therapeutic indication.

Overall, in this line of therapy, a change of product class or a change within the product class is considered appropriate. However, in the event of primary failure on TNF-α antagonists, switching within the product class is not recommended due to the low success rate. When selecting the active ingredient in patient group b), the previous therapy and also the authorisation status must be taken into account.

[2] Kucharzik T et al. Updated S3 guideline ulcerative colitis (version 6.1). Z Gastroenterol 2023; 61: 1046–1134
[3] see product information for Xeljanz (tofacitinib) last revised October 2023 and Jyseleca (filfotinib) last revised March 2023

As already explained, the active ingredient upadacitinib was only recently approved (marketing authorisation on 22 July 2022) and is not yet mentioned in guidelines. Based on the generally accepted state of medical knowledge, upadacitinib is not determined to be an appropriate comparator therapy for the present resolution for both patient groups.

The therapeutic indication for mirikizumab includes only adult subjects with moderately to severely active ulcerative colitis. Based on the systematic literature review, no recommendations can be derived for the use of Escherichia coli in the treatment of moderately to severely active ulcerative colitis after failure of conventional therapy or therapy with biologic agents.

It is assumed that for patients who are still eligible for medicinal therapy, surgical resection represents a patient-individual case-by-case decision when required, which does not represent the standard case and is therefore not to be considered for the determination of the appropriate comparator therapy.

In the overall assessment, a TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or ustekinumab or ozanimod are determined to be equally appropriate therapy options for a) adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to conventional therapy. For b) adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor), a change of therapy to vedolizumab or ustekinumab or a JAK inhibitor (filgotinib, tofacitinib) or ozanimod or a TNF-α antagonist (adalimumab or infliximab or golimumab) is determined to be an equally appropriate therapy option, in each case taking into account the marketing authorisation and the previous therapy (therapies).

Change of the appropriate comparator therapy

The adjustment of the appropriate comparator therapy primarily takes into account the changes in the updated S3 guideline and the related statements by clinical experts. The G-BA therefore considers it appropriate to change the appropriate comparator therapy at this point in time and to adapt it to the current state of medical knowledge. Accordingly, ozanimod for patient group a) and filgotinib and ozanimod for patient group b) are added as equally appropriate therapy options.

The adjustment to the wording in patient group b) is editorial.

The change in the appropriate comparator therapy has no impact on the present benefit assessment.

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 mirikizumab is assessed as follows:

a) For adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to conventional therapy, the additional benefit is not proven.

b) For adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor), the additional benefit is not proven.

Justification:

For adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or treatment with a biologic agent, there are no direct comparator studies of mirikizumab versus the appropriate comparator therapy.

In the dossier, the pharmaceutical company presents the data from the randomised consecutive studies LUCENT 1 and LUCENT 2 comparing mirikizumab with placebo. These are the evaluations of patients who had a response to mirikizumab in the LUCENT 1 study and were rerandomised into the LUCENT 2 study. Adult with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to at least a conventional or biological therapy were enrolled in the study. During the entire 52-week study phase, the use of all active ingredients listed in the G-BA's appropriate comparator therapy was prohibited in accordance with the study protocols. The studies are thus unsuitable for deriving an additional benefit of mirikizumab compared to the appropriate comparator therapy.

In the overall assessment, this means that for a) adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy and for b) adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor), an additional benefit of mirikizumab compared with the appropriate comparator therapy has not been proven in each case.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product "Omvoh" with the active ingredient mirikizumab. Mirikizumab is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic treatment.

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

a) Adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy

b) Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

For both patient groups, there are no direct comparator studies of mirikizumab versus the appropriate comparator therapy.

In the dossier, the pharmaceutical company presents the data from the randomised consecutive studies LUCENT 1 and LUCENT 2 comparing mirikizumab with placebo. These are the evaluations of patients who had a response to mirikizumab in the LUCENT 1 study and were rerandomised into the LUCENT 2 study. During the entire 52-week study phase, the use of all active ingredients listed in the G-BA's appropriate comparator therapy was prohibited. The studies are thus unsuitable for deriving an additional benefit of mirikizumab compared to the appropriate comparator therapy.

In the overall assessment, an additional benefit of mirikizumab over the appropriate comparator therapy is thus not proven for patient groups a) and b).

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).

The information from the benefit assessment procedure for tofacitinib (resolution of 21.02.2019) is used to determine the number of patients in the target population in SHI.

The SHI target population presented at that time in the procedure for tofacitinib was also fraught with uncertainties. Despite the uncertainties, the figures from the tofacitinib procedure are considered less uncertain than those from the pharmaceutical company in the present procedure.

Based on the documents submitted so far on the SHI target population, taking into account the most current sources, it can be assumed that the number of patients in both patient populations is rather in the upper range.

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 Omvoh (active ingredient: mirikizumab) at the following publicly accessible link (last access: 9 October 2023):

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

Treatment with mirikizumab should only be initiated and monitored by doctors experienced in treating ulcerative colitis.

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 January 2024).

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

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

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.

Treatment period:

a) Adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Mirikizumab	Continuously, every 28 days	13.0	1	13.0
Appropriate comparator therapy				
A TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or ustekinumab or ozanimod				
Adalimumab	Continuously, every 14 days	26.1	1	26.1
Infliximab	Continuously, every 14 days	26.1	1	26.1
Golimumab	Continuously, every 28 days	13.0	1	13.0
Vedolizumab	Continuously, every 14 days	26.1	1	26.1
Ustekinumab	Continuously, every 84 days	4.3	1	4.3
Ozanimod	Continuously, 1 x daily	365.0	1	365.0

b) Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Mirikizumab	Continuously, every 28 days	13.0	1	13.0
Appropriate comparator therapy				
Vedolizumab or tofacitinib or ustekinumab or ozanimod or filgotinib or a TNF-α antagonist (adalimumab or infliximab or golimumab)				
Vedolizumab	Continuously, every 14 days	26.1	1	26.1
Tofacitinib	Continuously, 2 x daily	365.0	1	365.0
Ustekinumab	Continuously, every 84 days	4.3	1	4.3
Adalimumab	Continuously, every 14 days	26.1	1	26.1
Infliximab	Continuously, every 14 days	26.1	1	26.1
Golimumab	Continuously, every 28 days	13.0	1	13.0
Ozanimod	Continuously, 1 x daily	365.0	1	365.0
Filgotinib	Continuously, 1 x daily	365.0	1	365.0

Consumption:

a) Adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy

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					
Mirikizumab	200 mg	200 mg	2 x 100 mg	13.0	26 x 100 mg
Appropriate comparator therapy					
A TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or ustekinumab or ozanimod					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Infliximab	120 mg	120 mg	1 x 120 mg	26.1	26.1 x 120 mg
Golimumab	50 mg	50 mg	1 x 50 mg	13.0	13.0 x 50 mg
Vedolizumab	108 mg	108 mg	1 x 108 mg	26.1	26.1 x 108 mg
Ustekinumab	90 mg	90 mg	1 x 90 mg	4.3	4.3 x 90 mg
Ozanimod	0.92 mg	0.92 mg	1 x 0.92 mg	365.0	365 x 0.92 mg

b) Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

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					
Mirikizumab	200 mg	200 mg	2 x 100 mg	13.0	26 x 100 mg
Appropriate comparator therapy					
Vedolizumab or tofacitinib or ustekinumab or filgotinib or ozanimod or a TNF-α antagonist (adalimumab or infliximab or golimumab)					
Vedolizumab	108 mg	108 mg	1 x 108 mg	26.1	26.1 x 108 mg
Tofacitinib	5 mg	10 mg	2 x 5 mg	365.0	730 x 5 mg
Ustekinumab	90 mg	90 mg	1 x 90 mg	4.3	4.3 x 90 mg
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 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
Infliximab	120 mg	120 mg	1 x 120 mg	26.1	26.1 x 120 mg
Golimumab	50 mg	50 mg	1 x 50 mg	13.0	13.0 x 50 mg
Ozanimod	0.92 mg	0.92 mg	1 x 0.92 mg	365.0	365 x 0.92 mg
Filgotinib	200 mg	200 mg	1 x 200 mg	365.0	365 x 200 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. Any fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

Costs of the medicinal products:

a) Adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy

and

b) Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

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					
Mirikizumab 100 mg	6 PEN	€ 4,878.33	€ 2.00	€ 275.31	€ 4,601.02
Appropriate comparator therapy					

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
Adalimumab 40 mg[4]	6 SFI	€ 2,859.20	€ 2.00	€ 0.00	€ 2,857.20
Golimumab 50 mg[4]	3 IFE	€ 2,605.96	€ 2.00	€ 0.00	€ 2,603.96
Infliximab 120 mg	6 IFE	€ 4,118.45	€ 2.00	€ 231.91	€ 3,884.54
Tofacitinib 5 mg	182 FCT	€ 2,924.03	€ 2.00	€ 0.00	€ 2,922.03
Ustekinumab 90 mg	1 PEN	€ 5,818.60	€ 2.00	€ 329.01	€ 5,487.59
Vedolizumab 108 mg	6 SFI	€ 3,656.49	€ 2.00	€ 205.53	€ 3,448.96
Filgotinib 200 mg	90 FCT	€ 3,048.17	€ 2.00	€ 170.79	€ 2,875.38
Ozanimod 0.92 mg	98 HC	€ 5,494.97	€ 2.00	€ 310.53	€ 5,182.44
Abbreviations: FCT = film-coated tablets, IFE = solution for injection in a pre-filled syringe, HC = hard capsules; SFI = solution for injection; PEN = solution for injection in a pre-filled pen					

LAUER-TAXE® last revised: 1 January 2024

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 administration of the active ingredients adalimumab, golimumab, infliximab, vedolizumab, ustekinumab, tofacitinib and filgotinib, as well as mirikizumab, patients must be examined for active and inactive ("latent") tuberculosis infections. In addition, patients must be tested for the presence of HBV infection prior to a therapy with the TNF-α inhibitors (adalimumab, golimumab and infliximab) and JAK inhibitors (filgotinib, tofacitinib) of the appropriate comparator therapy.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Mirikizumab Adalimumab	Quantitative determination of an in vitro interferon-gamma	1	€ 58.00	€ 58.00

[4] Fixed reimbursement rate

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Golimumab Infliximab Vedolizumab Ustekinumab Tofacitinib Filgotinib	release after ex vivo stimulation with antigens (at least ESAT-6 and CFP-10) specific for Mycobacterium tuberculosis-complex (except BCG) (GOP 32670)			
	Chest radiograph (GOP 34241)	1	€ 17.42	€ 17.42
Adalimumab Golimumab Infliximab Tofacitinib Filgotinib	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)[5]	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32817)[6]	1	€ 89.50	€ 89.50

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

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.

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

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 moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were 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.

c) Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)
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 mirikizumab (Omvoh); Omvoh ® 100 mg solution for injection in a pre-filled syringe/ pre-filled pen Omvoh ® 300 mg concentrate for solution for infusion; last revised: May 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 January 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 25 July 2023.

On 14 July 2023, the pharmaceutical company submitted a dossier for the benefit assessment of mirikizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 14 July 2023 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 mirikizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 9 October 2023, and the written statement procedure was initiated with publication on the G-BA website on 16 October 2023. The deadline for submitting statements was 6 November 2023.

The oral hearing was held on 27 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 9 January 2024, and the proposed resolution was approved.

At its session on 18 January 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 January 2022	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	25 July 2023	New implementation of the appropriate comparator therapy
Working group Section 35a	14 November 2023	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	27 November 2023	Conduct of the oral hearing,
Working group Section 35a	05.12.2023 19.12.2023	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	9 January 2024	Concluding discussion of the draft resolution
Plenum	18 January 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 18 January 2024

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

Prof. Hecken