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
Risankizumab (new therapeutic indication: ulcerative colitis, pretreated)

of 20 February 2025

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1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of all 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 risankizumab (Skyrizi) was listed for the first time on 1 June 2019 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 24 July 2024, risankizumab 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 19 August 2024, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with

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Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient risankizumab with the new therapeutic indication

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

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The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 December 2024 on the G-BA website (www.g-ba.de), therefore initiating the written statement procedure. In addition, an oral hearing was held.

Based on 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, the G-BA decided on the question on whether an additional benefit of risankizumab compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by IQWiG according to the General Methods was not used in the benefit assessment of risankizumab – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

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 Risankizumab (Skyrizi) in accordance with the product information

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

Therapeutic indication of the resolution (resolution of 20.02.2025):

see the approved therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for risankizumab:

- Adalimumab or golimumab or infliximab or ozanimod or ustekinumab or vedolizumab

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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 risankizumab:

- Adalimumab or filgotinib or golimumab or infliximab or ozanimod or tofacitinib or ustekinumab or vedolizumab

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 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.

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

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

on 1. In addition to the medicinal product to be assessed here, the following medicinal products are approved for the treatment of ulcerative colitis in adults: 5-aminosalicylates (mesalazine, olsalazine, sulfasalazine), azathioprine, glucocorticoids, TNF-α antagonists (adalimumab, golimumab, infliximab), interleukin inhibitors (mirikizumab, ustekinumab), the integrin inhibitor vedolizumab, JAK inhibitors (filgotinib, tofacitinib, upadacitinib) and the sphingosine-1-phosphate receptor modulators (etrasimod, 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 in the indication of ulcerative colitis. Escherichia coli was exempt from the exclusion from prescription according to Annex III No. 22 of the Pharmaceuticals Directive. 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, for the active ingredient upadacitinib, the resolution of 16 February 2023, for the active ingredient mirikizumab, the resolution of 18 January 2024 and for the active ingredient etrasimod, the resolution of 2 October 2024.

There is also a resolution on the off-label use (Annex VI to Section K of the Pharmaceuticals Directive, Part A) of 6-mercaptopurine for immunosuppression in the therapy of chronic inflammatory bowel disease (resolution of 21 October 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, lost response or were intolerant to conventional therapy

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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 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 and guidelines are available for the indication of moderately to severely active ulcerative colitis to be assessed.

Conventional treatment for ulcerative colitis includes 5-aminosalicylates, azathioprine, glucocorticoids and 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 (adalimumab, golimumab, infliximab), interleukin inhibitors (mirikizumab, ustekinumab), JAK inhibitors (filgotinib, tofacitinib, upadacitinib), the integrin inhibitor vedolizumab, and the sphingosine-1-phosphate receptor modulators etrasimod and ozanimod as appropriate comparator therapy can still be considered as approved medicinal treatment options.

The current German S3 guideline[1] 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 active ingredient etrasimod recently approved for this therapeutic indication. Individual active ingredients or product classes are 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[2], the G-BA believes that filgotinib, tofacitinib and upadacitinib do not have the same significance in clinical care as the other active ingredients recommended in the guidelines in the earlier treatment setting, i.e. after failure of or intolerance to conventional therapy. The JAK inhibitors filgotinib, tofacitinib and upadacitinib 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 a biologic agent or have not tolerated it (patient group b), the JAK inhibitors filgotinib, tofacitinib and upadacitinib are viewed to be another suitable therapy option, taking into account the authorisation status and previous therapy (therapies), and are therefore considered as appropriate comparator therapy for this patient group.

After failure of a prior 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 small overall. The S3 guideline[2] contains specific therapy recommendations for this treatment setting only 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 interleukin inhibitors (mirikizumab, ustekinumab), JAK inhibitors (filgotinib, tofacitinib, upadacitinib), the integrin inhibitor vedolizumab, the sphingosine-1-phosphate

[1] Kucharzik T et al. Updated S3 guideline ulcerative colitis (version 6.2). Z Gastroenterol 2024; 62: 769–858
[2] see product information for Xeljanz (tofacitinib) last revised October 2023, Jyseleca (filgotinib) last revised July 2024, Rinvoq (upadacitinib) last revised July 2024

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receptor modulator ozanimod or calcineurin inhibitors should be made after possible intensification of therapy. Switching to an alternative TNF-α antagonist 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 a TNF-α antagonist, switching within the product class is not recommended due to the low success rate. When selecting the active ingredient for patient group b), the previous therapy and also the authorisation status must be taken into account in general.

For the active ingredients upadacitinib, mirikizumab and etrasimod recently approved (marketing authorisation on 22 July 2022, 26 May 2023 and 16 February 2024) in the indication of ulcerative colitis, no additional benefit over the appropriate comparator therapy could be shown in the benefit assessment. So far, there is only limited experience with these active ingredients in care, which is why the significance cannot be conclusively assessed. Overall, the G-BA therefore came to the conclusion that these active ingredients should not be determined as appropriate comparator therapy in either patient group a) or patient group b).

Based on the available evidence, 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 therapies or therapy with biologic agents.

It is also assumed that a patient-individual, case-by-case decision may be made on surgical resection for patients who are still eligible for medicinal therapy; however, this does not represent the standard case. Thus, surgical resection is not considered for the determination of the appropriate comparator therapy.

In the overall assessment, the active ingredients adalimumab, golimumab, infliximab, ozanimod, ustekinumab and vedolizumab are determined to be equally appropriate therapy options for patient group 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 patient group 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 adalimumab, filgotinib, golimumab, infliximab, ozanimod, tofacitinib, ustekinumab or vedolizumab is determined as the appropriate comparator therapy. For all options, both the previous therapy given in each case and the marketing authorisation of the respective active ingredients must be taken into account.

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 risankizumab is assessed as follows:

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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:

No direct comparator data of risankizumab versus the appropriate comparator therapy is neither available for patient group a) nor patient group b).

In the dossier, the pharmaceutical company presented the data from the randomised studies INSPIRE (induction study) and COMMAND (maintenance study) for the comparison of risankizumab with placebo. Adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a conventional therapy or a therapy with a biologic agent were enrolled. In accordance with the study protocol, the use of almost all of the active ingredients named as appropriate comparator therapy was excluded for the entire study duration. Only the active ingredient ozanimod was not explicitly listed as a prohibited concomitant medication in the respective study protocols. However, no subject was treated with ozanimod during the INSPIRE and COMMAND studies. The studies are thus unsuitable for deriving an additional benefit of risankizumab compared to the appropriate comparator therapy.

In the overall assessment, this means that an additional benefit of risankizumab compared with the appropriate comparator therapy is not proven for both patient group 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 patient group 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, integrin inhibitor or interleukin inhibitor).

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient risankizumab. Risankizumab is approved for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to, lost response to, or were intolerant to conventional therapy or a biologic therapy.

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 risankizumab versus the appropriate comparator therapy.

In the dossier, the pharmaceutical company presented the data from the randomised INSPIRE and COMMAND studies, comparing risankizumab with placebo. Due to the lack of comparison

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with an active ingredient of the appropriate comparator therapy, the data presented are therefore unsuitable for deriving an additional benefit.

In the overall assessment, an additional benefit of risankizumab over the appropriate comparator therapy is thus not proven for patient group a) as well as patient group 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 etrasimod (resolution of 2 October 2024) is used to determine the number of patients in the target population in SHI.

The SHI target population used at that time as a basis for the etrasimod procedure was also fraught with uncertainty. The routine data analysis on which the calculation is based does not take into account patients who have had an inadequate response to conventional therapy but have not (yet) been switched to a biologic agent. Despite these uncertainties, the figures from the etrasimod procedure are considered less uncertain than the figures calculated by the pharmaceutical company in the present procedure. Overall, the patient numbers represent a better estimate in the resolution on etrasimod.

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 Skyrizi (active ingredient: risankizumab) at the following publicly accessible link (last access: 15 October 2024):

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

Treatment with risankizumab 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 February 2025).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) 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

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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				
Risankizumab	Continuously, every 56 days	6.5	1	6.5
Appropriate comparator therapy				
Adalimumab or golimumab or infliximab or ozanimod or ustekinumab or vedolizumab				
Adalimumab	Continuously, every 14 days	26.1	1	26.1
Golimumab	Continuously, every 28 days	13.0	1	13.0
Infliximab	Continuously, every 14 days	26.1	1	26.1
Ozanimod	Continuously, 1 x daily	365.0	1	365.0
Ustekinumab	Continuously, every 84 days	4.3	1	4.3
Vedolizumab	Continuously, every 14 days	26.1	1	26.1

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)

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Risankizumab	Continuously, every 56 days	6.5	1	6.5
Appropriate comparator therapy				

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Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Adalimumab or filgotinib or golimumab or infliximab or ozanimod or tofacitinib or ustekinumab or vedolizumab				
Adalimumab	Continuously, every 14 days	26.1	1	26.1
Filgotinib	Continuously, 1 x daily	365.0	1	365.0
Golimumab	Continuously, every 28 days	13.0	1	13.0
Infliximab	Continuously, every 14 days	26.1	1	26.1
Ozanimod	Continuously, 1 x daily	365.0	1	365.0
Tofacitinib	Continuously, 2 x daily	365.0	1	365.0
Ustekinumab	Continuously, every 84 days	4.3	1	4.3
Vedolizumab	Continuously, every 14 days	26.1	1	26.1

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					
Risankizumab	180 mg – 360 mg	180 mg – 360 mg	1 x 180 mg – 1 x 360 mg	6.5	6.5 x 180 mg – 6.5 x 360 mg
Appropriate comparator therapy					
Adalimumab or golimumab or infliximab or ozanimod or ustekinumab or vedolizumab					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Golimumab	50 mg	50 mg	1 x 50 mg	13.0	13.0 x 50 mg
Infliximab	120 mg	120 mg	1 x 120 mg	26.1	26.1 x

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Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
					120 mg
Ozanimod	0.92 mg	0.92 mg	1 x 0.92 mg	365.0	365 x 0.92 mg
Ustekinumab	90 mg	90 mg	1 x 90 mg	4.3	4.3 x 90 mg
Vedolizumab	108 mg	108 mg	1 x 108 mg	26.1	26.1 x 108 mg

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)

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					
Risankizumab	180 mg – 360 mg	180 mg – 360 mg	1 x 180 mg – 1 x 360 mg	6.5	6.5 x 180 mg – 6.5 x 360 mg
Appropriate comparator therapy					
Adalimumab or filgotinib or golimumab or infliximab or ozanimod or tofacitinib or ustekinumab or vedolizumab					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Golimumab	50 mg	50 mg	1 x 50 mg	13.0	13.0 x 50 mg
Filgotinib	200 mg	200 mg	1 x 200 mg	365.0	365 x 200 mg
Infliximab	120 mg	120 mg	1 x 120 mg	26.1	26.1 x 120 mg
Ozanimod	0.92 mg	0.92 mg	1 x 0.92 mg	365.0	365 x 0.92 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
Vedolizumab	108 mg	108 mg	1 x 108 mg	26.1	26.1 x 108 mg

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Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a 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 reference prices 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, lost response 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					
Risankizumab 2 mg	1 SFI	€ 2,942.76	€ 1.77	€ 0.00	€ 2,940.99
Appropriate comparator therapy					
Adalimumab 40 mg[3]	6 SFI	€ 2,804.97	€ 1.77	€ 0.00	€ 2,803.20
Golimumab 50 mg[3]	3 SPF	€ 2,548.84	€ 1.77	€ 0.00	€ 2,547.07
Filgotinib 200 mg	90 FCT	€ 3,048.17	€ 1.77	€ 170.79	€ 2,875.61
Infliximab 120 mg	6 SPF	€ 4,118.45	€ 1.77	€ 231.91	€ 3,884.77
Ozanimod 0.92 mg	98 HC	€ 5,469.17	€ 1.77	€ 309.05	€ 5,158.35
Tofacitinib 5 mg	182 FCT	€ 2,924.03	€ 1.77	€ 0.00	€ 2,922.26
Ustekinumab 90 mg	1 SFI	€ 5,818.60	€ 1.77	€ 329.01	€ 5,487.82
Vedolizumab 108 mg	6 SFI	€ 3,632.34	€ 1.77	€ 204.15	€ 3,426.42
Abbreviations: FCT = film-coated tablets, HC = hard capsules, SPF = solution for injection in a pre-filled syringe, SFI = solution for injection, PIC = powder for the preparation of an infusion solution concentrate					

LAUER-TAXE® last revised: 1 February 2025

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

[3] Fixed reimbursement rate

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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 risankizumab, adalimumab, filgotinib, golimumab, infliximab, tofacitinib, ustekinumab and vedolizumab, patients must be examined for active and inactive ("latent") tuberculosis infections. In addition, patients must be tested for the presence of an infection with hepatitis B prior to initiation of a therapy with risankizumab as well as the active ingredients adalimumab, filgotinib, golimumab, infliximab, tofacitinib, ustekinumab and vedolizumab of the appropriate comparator therapy. Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. In certain case constellations, further steps may be necessary in accordance with current guideline recommendations[4].

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, lost response or were intolerant to a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Risankizumab Adalimumab Filgotinib Golimumab Infliximab Tofacitinib Ustekinumab Vedolizumab	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	€ 53.36	€ 53.36
	Chest radiograph (GOP 34241)	1	€ 18.09	€ 18.09
Risankizumab	HBs antigen	1	€ 5.06	€ 5.06

[4] S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011; https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

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Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Adalimumab Golimumab Filgotinib Infliximab Tofacitinib Ustekinumab Vedolizumab	(GOP 32781)			
	Anti-HBc antibody (GOP 32614)	1	€ 5.43	€ 5.43

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

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

Basic principles of the assessed medicinal product

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

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

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

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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 requirements 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

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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

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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 and fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for risankizumab (Skyrizi); Skyrizi® 600 mg concentrate for preparation
of an infusion solution; last revised: July 2024

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)

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 risankizumab (Skyrizi); Skyrizi® 600 mg concentrate for preparation
of an infusion solution; last revised: July 2024

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.

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4. Process sequence

At its session on 8 June 2021, 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. At its session on 25 June 2024, the Subcommittee on Medicinal Products adjusted the appropriate comparator therapy.

On 19 August 2024, the pharmaceutical company submitted a dossier for the benefit assessment of risankizumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 20 August 2024 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 risankizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 18 November 2024, and the written statement procedure was initiated with publication on the G-BA website on 2 December 2024. The deadline for submitting statements was 23 December 2024.

The oral hearing was held on 6 January 2025.

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 11 February 2025, and the proposed draft resolution was approved.

At its session on 20 February 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	8 June 2021	Determination of the appropriate comparator therapy
Subcommittee on Medicinal Products	25 June 2024	Adjustment of the appropriate comparator therapy after positive opinion
Subcommittee on Medicinal Products	6 January 2025	Information on statements received, conduct of the oral hearing,

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Working group Section 35a	15 January 2025 5 February 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	11 February 2025	Concluding discussion of the draft resolution
Plenum	20 February 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 20 February 2025

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

Prof. Hecken

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