

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: Crohn's Disease,
pretreated)

of 15 June 2023

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1. Legal basis

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

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient 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 21 November 2022, 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 December 2022, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient risankizumab with the new therapeutic indication (Crohn's disease, pretreated) in due time (i.e. at the latest within

four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 03 April 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 risankizumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure as well the addendum drawn up by the IQWiG on the benefit assessment. 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 risankizumab.

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 Crohn's disease 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 15.06.2023):

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 Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

Appropriate comparator therapy for risankizumab:

A TNF- α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)

- b) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy TNF- α antagonist or integrin inhibitor or interleukin inhibitor).

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

Appropriate comparator therapy for risankizumab:

A change of therapy to a TNF- α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

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.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

- on 1. Taking into account the specifications in the respective product information, medicinal products that are generally approved in the therapeutic indication, in addition to the medicinal product to be assessed here, are corticosteroids (topical, systemic: prednisone, prednisolone, hydrocortisone acetate, methylprednisolone budesonide), Indian psyllium and psyllium husk, immunosuppressants (azathioprine, methotrexate) as well as 5-aminosalicylates (mesalazine, sulphasalazine), TNF- α antagonists infliximab and adalimumab, the interleukin inhibitor ustekinumab, the integrin inhibitor vedolizumab and the JAK inhibitor upadacitinib. The therapeutic indications for mesalazine, sulphasalazine, methotrexate and budesonide are only partially consistent with the indication "moderately to severely active Crohn's disease".
- on 2. A non-medicinal treatment cannot be considered as an appropriate comparator therapy in this therapeutic indication. Surgical resection is a patient-individual option that requires a case-by-case decision and is not the standard case. Thus, surgical resection is not to be considered for the determination of the appropriate comparator therapy.
- on 3. In the therapeutic indication "treatment of moderately to severely active Crohn's disease", there is a resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient vedolizumab of 8 January 2015, which was decided with an unproven additional benefit.

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 therapeutic indication.

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

Extensive published data as well as guidelines are available for determining the appropriate comparator therapy for patients who are eligible for systemic therapy. 5-aminosalicylates, corticosteroids and immunosuppressants were not further considered in the determination of the appropriate comparator therapy, as the therapeutic indication of risankizumab requires an inadequate response or no longer present response or intolerance to conventional therapy. Indian psyllium and psyllium husks are only used as supportive therapy in Crohn's disease and are therefore not considered as an appropriate comparator therapy.

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

a) After failure of conventional therapy, two TNF- α antagonists whose efficacy and tolerability are equally supported by the current guidelines (including the German S3 guideline) are available. The administration of TNF- α antagonists requires patients who have responded inadequately despite complete and adequate therapy with a glucocorticoid and/or an immunosuppressant, or who have been intolerant to such therapy, or in whom such therapy is contraindicated. According to the current German S3 guideline, the integrin inhibitor vedolizumab and the interleukin inhibitor ustekinumab are also considered equivalent to TNF- α antagonists after failure of conventional therapy. Based on the generally recognised state of medical knowledge and taking into account the German standard of care, the JAK inhibitor upadacitinib is not determined as appropriate comparator therapy for patient population a in the present resolution. Thus, the appropriate comparator therapy for patient population a includes the TNF- α inhibitors infliximab and adalimumab, as well as the integrin inhibitor vedolizumab and the interleukin inhibitor ustekinumab.

b) When determining the appropriate comparator therapy for patients who failed a biologic agent (TNF- α antagonist or integrin inhibitor or interleukin inhibitor), the evidence search showed the availability of four options – infliximab, adalimumab, the

integrin inhibitor vedolizumab and the interleukin inhibitor ustekinumab. With regard to therapeutic efficacy as well as to the question of the side-effect profile or the safety risk, no evidence-based information was found that one of the four active ingredients mentioned is generally preferable in patients who have a failed response to a biologic agent. As already described above, no prioritisation can be made within the TNF- α antagonists either. In addition to a change of product class, a change within the product class can also be considered. The addition of "A change of therapy to" merely clarifies linguistically that the unchanged continuation of the previous therapy is not regarded as implementation of the appropriate comparator therapy. Based on the generally recognised state of medical knowledge and taking into account the German standard of care, the JAK inhibitor upadacitinib is not determined as appropriate comparator therapy for patient population b in the present resolution. Thus, the appropriate comparator therapy for patient population b includes the TNF-alpha inhibitors infliximab and adalimumab, as well as the integrin inhibitor vedolizumab and the interleukin inhibitor ustekinumab. These active ingredients are equally suitable therapeutic alternatives in the described treatment setting.

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:

- a) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

An additional benefit is not proven.

- b) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy TNF- α antagonist or integrin inhibitor or interleukin inhibitor).

Hint for a minor additional benefit

Justification:

On patient population a)

For the assessment of the additional benefit of risankizumab in adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy, the pharmaceutical company does not submit any (comparator) studies. An additional benefit for patient population a is not proven due to the absence of data.

On patient population b)

For the assessment of the additional benefit of risankizumab in adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy (TNF- α antagonist or integrin inhibitor or interleukin inhibitor), the pharmaceutical company submits the SEQUENCE study.

The SEQUENCE study is an ongoing, open-label RCT comparing risankizumab with ustekinumab in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to, or were intolerant to TNF- α antagonists. The treatment with risankizumab took place in compliance with the product information from protocol version 2 and above.

The study is divided into a 35-day screening phase, a 48-week treatment phase (48 weeks or until the occurrence of unacceptable toxicity or therapy discontinuation at the principal investigator's or patient's discretion) and a 140-day follow-up phase.

Patients were randomly assigned to the study arms in a 1:1 ratio. Randomisation was stratified by the number of previous failed TNF- α antagonists (≤ 1 , > 1) and corticosteroid administration at baseline (yes, no). A total of 265 patients were randomised to the risankizumab arm and 262 patients to the ustekinumab arm.

As the primary endpoint, clinical remission (CDAI < 150) at week 24 and endoscopic remission at week 48 are recorded. In addition, endpoints on morbidity, health-related quality of life and side effects are assessed.

Along with the statement, the pharmaceutical company submits results of the SEQUENCE study at the 2nd prespecified data cut-off (HTA Interim Lock) of 12.01.2023. At the time of the data cut-off, 88% of the randomised patients (232 patients in the risankizumab arm and 234 patients in the ustekinumab arm) had been on treatment for at least 24 weeks or had discontinued the study prematurely. The sub-population relevant for the assessment comprises 222 patients in the intervention arm and 224 patients in the comparator arm and only takes into account patients who were enrolled in the study from protocol version 2 and above. In addition, the patients are included here in the analyses of the efficacy endpoints with their observed values in each case, regardless of whether therapy with corticosteroids above the level at the start of the study takes place.

Extent and probability of the additional benefit

Mortality

There were no deaths in none of the treatment arms.

Morbidity

Clinical remission (PRO-2)

In the present assessment, the PRO-2 (consisting of patient diary-reported symptoms of stool frequency and abdominal pain on a scale of 0 = none, 1 = mild, 2 = moderate, 3 = severe), operationalised as average stool frequency ≤ 2.8 /day and average abdominal pain ≤ 1 /day and both no worse than at baseline, at week 24, is used for the endpoint of clinical remission.

For the endpoint of clinical remission, collected with the PRO-2, there is a statistically significant difference between the treatment groups to the advantage of risankizumab compared to ustekinumab.

Steroid-free remission (PRO-2)

The endpoint of steroid-free remission was operationalised as mean daily stool frequency ≤ 2.8 and mean daily abdominal pain ≤ 1 and both respectively not worse than at baseline with concomitant steroid freedom at week 24.

Although it remains unclear how many patients were treated with topical corticosteroids alone, the endpoint is considered to be patient-relevant. Freedom from the administration of steroids is seen as the overriding therapeutic goal in the treatment of Crohn's disease. Even though systemic glucocorticoids basically have a higher side-effect profile, freedom from topical glucocorticoids is also sought. This was confirmed by the assessment experts at the oral hearing. Uncertainties remain, however, as only 25% of patients received corticosteroids at the start of the study. Moreover, with the present operationalisation, no information on the duration of steroid-free remission is available at the time of the present data cut-off.

For the endpoint of steroid-free remission, collected with the PRO-2, there is a statistically significant difference between the treatment arms to the advantage of risankizumab compared to ustekinumab.

Hospitalisation (disease-specific hospitalisation and total hospitalisation)

Overall, it is not sufficiently ensured that the endpoint of disease-specific hospitalisation actually reflects predominantly severe events caused by Crohn's disease. Therefore, it is not used for the assessment in the present case. Furthermore, it can be assumed that data on subsequent therapy were also included in the evaluations, although it remains unclear whether hospitalisations were also carried out to initiate subsequent therapies. Both also affect the endpoint of total hospitalisation, which is why it cannot be meaningfully interpreted and is also not used in the present case.

Inflammatory Bowel Disease Questionnaire (IBDQ)

In addition to the total score (see comments on quality of life), the 2 sub-scores bowel symptoms and systemic symptoms of the IBDQ are used to assess symptomatology.

Bowel symptoms (IBDQ)

For the endpoint of bowel symptoms, assessed with the corresponding sub-score of the IBDQ, there is a statistically significant difference between the treatment groups to the advantage of risankizumab compared to ustekinumab.

Systemic symptoms (IBDQ)

For the endpoint of systemic symptoms, assessed with the corresponding sub-score of the IBDQ, there is no statistically significant difference between the treatment groups.

Quality of life

Inflammatory Bowel Disease Questionnaire (IBDQ)

The IBDQ is a widely used and validated disease-specific instrument in the present indication of Crohn's disease.

The IBDQ includes a total of 32 questions on aspects of inflammatory bowel disease. The questionnaire includes 4 domains, with 10 questions on bowel symptoms, 5 questions on systemic symptoms, 12 questions on emotional functioning and 5 questions on social functioning. Each question can be scored on a scale of 1 to 7, with higher scores indicating better condition. The total score (IBDQ total score) ranges from 32 to 224 points. Separate sub-scores can be calculated for the 4 domains.

The IBDQ total score is assigned to the endpoint category of health-related quality of life.

IBDQ total score

For health-related quality of life, assessed with the IBDQ total score, there is a statistically significant difference between the treatment groups to the advantage of risankizumab compared to ustekinumab.

Short Form (36) Health Survey (SF-36)

The SF-36 is a non-disease-specific measurement instrument for assessing health-related quality of life.

SF-36 Physical Component Summary (PCS) score

For health-related quality of life, assessed with the SF-36 Physical Component Summary (PCS) score, there is a statistically significant difference between the treatment groups to the advantage of risankizumab compared to ustekinumab. The 95% confidence interval of the standardised mean difference is completely outside the irrelevance range [-0.2; 0.2]. This is interpreted as a clinically relevant effect.

SF-36 Mental Component Summary (MCS) score

For health-related quality of life, assessed with the SF-36 Mental Component Summary (MCS) score, there is a statistically significant difference between the treatment groups to the advantage of risankizumab compared to ustekinumab. However, the 95% confidence interval of the standardised mean difference is not completely outside the irrelevance range [-0.2; 0.2]. Thus, it cannot be inferred that the observed effect is clinically relevant.

Side effects

No suitable data are available for the endpoint of side effects. This is due to the fact that the selection of events that the pharmaceutical company considers to be disease-related does not appear to be complete on the one hand, and it remains unclear with which clinical rationale the corresponding events were selected by the pharmaceutical company on the other.

Overall assessment

The ongoing, open-label SEQUENCE study comparing risankizumab with ustekinumab in adult patients with moderately to severely active Crohn's disease, who have had an inadequate response to, or were intolerant to TNF- α antagonists is available for the benefit assessment.

No deaths occurred.

In the morbidity category, there are statistically significant benefits to the advantage of risankizumab for the endpoints of clinical remission (PRO-2), steroid-free remission (PRO-2) and bowel symptoms (IBDQ).

In the health-related quality of life category, there are statistically significant and clinically relevant benefits to the advantage of risankizumab for the endpoints IBDQ total score and the SF-36 physical component summary score.

No suitable data are available for side effects category.

Based on the positive effects of risankizumab in the endpoint categories of morbidity (clinical remission, steroid-free remission, bowel symptoms) and health-related quality of life (IBDQ total score, SF-36 physical component summary score), the overall assessment of the results shows a previously unattained moderate improvement compared to the appropriate

comparator therapy, so that overall a minor additional benefit is derived for risankizumab compared to ustekinumab.

Reliability of data (probability of additional benefit)

Overall, the SEQUENCE study shows uncertainties that limit the significance of the results. Uncertainties exist with regard to the high percentage of replaced or missing values as well as the lack of blinding in the subjective endpoint survey. Further uncertainties arise from the administration of ustekinumab in the control arm, which does not fully comply with the product information.

Against the background of these uncertainties, the reliability of data is therefore classified as "hint".

2.1.4 Limitation of the period of validity of the resolution

The limitation of the period of validity of the resolution on the benefit assessment of risankizumab in the therapeutic indication of Crohn's disease finds its legal basis in Section 35a paragraph 3 sentence 4 SGB V. Thereafter, the G-BA may limit the validity of the resolution on the benefit assessment of a medicinal product. In the present case, the limitation is justified by objective reasons consistent with the purpose of the benefit assessment according to Section 35a, paragraph 1 SGB V.

The data from the SEQUENCE study available for the present assessment are data at week 24. The final results from the ongoing study are still pending.

Since more clinical data are expected which are relevant for the benefit assessment of the medicinal product, it is justified to limit the validity of the resolution until further scientific knowledge is available for the assessment of the additional benefit of risankizumab. The limitation enables the expected interim results from the SEQUENCE study to be included in the benefit assessment of the medicinal product in accordance with Section 35a SGB V in a timely manner.

For this purpose, the G-BA considers a limitation of the resolution until 1 August 2028 to be appropriate.

Conditions of the limitation:

For the new benefit assessment after expiry of the deadline, the final SEQUENCE study results on all patient-relevant endpoints used for the evidence of an additional benefit are to be presented in the dossier.

A change in the limitation can generally be granted if it is justified and clearly demonstrated that the limitation is insufficient or too long.

In accordance with Section 3, No. 7 AM-NutzenV in conjunction with Chapter 5, Section 1, paragraph 2, No. 7 VerfO, the procedure for the benefit assessment of the medicinal product risankizumab recommences when the deadline has expired. For this purpose, the pharmaceutical company must submit a dossier to the G-BA at the latest on the date of expiry to prove the extent of the additional benefit of risankizumab in comparison with the appropriate comparator therapy (Section 4, paragraph 3, number 5 AM-NutzenV in conjunction with Chapter 5 Section 8, paragraph 1, number 5 VerfO). If the dossier is not submitted or is incomplete, the G-BA may determine that an additional benefit has not been proven.

The possibility that a benefit assessment for the medicinal product risankizumab can be carried out at an earlier point in time due to other reasons (cf. Chapter 5, Section 1, paragraph 2, nos. 2 to 4 VerfO) remains unaffected hereof.

2.1.5 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient risankizumab. The therapeutic indication assessed here is "Skyrizi is indicated for the treatment of adult patients with moderately to severely active Crohn's disease 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 Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy
- b) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to a biologic therapy (TNF- α antagonist or integrin inhibitor or interleukin inhibitor).

The G-BA determined "a TNF- α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)" as the appropriate comparator therapy for both patient groups a) and b).

About patient group a)

For this patient group, the pharmaceutical company does not present any (comparator) studies. An additional benefit for patient population a is not proven due to the absence of data.

About patient group b)

For this patient group, the SEQUENCE study, which investigated risankizumab compared to ustekinumab in adult patients with moderately to severely active Crohn's disease, who have had an inadequate response to, or were intolerant to TNF- α antagonists is available.

No deaths occurred.

With regard to morbidity, the endpoints "clinical remission (PRO-2)", "steroid-free remission (PRO-2)" and "bowel symptoms (IBDQ)" show statistically significant benefits to the advantage of risankizumab.

For health-related quality of life, the endpoints "IBDQ total score" and "SF-36 physical component summary score" show statistically significant and clinically relevant benefits to the advantage of risankizumab.

No suitable data are available in the side effects category.

Overall, the study shows uncertainties, particularly with regard to the high percentage of replaced or missing values as well as the lack of blinding in the subjective endpoint survey and due to the administration of ustekinumab in the control arm that did not fully comply with the product information.

In the overall assessment of the positive effects, taking into account the uncertainties mentioned, the G-BA found a hint for a minor additional benefit.

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 data is based on the patient numbers from the dossier of the pharmaceutical company.

Overall, the number of patients is subject to uncertainty. Operationalisation of patient population b as such with a change in therapy from one biologic agent to another results in a tendency to underestimate for this patient population. Operationalisation of patient population a as the percentage of patients who did not change a biologic agent results in a tendency to overestimate for this patient population. The quantitative extent of the under or overestimation cannot be conclusively assessed.

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: 5 April 2023):

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 Crohn's disease.

Discontinuation of treatment should be considered for patients who do not show signs of therapeutic benefit after 24 weeks.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 May 2023).

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

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

The 360 mg cartridge dosage form of risankizumab required for maintenance treatment in this indication is not yet available at the time the therapy costs are calculated and at the time the resolution is passed. Representation of the costs is therefore not possible here.

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration varies from patient to patient and/or is shorter on average. The time unit "days" is used to calculate

the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

a) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, lost response to, or were intolerant to conventional therapy

b) Adults with moderately to severely active Crohn's disease who have had an inadequate response to, 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				
Risankizumab	Continuously, 1 x every 56 days	6.5	1	6.5
Appropriate comparator therapy				
A TNF- α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)				
Adalimumab	Continuously, 1 x every 14 days	26.1	1	26.1
Infliximab	Continuously, 1 x every 56 days	6.5	1	6.5
Vedolizumab	Continuously, 1 x every 14 days	26.1	1	26.1
Ustekinumab	Continuously, 1 x every 84 days	4.3	1	4.3

Consumption:

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg).²

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	360 mg	360 mg	1 x 360 mg	6.5	6.5 x 360 mg

² Federal Statistical Office, Wiesbaden 2018: <http://www.gbe-bund.de/>

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
A TNF- α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Infliximab	$\frac{5 \text{ mg/kg BW}}{= 385 \text{ mg}}$	385 mg	4 x 100 mg	6.5	26 x 100 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

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Risankizumab 360 mg ³					
Appropriate comparator therapy					
Adalimumab 40 mg ⁴	6 SFI	€ 2,859.17	€ 2.00	€ 228.57	€ 2,628.60
Infliximab 100 mg ⁴	5 PIC	€ 3,490.53	€ 2.00	€ 280.08	€ 3,208.45
Vedolizumab 108 mg	6 SFI	€ 3,656.45	€ 2.00	€ 352.34	€ 3,302.11
Ustekinumab 90 mg	1 SFIPFS	€ 5,446.71	€ 2.00	€ 527.61	€ 4,917.10
Abbreviations: SFI = solution for injection; SFIPFS = solution for injection in a pre-filled syringe; PIC = powder for the preparation of an infusion solution concentrate					

LAUER-TAXE® last revised: 15 May 2023

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

³ 360 mg cartridge of risankizumab is currently unavailable on the German market, therefore a cost representation is not possible

⁴ Fixed reimbursement rate

(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.

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

Test for the presence of hepatitis B viral infection prior to the administration of active ingredients of the appropriate comparator therapy (adalimumab and infliximab).

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Adalimumab Infliximab	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

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs do not add to the pharmacy sales price but follow the rules for calculation in the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe). The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing

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.

of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe).

2.5 Medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with Risankizumab

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.

In accordance with Section 2, paragraph 1, sentence 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), only medicinal products containing active ingredients whose effects are not generally known in medical science at the time of initial marketing authorisation are to be considered within the framework of the designation of medicinal products with new active ingredients that can be used in a combination therapy. According to Section 2, paragraph 1, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), a medicinal product with a new active ingredient is considered to be a medicinal product with a new active ingredient for as long as there is dossier protection for the medicinal product with the active ingredient that was authorised for the first time.

The designation of the combination therapies is based solely on the specifications according to Section 35a, paragraph 3, sentence 4. The G-BA does not conduct a substantive review based on the generally recognised state of medical knowledge. Thus, the designation is not associated with a statement as to the extent to which a therapy with the designated medicinal product with new active ingredient in combination with the medicinal product to be assessed corresponds to the generally recognised state of medical knowledge.

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 28 September 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 5 October 2022, the Subcommittee on Medicinal Products adjusted the appropriate comparator therapy.

On 19 December 2022, 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, sentence 1 VerfO.

By letter dated 21 December 2022 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 30 March 2023, and the written statement procedure was initiated with publication on the G-BA website on 3 April 2023. The deadline for submitting statements was 24 April 2023.

The oral hearing was held on 2 May 2023.

By letter dated 2 May 2023, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 26 May 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 6 June 2023, and the proposed resolution was approved.

At its session on 15 June 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 September 2021	Determination of the appropriate comparator therapy
Subcommittee Medicinal products	5 October 2022	Implementation of the appropriate comparator therapy
Working group Section 35a	26 April 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	2 May 2023	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	10.05.2023 31.05.2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	6 June 2023	Concluding discussion of the draft resolution
Plenum	15 June 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 June 2023

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

Prof. Hecken