

Justification



to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Risankizumab

of 22 November 2019

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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 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 shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient risankizumab in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 June 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 2 May 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 2 September 2019, 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, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the

IQWiG in accordance with the General Methods ¹ was not used in the benefit assessment of risankizumab.

In light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at 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 moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

- a) Adult patients with moderate to severe plaque psoriasis who are not candidates for conventional therapy as part of an initial systemic therapy.
 - Adalimumab or guselkumab or ixekizumab or secukinumab

- b) Adult patients with moderate to severe plaque psoriasis who have responded inadequately to or did not tolerate systemic therapy.
 - Adalimumab or brodalumab or guselkumab or infliximab or ixekizumab or secukinumab or 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 according to 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 Federal Joint Committee 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.

¹ General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

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

On 1. Patient population a)

For the treatment of adult patients with moderate to severe plaque psoriasis who are not candidates for conventional therapy as part of an initial systemic therapy, the biologics adalimumab, brodalumab, certolizumab pegol, guselkumab, ixekizumab, secukinumab, and tildrakizumab are approved.

Patient population b)

For the treatment of adult patients with moderate to severe plaque psoriasis who have responded inadequately to or did not tolerate systemic therapy, the *TNF-alpha inhibitors* adalimumab, certolizumab pegol, etanercept, and infliximab, the *interleukin antagonists* brodalumab, guselkumab, ixekizumab, secukinumab, tildrakizumab, and ustekinumab, the *phosphodiesterase inhibitor* apremilast, and the active ingredient dimethyl fumarate are approved.

On 2. No non-medicinal therapies are considered in this therapeutic indication.

On 3. The following resolutions of the G-BA are available in the therapeutic indication considered here:

- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient apremilast dated 6 August 2015.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient secukinumab dated 27 November 2015.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient secukinumab dated 17 August 2017.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient ixekizumab dated 17 August 2017.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient brodalumab dated 1 March 2018.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient dimethyl fumarate dated 16 March 2018.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient guselkumab dated 17 May 2018.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient tildrakizumab dated 2 May 2019.

On 4. The general accepted state of medical knowledge on which the decision of the G-BA is based was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

In accordance with the marketing authorisation, those patients who are eligible for systemic therapy are included in the therapeutic indication.

For the purposes of this benefit assessment, the therapeutic indication to be assessed is divided into two patient groups: Patient group a) comprises adult patients with moderate to severe plaque psoriasis who are not candidates for conventional therapy as part of an initial systemic therapy. Patient group b) comprises adult patients with moderate to severe plaque psoriasis who have responded inadequately to or did not tolerate systemic therapy.

Changes of the appropriate comparator therapy

Based on a direct comparative study, it was shown that a biologic therapy with the interleukin inhibitors guselkumab, ixekizumab, or secukinumab is clearly superior to therapy with fumaric acid esters with respect to the therapy-relevant benefit. Within the scope of the benefit assessment according to Section 35a SGB V, the three aforementioned biologics in the partial therapeutic indication of the systemic first-line therapy were each assessed as having a considerable additional benefit. Based on these studies, it can no longer be derived that for patients without previous systemic therapy, a medical intervention with fumaric acid esters can be classified as equally appropriate with a treatment with biologics. The results of these studies as well as the care practice that has been established in the meantime and the written statements of the clinical specialist societies show that conventional and biological therapies address different patient groups. Based on the German guideline for the treatment of plaque psoriasis², a distinction is made between patients in whom systemic therapy is started with a conventional active ingredient and patients in whom conventional first-line therapies do not promise sufficient therapeutic success. This is why systemic first-line therapy is not started with a conventional active ingredient. Currently, only biologics are approved as non-conventional active ingredients in this line of therapy. Because only patients for whom no conventional therapy but rather treatment with a biologic is indicated as part of an initial systemic therapy are eligible for treatment with the interleukin-23 antagonist risankizumab in systemic first-line therapy, only these patients are included in the target population (corresponding to patient population a).

Conversely, patients for whom treatment with a conventional active ingredient (e.g. fumaric acid ester, methotrexate, or ciclosporin) is indicated as part of an initial systemic therapy do not correspond to the target population of a biologic. Consequently, these patients do not represent a suitable comparator group for assessing the additional benefit of risankizumab.

Patient population a)

The German guideline for the treatment of plaque psoriasis² recommends treatment with the *TNF-alpha inhibitor* adalimumab or the *interleukin inhibitor* secukinumab for patients in systemic first-line therapy for whom conventional first-line therapies (e.g. fumaric acid ester, methotrexate, and ciclosporin) are not expected to be successful.

The biologics brodalumab, guselkumab, ixekizumab, and tildrakizumab were approved in Germany only after completion of the aforementioned guideline. These could therefore not be taken into account in the recommendations.

The *interleukin inhibitors* brodalumab, guselkumab, ixekizumab, secukinumab, and tildrakizumab were evaluated in the context of the benefit assessment according to Section 35a SGB V in the partial therapeutic indication of the systemic first-line therapy. Guselkumab, ixekizumab, and secukinumab showed a considerable additional benefit compared with fumaric acid esters. Consequently, the biologics mentioned are to be

² Nast A, Amelunxen L, Augustin M, Boehncke WH, Dressler C, Gaskins M, et al. S3-Leitlinie zur Therapie der Psoriasis vulgaris [S3 guideline for the therapy of psoriasis vulgaris]; Update 2017 [online]. AWMF register No. 013-001. Berlin (GER): Working Group of the Scientific Medical Societies; 2017. [Access: 7 October 2019]. URL: http://www.awmf.org/uploads/tx_szleitlinien/013-001l_S3_Therapie_Psoriasis-vulgaris_2017-12.pdf.

regarded as useful for patients who are not candidates for conventional therapy as part of an initial systemic therapy. Thus, in addition to adalimumab and secukinumab, guselkumab and ixekizumab are also part of the appropriate comparative therapy.

On the other hand, the interleukin antagonists brodalumab and tildrakizumab did not show any additional benefit compared with the active ingredients of the appropriate comparator therapy in the context of the benefit assessment according to Section 35a SGB V. These are therefore not regarded as equally appropriate therapy alternatives.

Against the background of the evidence available, the biologics adalimumab, guselkumab, ixekizumab, and secukinumab are therefore determined as equally appropriate comparator therapies for patients who are not candidates for conventional therapy as part of an initial systemic therapy. It must be considered that the continuation of an inadequate therapy does not correspond to the implementation of the appropriate comparative therapy.

Patient population b)

Patient group b) comprises patients who have responded inadequately to or did not tolerate systemic therapy. This applies to both conventional active ingredients and biologics.

In accordance with the German guideline for the treatment of plaque psoriasis², the biologics adalimumab, infliximab, secukinumab, and ustekinumab are recommended for patients who have responded inadequately to or did not tolerate systemic therapy. The active ingredients etanercept and apremilast are also mentioned. However, for both etanercept and apremilast, a weaker recommendation is given. The available evidence shows that etanercept has a lower efficacy than other biologics authorised for this indication. Against the background of the availability of more effective alternatives with sufficient evidence, etanercept is not regarded as an appropriate comparator therapy in the therapeutic indication under consideration. For the *phosphodiesterase inhibitor* apremilast, no additional benefit could be determined in the context of the benefit assessment according to Section 35a SGB V compared with the biologics defined as appropriate comparator therapy. This is therefore also not included in the appropriate comparator therapy.

The *interleukin antagonists* brodalumab, guselkumab, ixekizumab, and secukinumab received an additional benefit in the context of the benefit assessment according to Section 35a SGB V for the treatment of patients who did not respond adequately to a systemic therapy or did not tolerate it, and are now established in care. These active ingredients are therefore part of the appropriate comparative therapy alongside adalimumab, infliximab, and ustekinumab.

For the *interleukin antagonist* tildrakizumab, the benefit assessment according to Section 35a SGB V for patients who did not respond adequately to systemic therapy or did not tolerate it showed no additional benefit compared with the appropriate comparator therapy.

Against the background of the available evidence, the biologics adalimumab, brodalumab, guselkumab, infliximab, ixekizumab, secukinumab, and ustekinumab are determined as equally appropriate comparator therapies for patients who did not respond adequately to or did not tolerate systemic therapy. It must be considered that the continuation of an inadequate therapy does not correspond to the implementation of the appropriate comparative therapy.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of risankizumab is assessed as follows:

- a) For adult patients with moderate to severe plaque psoriasis who are not candidates for conventional therapy as part of an initial systemic therapy, the additional benefit is not proven.

Justification:

The pharmaceutical company has submitted the results of study M16-178 to demonstrate the additional benefit of risankizumab in the population a).

Study M16-178 is a randomised, open, parallel group study in which risankizumab was compared with fumaric acid esters in adult patients with moderate to severe plaque psoriasis who have not yet received systemic therapy. The severity of plaque psoriasis was defined as PASI > 10, BSA > 10%, and DLQI > 10. Included were patients who, according to the investigator's assessment, are eligible for systemic therapy and who are eligible for therapy with conventional active ingredients (e.g. fumaric acid esters, ciclosporin, and methotrexate) or phototherapy. Patients should continue to have an inadequate response, contraindication, or intolerance to previous topical therapies.

In the study M16-178, 120 patients were randomised at a ratio of 1:1 to the study arms risankizumab (N = 60) and fumaric acid ester (N = 60). In the study, stratification was performed after previous phototherapy. A maximum of 20% of the patients included were allowed to receive such previous therapy. The study included a screening phase (30 days) followed by a 24-week open treatment phase.

The primary endpoint of the study was PASI 90 at week 24. Patient-relevant secondary endpoints were total mortality and remission (PASI 100) as well as endpoints on symptomatology, health-related quality of life, and side effects.

Implementation of the appropriate comparator therapy

As part of a reassessment of the generally accepted state of scientific knowledge, in September 2018, a change was made to the appropriate comparator therapy for patient population a) (*see comments on appropriate comparator therapy*). According to this amendment as well as the current determination of the appropriate comparator therapy with the resolution on tildrakizumab of 2 May 2019, fumaric acid esters are no longer an option of the appropriate comparator therapy. The comparison of risankizumab with fumaric acid esters is therefore not relevant for the present assessment.

The change in the appropriate comparator therapy also resulted in a new composition of patient population a). In accordance with the current appropriate comparative therapy, the patient population comprises a) adult patients who are not eligible for conventional therapy as part of an initial systemic therapy. However, study M16-178 explicitly included patients who were eligible for initial systemic therapy with a conventional active ingredient (e.g. fumaric acid ester, methotrexate, or ciclosporin). Thus, the patient population included does not correspond to the patients of patient population a).

Because study M16-178 does not provide any data compared with the currently determined appropriate comparator therapy, and because the patients included do not correspond to patient population a), the study cannot be used to derive the additional benefit of risankizumab. Nevertheless, the results of study M16-178 are additionally shown.

Below the results of study M16-178, which shows a comparison of risankizumab with fumaric acid esters, are additionally shown:

Mortality

Until week 24, no deaths occurred in study M16-178.

Morbidity

For the endpoint remission, which was determined by the PASI 100, a statistically significant effect to the advantage of risankizumab compared with fumaric acid esters can be observed (RR 9.91 [95% CI 3.20; 30.71]; p value < 0.001). The proportion of patients with an improvement in the PASI score from the start of study at week 24 by 75% (PASI 75) and 90% (PASI 90) also shows a statistically significant advantage for risankizumab compared with fumaric acid esters (PASI 75: RR 1.96 [95% CI 1.51; 2.54]; p value < 0.001; PASI 90: RR 8.36 [95% CI 3.88; 18.00]; p value < 0.001).

These positive effects are also reflected in the absence of symptoms reported by patients: For the endpoints PSS itching, PSS pain, PSS redness, and PSS burning of the freedom from symptoms reported by the patient, there is a statistically significant advantage in favour of risankizumab compared with fumaric acid esters. Further advantages in favour of risankizumab are shown in the endpoints "Absence of symptoms of the scalp (PSSI 0)", "Absence of symptoms of the nail (NAPSI 0)", and health status as measured by EQ-5D VAS.

Quality of life

In this study, the health-related quality of life was assessed using DLQI and SF-36.

For DLQI (DLQI 0 or 1), there is a statistically significant difference to the advantage of risankizumab compared with fumaric acid esters.

For the SF-36, the physical total score (PCS) and the psychological total score (MCS) are considered separately. The mean difference of the change from the start of study to treatment week 24 is taken into account in each case. Looking at the mean differences, a statistically significant difference to the advantage of risankizumab compared with fumaric acid esters can be observed for both the PCS and the MCS. Because both the PCS and the MCS have a confidence interval for the Hedges' g that is completely outside the irrelevance range [-0.2; 0.2], this is interpreted as a relevant effect.

Side effects

For the endpoints SAEs, discontinuation because of AEs, and infections and infestations (SOC), there is no statistically significant difference between the treatment groups.

However, for the specific AE gastrointestinal disorders (SOC, including the associated PTs diarrhoea, pain in the upper abdomen, abdominal pain, and nausea), vascular diseases (SOC, including the associated PTs heat sensation), and nervous system disorders (SOC), a statistically significant difference to the advantage of risankizumab is observed.

- b) For adult patients with moderate to severe plaque psoriasis who have responded inadequately to or did not tolerate systemic therapy, risankizumab has proven to have a considerable additional benefit compared with the appropriate comparator therapy ustekinumab.

Justification:

The benefit assessment for patient population b) is based on the UltIMMa-1 and UltIMMa-2 studies and their meta-analysis at week 52.

The UltIMMa-1 and UltIMMa-2 studies are randomised, double-blind parallel group studies with identical protocols (twin studies). The studies compare risankizumab to placebo and ustekinumab in adults with moderate to severe plaque psoriasis. In both studies, the severity of the disease was defined using the criteria body surface area (BSA) \geq 10%, Psoriasis Area and Severity Index (PASI) \geq 12, and Static Physician's Global Assessment (sPGA) \geq 3.

In the UltIMMa-1 and UltIMMa-2 studies 506 and 491 patients, respectively were randomised at a ratio of 3:1:1 to the study arms risankizumab (UltIMMa-1: N = 304; UltIMMa-2: N = 294), placebo (UltIMMa-1: N = 102; UltIMMa-2: N = 98), and ustekinumab (UltIMMa-1: N = 100; UltIMMa-2: N = 99). In both studies, stratification was performed according to the factors body weight (≤ 100 kg vs > 100 kg) and pretreatment with *TNF-alpha antagonists* (0 vs ≥ 1).

The design of the two studies included a screening phase (1 to 6 weeks) followed by a 52-week blinded treatment phase (last dose of study medication in week 40). The patients were then able to either end their study participation or participate in an open extension study (study M15-997). The present benefit assessment is based on the data at the end of treatment after 52 weeks.

The primary endpoints of both studies were PASI 90 and an sPGA value of 0 or 1 at week 16. Patient-relevant secondary endpoints were total mortality and remission (PASI 100) as well as endpoints on symptomatology, health-related quality of life, and side effects.

For the benefit assessment of the relevant sub-population

In both studies, patients were included for whom (according to the investigator) a systemic therapy or phototherapy is possible. Accordingly, in both studies, the inclusion criteria were not restricted to patients with the present question b). Therefore, only those patients in whom a systemic therapy did not respond adequately or who did not tolerate it are relevant for the present benefit assessment.

In addition, it should be noted that ustekinumab has different marketing authorisations in different countries. The UltIMMa-1 and UltIMMa-2 studies therefore included patients who are eligible for therapy with ustekinumab in accordance with local product information. For this benefit assessment, however, only the results of those patients who are eligible for treatment with ustekinumab in accordance with the German marketing authorisation are taken into account.

Nevertheless, the sub-population formed by the pharmaceutical company also includes patients who have not received any systemic therapy before (UltIMMa-1: n = 15; UltIMMa-2: n = 13) and therefore cannot be assigned to the present question b). However, the proportion of these therapy-naïve patients (10.8%) accounts for less than 20% of the sub-population and does not call into question the transferability of the results. The sub-population formed by the pharmaceutical company can therefore be used for the present benefit assessment. For both studies, this corresponds to about one third of the patients originally randomised to the study arms. It comprises n = 100 (UltIMMa-1) or n = 90 (UltIMMa-2) patients in the risankizumab arm and n = 34 (UltIMMa-1) or n = 36 (UltIMMa-2) patients in the ustekinumab arm.

Extent and probability of the additional benefit

Mortality

Until week 52, no deaths occurred in the UltIMMa-1 and UltIMMa-2 studies.

Morbidity

Psoriasis Area and Severity Index (PASI)

In the German health care context, the PASI is a standard instrument for the classification of the degree of severity by the physician and is highly relevant for the diagnosis and monitoring of the severity of the disease in health care. The PASI is used in conjunction with other instruments to determine the severity of psoriasis. The symptoms redness, thickness, and scaling of the skin for the body regions head, trunk, arms, and legs are evaluated by the physician with a score between 0 (not present) and 4 (very severe). The proportion of the

affected body surface is estimated by the investigator as a percentage of the total surface area of the body region. An overall score is formed based on the evaluation of the symptoms and the assessment of the affected body surface. The PASI score can range from 0 (no signs of psoriasis) to 72.

For this benefit assessment, the results on the proportion of patients with an improvement in the PASI score from the start of study at week 52 by 100% (PASI 100), 90% (PASI 90), and 75% (PASI 75) are used.

Remission (PASI 100)

A remission (PASI 100) is considered patient-relevant. At week 52, 64% (UltIMMa-1) and 62% (UltIMMa-2) of the patients in the risankizumab arm achieved a PASI 100 and thus a complete remission; in the ustekinumab arm, however, only 15% (UltIMMa-1) and 31% (UltIMMa-2) achieved a complete remission.

The meta-analysis of both studies shows a statistically significant effect to the advantage of risankizumab.

PASI 75 and PASI 90 response

A PASI 75 or PASI 90 response is also considered patient-relevant. The meta-analyses of both studies showed statistically significant advantages for risankizumab over ustekinumab in the proportion of patients with an improvement in the PASI score of 75% (PASI 75) and 90% (PASI 90) from the start of study at week 52.

Freedom from symptoms reported by the patient – collected by PSS itching 0, PSS pain 0, PSS redness 0, and PSS burning 0

The Psoriasis Symptom Scale (PSS) is a questionnaire completed by patients to assess the severity of the symptoms itching, pain, redness, and burning in the last 24 hours, each on a scale of 0 (no symptoms) to 4 (very severe symptoms). For this benefit assessment, the results of the proportion of patients with no symptoms (PSS of 0) at week 52 are used for all endpoints.

In the meta-analysis for the endpoints PSS itching, PSS pain, PSS redness and PSS burning of the freedom from symptoms reported by the patient, there is a statistically significant effect to the advantage of risankizumab compared with ustekinumab.

Symptomatology Absence of symptoms of the fingernail (NAPSI finger 0)

The Nail Psoriasis Severity Index (NAPSI) is a validated instrument for the assessment and severity classification of nail psoriasis by the investigator. The absence of symptoms of the nail (NAPSI of 0) is considered patient-relevant. The endpoint was determined only in patients with nail psoriasis (NAPSI finger > 0) at the start of study.

The meta-analysis of the UltIMMa-1 and UltIMMa-2 studies showed no statistically significant difference between the treatment arms for the endpoint “Absence of symptoms of the fingernail (NAPSI finger 0)”.

Symptomatology Absence of symptoms of the scalp (PSSI 0)

The Psoriasis Scalp Severity Index (PSSI) is an instrument used to assess scalp psoriasis. The scalp is examined for the symptoms of redness, induration, and scaling. The extent of the affected skin surface as well as the severity of the skin changes are determined similar to PASI. This results in a total value that can lie between 0 (no scalp psoriasis) and 72 (very severe scalp psoriasis). The assessment of the involvement in the scalp area is considered patient-relevant, in particular the absence of symptoms of the scalp (PSSI of 0). With other forms of the scale, the impairment of the patients by the remaining symptoms remains unclear. Only patients with scalp psoriasis (PSSI > 0) at the start of study were included in the evaluation of the proportion of patients with a PSSI 0.

For the endpoint “Absence of symptoms of the scalp (PSSI 0)”, the meta-analysis of the UltIMMa-1 and UltIMMa-2 studies shows a statistically significant difference in favour of risankizumab compared with ustekinumab.

Health status (EQ-5D VAS)

The health status was surveyed using the VAS of the EQ-5D. Here the patient estimates the current health status on a VAS of 0 mm to 100 mm. 0 mm stands for the worst health status imaginable and 100 mm for the best.

The assessment of the health status by means of a VAS is classified as patient-relevant. For the benefit assessment, the evaluation of the mean change in health status from the start of study at week 52 is used.

For the endpoint health status measured using the EQ-5D VAS, the meta-analysis of the UltIMMa-1 and UltIMMa-2 studies showed a statistically significant difference to the advantage of risankizumab compared with ustekinumab.

Quality of life

Dermatology Life Quality Index (DLQI) Response

The DLQI is a validated questionnaire used to determine the disease-specific health-related quality of life in adult patients with dermatological diseases. 10 items in 6 domains are surveyed: Symptoms and well-being, daily activities, leisure, work, and school, personal relationships, and treatment; the questionnaire is completed by the patient. Each item has 4 answer categories ranging from 0 (not at all) to 3 (very strong). A total score is then formed (values from 0 to 30). The lower the score, the better the health-related quality of life. A DLQI of 0 or 1 shows a hardly or no longer impaired quality of life.

The assessment of health-related quality of life via the DLQI is classified as patient-relevant. For this benefit assessment, the results of the proportion of patients with a DLQI of 0 or 1 at week 52 are used.

For the endpoint health-related quality of life measured using the DLQI, the meta-analysis of the UltIMMa-1 and UltIMMa-2 studies showed a statistically significant difference to the advantage of risankizumab compared with ustekinumab.

Side effects

SAE

For the patient-relevant endpoint SAE, both studies at week 52 showed no statistically significant advantage or disadvantage for risankizumab compared with ustekinumab.

Discontinuation because of AE

For the patient-relevant endpoint “Discontinuation because of AE”, neither advantages nor disadvantages for risankizumab compared with ustekinumab were found in both studies at week 52.

Specific AE

For the endpoint “Infections and infestations”, no statistically significant difference between the treatment arms was found in both studies at week 52.

Overall assessment

For adult patients with moderate to severe plaque psoriasis who have responded inadequately to or did not tolerate systemic therapy, the morbidity endpoint category shows a statistically significant advantage in favour of risankizumab compared with the appropriate comparator therapy ustekinumab both in remission based on the PASI 100 and in the improvement of the PASI score by 75% and 90% at week 52. These positive effects are also reflected in the absence of symptoms reported by patients: For the endpoints PSS itching, PSS pain, PSS redness, and PSS burning of the freedom from symptoms reported by the patient, there is a statistically significant advantage in favour of risankizumab compared with ustekinumab. Further statistically advantages in favour of risankizumab are shown in the endpoints "Absence of symptoms of the scalp" and health status of the patients as measured by EQ-5D VAS.

In the endpoint category health-related quality of life, the DLQI of 0 or 1 at week 52 also shows positive effects in favour of risankizumab compared with ustekinumab therapy.

In the category side effects, there is neither an advantage nor a disadvantage for risankizumab compared with ustekinumab.

In the overall assessment, the positive effects of risankizumab on the morbidity endpoints investigated as well as on the health-related quality of life without disadvantages in the side-effect profile compared with the appropriate comparator therapy are assessed as the previously unattained significant improvement of the therapy-relevant benefit, and the extent of the additional benefit is classified as considerable.

Reliability of data (probability of additional benefit)

In the UltIMMa-1 and UltIMMa-2 studies, the additional benefit is assessed based on two randomised, double-blind, and directly comparative Phase III studies. However, only about one third of the patients included in each study were relevant for the benefit assessment because they fulfilled the characteristics of patient population b) because of the previous therapies and were eligible for therapy with ustekinumab in accordance with the German marketing authorisation.

The risk of bias at the study level is classified as low. At the endpoint level, the risk of bias is classified as potentially highly biased because of the high and differential proportions of patients replaced by non-responder imputation (NRI). For the endpoint PASI 100, the endpoints freedom from symptoms reported by the patient (PSS itching, PSS pain, PSS redness, and PSS burning) and for the DLQI of health-related quality of life, sensitivity analyses were therefore additionally evaluated. Missing values were replaced by Last Observation carried forward (LOCF) and Multiple Imputation (MI). The results of the sensitivity analyses show consistent effects of comparable magnitude compared with the primary NRI analysis. Thus, the sensitivity analyses have shown that the results are robust. Despite the high risk of bias at the endpoint level, it is therefore assumed that the results will be highly reliable.

The overall rating of the reliability of data is based on one proof.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Skyrizi™ with the active ingredient risankizumab. Risankizumab is authorised for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

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

a) Adult patients with moderate to severe plaque psoriasis who are not candidates for conventional therapy as part of an initial systemic therapy

and

b) Adult patients with moderate to severe plaque psoriasis who have responded inadequately to or did not tolerate systemic therapy.

About patient group a)

The G-BA identified the biologics adalimumab, guselkumab, ixekizumab, and secukinumab as equally appropriate therapy options for appropriate comparator therapy.

For this patient group, the pharmaceutical company does not provide comparative data for an active ingredient of the appropriate comparator therapy. Thus, no suitable data are available for the assessment of the additional benefit of risankizuamb for adult patients with moderate to severe plaque psoriasis who are not candidates for conventional therapy as part of an initial systemic therapy. Therefore, in the overall view, no additional benefit is proven.

About patient group b)

The G-BA identified the biologics adalimumab, brodalumab, guselkumab, infliximab, ixekizumab, secukinumab, and ustekinumab as equally appropriate therapy options for appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the two RCTs UltIMMa-1 and UltIMMa-2 in which risankizumab was compared with ustekinumab over a period of 52 weeks.

In the morbidity endpoint category, a statistically significant advantage in favour of risankizumab is shown at week 52 both in the remission based on the PASI 100 and in the improvement of the PASI score by 75% and 90%. These positive effects are also reflected in the freedom from symptoms PSS itching, PSS pain, PSS redness, and PSS burning reported by the patient. Further statistically significant advantages in favour of risankizumab are shown in the endpoints "Absence of symptoms of the scalp" and health status as measured by EQ-5D VAS.

In the endpoint category health-related quality of life, the DLQI of 0 or 1 at week 52 also shows positive effects in favour of risankizumab compared with ustekinumab therapy.

In the category side effects, there is neither an advantage nor a disadvantage for risankizumab compared with ustekinumab.

Thus, for risankizumab in patients with moderate to severe plaque psoriasis who did not respond adequately to systemic therapy or did not tolerate it, only positive effects in morbidity and quality of life without disadvantages in the side effect profile were observed. In the overall view, there is proof of a considerable additional benefit of risankizumab compared with ustekinumab.

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

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

Patient population a)

Data on patient population a) is based on data provided by the pharmaceutical company in the written statement procedure.

In analogy to the resolution of the G-BA on secukinumab in the therapeutic indication of plaque psoriasis in 2015, the pharmaceutical company assumes that 19,800 to 137,300 of adult patients with moderate to severe plaque psoriasis are eligible for systemic and/or

phototherapy. However, patient population a) comprises only those patients who are not candidates for conventional therapy as part of an initial systemic therapy. On the other hand, patients for whom treatment with a conventional active ingredient (e.g. fumaric acid ester) is indicated as part of an initial systemic therapy are not included in patient population a).

To calculate the number of patients in group a), data from the German Psoriasis Register PsoBest are used by the Competence Centre for Health Services Research in Dermatology. The patients were first identified with initial systemic therapy. This was followed by a determination of the proportion of patients who received a biologic as part of the first systemic therapy. In these patients, it can be assumed that conventional therapy was not expected to be successful enough and that they therefore belong to patient population a).

On the other hand, calculations based on pharmacy dispensing data from the IMS LRx database are not taken into account for determining patient numbers because the methodology is inadequately described and the prescription data on which the database is based contain no information for diagnosis. The analysis of the IMS LRx database is therefore less meaningful than the analysis of the PsoBest register data.

Based on the evaluation of the data from the PsoBest register, 17.8% of patients who received a biologic as part of their first systemic therapy were identified as having received systemic therapy for the first time. It can be assumed that this proportion is slightly overestimated because the PsoBest register is more likely to include specialist practices and treatment centres in which biologics are likely to be prescribed with above-average frequency. The pharmaceutical company transfers the calculated unit value to the starting basis of 19,800 to 137,300 adult patients with moderate to severe plaque psoriasis who are eligible for systemic and/or phototherapy. This step also leads to an overestimation of the number of patient populations a) because the unit value calculated would have to be related to the number of patients who received systemic therapy for the first time.

Patient population b)

The patient numbers for patient population b) refer to the resolution of G-BA on apremilast in the indication area plaque psoriasis in 2015.

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: 20 September 2019):

>https://www.ema.europa.eu/documents/product-information/skyrizi-epar-product-information_de.pdf<

In patients who do not respond after 16 weeks of treatment, discontinuation of treatment should be considered.

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: 1 November 2019).

It is assumed that one year will be used to calculate the costs for all medicinal products. This does not take into account the fact that treatment may be discontinued earlier because of non-response or intolerance. The discontinuation criteria according to the product information of the individual active ingredients shall be taken into account in the application of the medicinal products.

Treatment duration:

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	continuous; every 12 weeks	4.3	1	4.3 ³
Appropriate comparator therapy				
Patient population a)				
Adalimumab	continuous; every 2 weeks	26	1	26
Guselkumab	continuous, every 8 weeks	6.5	1	6.5
Ixekizumab	continuous; every 4 weeks	13	1	13
Secukinumab	continuous; 1 x monthly	12	1	12
Patient population b)				
Adalimumab	continuous; every 2 weeks	26	1	26
Brodalumab	continuous; every 2 weeks	26	1	26
Guselkumab	continuous, every 8 weeks	6.5	1	6.5
Infliximab	continuous; every 8 weeks	6.5	1	6.5

³ Data rounded here. The further calculation of the costs was carried out with non-rounded value.

Ixekizumab	continuous; every 4 weeks	13	1	13
Secukinumab	continuous; 1 x monthly	12	1	12
Ustekinumab	continuous; every 12 weeks	4.3	1	4.3 ³

Usage and consumption:

In general, initial induction schemes are not taken into account for the cost representation because 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.

In principle, the G-BA does not base the calculation of the consumption of weight-dependent medicinal products to be dispensed on indication-specific average weights. For body weight, the average weight of the German population aged 18 and over is assumed to be 77 kg according to the official representative statistic "Microcensus 2017".⁴ As a result, patient-specific weight differences between women and men, which may be above or below the average of 77 kg, are not taken into account in the cost calculation.

Designation of the therapy	Dosage	Dose/patient /treatment days	Consumption according to potency/treatment day	Treatment days/patient/year	Annual average consumption by potency
Medicinal product to be assessed					
Risankizumab	150 mg	150 mg	2 x 75 mg	4.3	8.6 x 75 mg
Appropriate comparator therapy					
Patient population a)					
Adalimumab	40 mg	40 mg	1 x 40 mg	26	26 x 40 mg
Guselkumab	100 mg	100 mg	1 x 100 mg	6.5	6.5 x 100 mg
Ixekizumab	80 mg	80 mg	1 x 80 mg	13	13 x 80 mg
Secukinumab	300 mg	300 mg	2 x 150 mg	12	24 x 150 mg
Patient population b)					
Adalimumab	40 mg	40 mg	1 x 40 mg	26	26 x 40 mg
Brodalumab	210 mg	210 mg	1 x 210 mg	26	26 x 210 mg
Guselkumab	100 mg	100 mg	1 x 100 mg	6.5	6.5 x 100 mg
Infliximab	385 mg	5 mg/kg BW;	4 x 100 mg	6.5	26 x 100 mg

⁴ Fragen zur Gesundheit – Körpermaße der Bevölkerung – Mikrozensus 2017 [Questions about health – body measurements of the population – Microcensus 2017]. <https://www.destatis.de> (last retrieved on: 26 September 2019)

Designation of the therapy	Dosage	Dose/patient /treatment days	Consumption according to potency/treatment day	Treatment days/patient/year	Annual average consumption by potency
		385 mg			
Ixekizumab	80 mg	80 mg	1 x 80 mg	13	13 x 80 mg
Secukinumab	300 mg	300 mg	2 x 150 mg	12	24 x 150 mg
Ustekinumab	45 mg	45 mg	1 x 45 mg	4.3	4.3 x 45 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. If a fixed amount is available, this will be used as the basis for the cost calculation.

Costs of the medicinal product:

Designation of the therapy	Package 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 SFI	€ 6,153.55	€ 1.77	€ 348.16	€ 5,803.62
Appropriate comparator therapy					
Patient population a)					
Adalimumab	6 SFI	€ 2,805.00	€ 1.77	€ 156.92	€ 2,646.31
Guselkumab	2 SFI	€ 6,468.29	€ 1.77	€ 0.00	€ 6,466.52
Ixekizumab	3 PEN	€ 4,175.67	€ 1.77	€ 0.00	€ 4,173.90
Secukinumab	6 SFI	€ 5,277.83	€ 1.77	€ 0.00	€ 5,276.06
Patient population b)					
Adalimumab	6 SFI	€ 2,805.00	€ 1.77	€ 156.92	€ 2,646.31
Brodalumab	6 SFI	€ 4,153.61	€ 1.77	€ 0.00	€ 4,151.84
Guselkumab	2 SFI	€ 6,468.29	€ 1.77	€ 0.00	€ 6,466.52
Infliximab ⁵	5 PIS	€ 3,649.77	€ 1.77	€ 293.09	€ 3,354.91
Ixekizumab	3 PEN	€ 4,175.67	€ 1.77	€ 0.00	€ 4,173.90
Secukinumab	6 SFI	€ 5,277.83	€ 1.77	€ 0.00	€ 5,276.06
Ustekinumab	1 SFI	€ 5,186.56	€ 1.77	€ 292.93	€ 4,891.86
Abbreviations: SFI = solution for injection; PEN = injection solution in a pre-fabricated pen; PIS = powder for the preparation of an infusion solution; TAB = tablets; SC = soft capsules					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 November 2019

⁵ Fixed amount

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

For the active ingredients risankizumab, adalimumab, infliximab, and ustekinumab, costs are regularly incurred for the investigation of both active and inactive (latent) tuberculosis infections. The costs shown are a blood test (quantitative determination of an *in vitro* interferon-gamma release after *ex vivo* stimulation with antigens specific for mycobacterium tuberculosis-complex (except BCG)). In addition, a chest radiograph is usually required for the detection of pulmonary tuberculosis. The tuberculin skin test is not mapped because of lack of sensitivity and specificity as well as the possibility of "sensitisation".

Patients treated with adalimumab and infliximab must also be tested for the presence of HBV infection before the respective treatment is initiated.

For the diagnosis of a suspected chronic hepatitis B, well coordinated steps are necessary⁶. A serological step-by-step diagnostic initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If the HBs antigen is positive, an active HBV infection has been detected.

Designation of the therapy	Description of the service	Number	Cost per unit	Cost per patient per year
Medicinal product to be assessed				
Risankizumab	Quantitative determination of an <i>in vitro</i> interferon-gamma release after <i>ex vivo</i> stimulation with antigens (at least ESAT-6 and CFP-10) specific for mycobacterium tuberculosis-complex (except for BCG) (GOP 32670)	1	€ 58.00	€ 58.00
	Chest radiograph (GOP 34241)	1	€ 16.45	€ 16.45
Appropriate comparator therapy				
Adalimumab infliximab ustekinumab	Quantitative determination of an <i>in vitro</i> interferon-gamma release after <i>ex vivo</i>	1	€ 58.00	€ 58.00

⁶ "Update of the S3 guideline on prophylaxis, diagnosis and therapy of hepatitis B virus infection; AWMF register No.: 021/011" http://www.dgvs.de/fileadmin/user_upload/Leitlinien/Hepatitis_B/Leitlinie_Hepatitis_B.pdf

Designation of the therapy	Description of the service	Number	Cost per unit	Cost per patient per year
	stimulation with antigens (at least ESAT-6 and CFP-10) specific for mycobacterium tuberculosis-complex (except for BCG) (GOP 32670)			
	Chest radiograph (GOP 34241)	1	€ 16.45	€ 16.45
Adalimumab infiximab	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	anti-HBs antibody (GOP 32617) ⁷	1	€ 5.50	€ 5.50
	anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823) ⁸	1	€ 89.50	€ 89.50

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy retail price publicly accessible in the directory services in accordance with Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe⁷] (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic products of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for production and is only an approximation of the treatment costs. This presentation does not take into account, for example, the discounts on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

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.

⁷ Only if HBs antigen negative and anti-HBc antibody positive.

⁸ Settlement of GOP 32823 possible before or during antiviral therapy with interferon and/or nucleic acid analogues.

4. Process sequence

At its session on 11 September 2018, the subcommittee on Medicinal Products determined the appropriate comparator therapy, which was adjusted again by resolution of tildrakizumab on 2 May 2019.

On 2 May 2019, 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 1, sentence 2 VerfO.

By letter dated 2 May 2019 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 29 August 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 September 2019. The deadline for submitting written statements was 23 September 2019.

The oral hearing was held on 7 October 2019.

By letter dated 7 October 2019, 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 30 October 2019. The additional addendum on the assessment of patient numbers prepared by the IQWiG was submitted to the G-BA on 29 October 2019.

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 were discussed at the session of the subcommittee on 12 November 2019, and the proposed resolution was approved.

At its session on 22 November 2019, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 September 2018	Determination of the appropriate comparator therapy
Working group Section 35a	1 October 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	7 October 2019	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	15 October 2019 22 October 2019 5 November 2019	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	12 November 2019	Concluding discussion of the proposed resolution
Plenum	22 November 2019	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 22 November 2019

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

Prof Hecken