

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
Upadacitinib (new therapeutic indication: atopic dermatitis, ≥
12 years)

of 17 February 2022

Contents

1.	Legal basis	2
2.	Key points of the resolution	2
2.1	Additional benefit of the medicinal product in relation to the appropriate comparator therapy.....	3
2.1.1	Approved therapeutic indication of Upadacitinib (RINVOQ) in accordance with the product information.....	3
2.1.2	Appropriate comparator therapy.....	3
2.1.3	Extent and probability of the additional benefit.....	6
2.1.4	Summary of the assessment	10
2.2	Number of patients or demarcation of patient groups eligible for treatment.....	11
2.3	Requirements for a quality-assured application	11
2.4	Treatment costs.....	12
3.	Bureaucratic costs calculation.....	15
4.	Process sequence	15

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 upadacitinib (Rinvoq) was listed for the first time on 1 February 2020 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 20 August 2021, Rinvoq 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, p. 7).

On 31 August 2021, i.e. at the latest within four weeks after the notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure

(VerfO) of the G-BA on the active ingredient upadacitinib with the new therapeutic indication atopic dermatitis, ≥ 12 years.

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 1 December 2021, 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 upadacitinib 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, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods¹ was not used in the benefit assessment of upadacitinib.

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 Upadacitinib (RINVOQ) in accordance with the product information

Rinvoq is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

Therapeutic indication of the resolution (resolution of 17.02.2022):

see new therapeutic indication according to marketing authorisation

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Patients 12 years and older with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy

- Dupilumab (in combination with TCS and/or TCI if required)

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.

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

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 Federal Joint Committee has already determined the patient-relevant advantage 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. Medicinal products with the following active ingredients are approved for the present therapeutic indication:
- Topical glucocorticoids of classes 2 to 4
 - Pimecrolimus (moderate atopic eczema) and tacrolimus (moderate to severe atopic eczema)
 - Systemic glucocorticoids (severe eczema)
 - Ciclosporin (severe atopic dermatitis)
 - Antihistamines
 - Dupilumab
 - Baricitinib
 - Tralokinumab
- on 2. UV treatments (UVA/NB-UVB/balneophototherapy) are eligible as non-medicinal treatments, but UVA1 is not eligible as it is not a reimbursable treatment.
- on 3. In the therapeutic indication under consideration here, the following resolutions of the G-BA are available:
- Therapeutic information on tacrolimus (resolution of 4 September 2003) and pimecrolimus (resolution of 4 September 2003)
 - Resolutions on the benefit assessment according to Section 35a SGB V for the active ingredient dupilumab dated 17 May 2018, 20 February 2020 and 1 July 2021
 - Resolution on the amendment of the Directive of Prescription of Medicinal Products in SHI-accredited Medical Care (MVV-RL): "Balneophototherapy for atopic eczema," dated 20 March 2020
 - Resolution on the benefit assessment according to Section 35a SGB V for the active ingredient baricitinib dated 6 May 2021
 - Resolution on the benefit assessment according to Section 35a SGB V for the active ingredient tralokinumab dated 6 January 2022

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

According to the marketing authorisation, those patients are included in the therapeutic indication who are eligible for a systemic therapy.

For the present benefit assessment, adult and adolescent patients with moderate to severe atopic dermatitis for whom continuous systemic therapy is indicated are considered, as the active ingredient upadacitinib is administered as a continuous therapy and is therefore only considered in adults and adolescents for whom continuous systemic therapy is indicated.

For the present patient population of adults and adolescents with moderate to severe atopic dermatitis who are candidates for a continuous systemic therapy, the active ingredient dupilumab is available as further therapy option. Based on the benefit assessment resolution of 17 May 2018, dupilumab was able to show an indication of a considerable additional benefit compared with the appropriate comparator therapy in adults. By resolution of 20 February 2020, a non-quantifiable additional benefit of dupilumab for adolescents aged 12 to 17 years was also identified. In the overall assessment of the available evidence, dupilumab represents an adequate therapy option for patients with moderate to severe atopic dermatitis who are candidates for a continuous systemic therapy. Therefore, there is beneficial evidence for an active ingredient that has now also proven itself in practical application.

The G-BA identified no additional benefit of the active ingredients baricitinib and tralokinumab in adults with moderate to severe atopic dermatitis who are candidates for a continuous systemic therapy, as no suitable data were available for a comparison with the appropriate comparator therapy. In addition, both active ingredients are comparatively new therapy options whose significance cannot yet be conclusively assessed. Therefore, baricitinib and tralokinumab are not found to be appropriate comparator therapy for the present patient group.

Even with permanent or continuous systemic therapy, topical glucocorticoids (TCS) in classes 2 to 4 and the calcineurin inhibitor (TCI) tacrolimus may also be indicated as topical therapy options for individual lesions or in a limited period of time.

For patients for whom continuous systemic therapy is indicated, dupilumab (in combination with TCS and/or TCI if required) is the appropriate comparator therapy.

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

2.1.3 Extent and probability of the additional benefit

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

- a) Adults with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy and for whom 30 mg upadacitinib is the appropriate dose

For the treatment of moderate to severe atopic dermatitis in adults who are candidates for a continuous systemic therapy and for whom 30 mg is the appropriate dose, there is indication of a considerable additional benefit of upadacitinib compared with the appropriate comparator therapy.

Justification:

For the benefit assessment, the pharmaceutical company submits the randomised controlled Heads Up trial, in which upadacitinib is compared with dupilumab.

The study population includes adults aged 18-75 years with moderate to severe atopic dermatitis that has been present for at least three years. Patients must have a *Validated Investigator Global Assessment for Atopic Dermatitis* (vIGA-AD) ≥ 3 , an *Eczema Area and Severity Index* (EASI) ≥ 16 points and an affected body surface area of $\geq 10\%$. They must also have inadequately responded to topical (TCS/TCI) or systemic therapy within six months prior to randomisation. Adolescents 12 years and older were not enrolled in the Heads Up study.

Patients were randomised to the intervention arm (n = 348) or the comparator arm (n = 344) according to age and disease severity grade. In the intervention arm, patients received 30 mg upadacitinib daily. This is an approved dosage in the therapeutic indication, also for patients with a high disease burden. The likewise approved 15 mg dose was not investigated. In the comparator arm, dupilumab was administered according to the product information.

The background therapy for the entire duration of the study was the use of emollients at least twice a day. Topical therapies with TCS and/or TCI had to be discontinued at least seven days before the start of the study. At the doctor's discretion, (re)initiation of topical therapy was possible during the course of the study. In both study arms, 24% of patients received topical rescue therapy with TCS and/or TCI. If patients did not respond to topical therapy within seven days, the use of systemic therapies and phototherapies was possible, but this led to permanent discontinuation of study medication (4% in the upadacitinib arm and 1% in the dupilumab arm).

The treatment duration was 24 weeks. The primary endpoint of the study was the EASI 75. In addition, further endpoints on morbidity and side effects were assessed. Quality of life endpoints were neither assessed with an established and validated disease-specific instrument (e.g., DLQI) nor generically (e.g., SF-36).

Extent and probability of the additional benefit

Mortality

For the endpoint of overall survival, no statistically significant difference was detected between the treatment arms.

Morbidity

Morbidity is presented in this assessment using disease severity and remission (assessed using EASI), itching (assessed using WP-NRS) and patient-reported symptomatology (assessed using HN-PGIS).

Eczema Area and Severity Index (EASI 75 and EASI 90 Response, EASI 100 Remission)

In the German health care context, the EASI represents a standard instrument for the classification of severity grade by doctors and is relevant for the diagnosis and monitoring of disease severity in health care. The EASI is used in conjunction with other instruments to determine the severity grade of atopic dermatitis. The symptoms erythema, oedema / papule formation, abrasions as well as lichenification of the skin are evaluated by the doctor for each of the body regions head and neck, trunk, arms and legs with a score between 0 (not present) and 3 (very severe). The percentage of the body surface area affected is estimated by the principal investigator as a percentage of the total body surface area. Based on the evaluation of the symptoms and the assessment of the affected body surface area, a total score is obtained. The EASI score can range from 0 (no evidence of atopic dermatitis) to 72.

The operationalisation of the EASI was based on the number of patients who achieved a 90% (EASI 90) and 75% (EASI 75) improvement in EASI score from the start of the study to week 24, respectively.

An EASI 75 or EASI 90 response is considered patient-relevant. While there is no statistically significant difference between the treatment groups for the EASI 75, there is a statistically significant difference to the advantage of upadacitinib for the response threshold value EASI 90.

EASI 100 means a complete remission of the external signs of atopic dermatitis (i.e., a 100% reduction of the EASI baseline) and is considered patient-relevant. In the present study, there was a statistically significant difference to the advantage of upadacitinib with regard to EASI 100.

Itching (Worst Pruritus Numerical Rating Scale, WP-NRS)

Itching was assessed using the Worst Pruritus NRS (numerical rating scale), a self-report instrument of the worst itching within the last 24 hours, with a score of 0 corresponding to no itching and a score of 10 corresponding to the worst imaginable itching.

On the one hand, the complete absence of symptoms of itching (WP-NRS = 0) and, on the other, the improvement of ≥ 4 points by week 24 are considered. For both operationalisations, there are statistically significant differences in favour of upadacitinib.

Patient-reported symptomatology (Head and Neck-Patient Global Impression of Severity, HN-PGIS)

The HN-PGIS is a patient-reported measurement tool to assess the severity of symptoms of atopic dermatitis in the head and neck area on a scale from 0 (no symptoms) to 6 (cannot be ignored and significantly limits my daily activities). Higher values are associated with more severe symptomatology and greater limitations for patients. For the benefit assessment, the percentage of patients with an HN-PGIS of 0 to week 24 is used. This shows a statistically significant effect to the advantage of upadacitinib compared to dupilumab.

Quality of life

No endpoints of the health-related quality of life category were assessed.

Side effects

Overall rate of serious adverse events (SAEs) and discontinuations due to AEs

For the endpoints SAEs and discontinuation due to AEs, there was no statistically significant difference between the treatment groups.

Overall rate of severe AEs (operationalised as CTCAE grade ≥ 3)

There was a statistically significant disadvantage of upadacitinib with regard to serious adverse events with CTCAE grade 3 or 4.

Furthermore, for the severe AEs (operationalised as CTCAE grade ≥ 3), there is an effect modification by the gender characteristic. This results in a statistically significant disadvantage of upadacitinib for the present endpoint in women, while no difference is shown in men. The overall rate of severe AEs is the only endpoint for which this effect modification by the gender characteristic is observed. These gender-specific effects were not observed in clinical practice. Therefore, the effect modification is not used further for the benefit assessment.

Specific AEs

Infections (SOC, AE) and serious infections (SOC, SAE)

In the present benefit assessment, the endpoint of (serious) infections is used via the (S)AEs that occurred in the SOC of infections and infestations. For the endpoint of infections, there is a statistically significant difference to the disadvantage of upadacitinib, but no such statistically significant difference for the serious infections.

Conjunctivitis (PT, AE) and eye disorders (SOC, AE)

For both endpoints, there was a statistically significant difference to the advantage of upadacitinib compared to dupilumab.

Acne (PT, AE)

For the acne endpoint (PT, AE), there is a statistically significant difference to the disadvantage of upadacitinib compared to dupilumab.

Overall assessment

The benefit assessment is based on the Heads Up randomised controlled trial, which compares upadacitinib with dupilumab at a dose of 30 mg. The study population includes adults with moderate to severe atopic dermatitis who are candidates for a continuous systemic therapy.

In the morbidity endpoint category, for adults for whom 30 mg is the appropriate dose, there is a statistically significant difference to the advantage of upadacitinib over dupilumab in each of the endpoints of EASI improvement by 90% (EASI 90), remission (EASI 100), itching (WP-NRS 0 and improvement by ≥ 4 points) and patient-reported symptomatology (HN-PGIS 0).

No endpoints were assessed in the endpoint category of health-related quality of life. Thus, no data on quality of life are available for the benefit assessment.

In the endpoint category of side effects, the overall rate of severe AEs (CTCAE grade ≥ 3) shows a disadvantage for upadacitinib, but this does not call into question the positive results. In

detail, the specific AEs show both advantages (conjunctivitis and eye disorders) and disadvantages (infections and acne) of upadacitinib compared to dupilumab.

In the overall assessment, the positive effects of upadacitinib on itching, EASI 90 and remission (EASI 100) compared to dupilumab are assessed as a significant improvement of the therapy-relevant benefit that has not been achieved so far, and the extent is classified as considerable. In the context of side effects, there were both positive and negative effects of upadacitinib compared to dupilumab.

Thus, overall, a considerable additional benefit of upadacitinib over dupilumab can be derived in adults with moderate to severe atopic dermatitis who are candidates for a continuous systemic therapy and for whom 30 mg is the appropriate dose.

Reliability of data (probability of additional benefit)

The assessment of additional benefit is based on a randomised, double-blind and direct comparator study in which all adults were treated for 24 weeks. The risk of bias across endpoints at the study level is rated as low for this study.

According to the marketing authorisation, a dose reduction from 30 mg to 15 mg is possible for upadacitinib. In the Heads Up study, a dose reduction to 15 mg upadacitinib was not planned in the case of an adequate response, so that no suitable data are available for this and uncertainties result with regard to the comparability with health care practice.

Overall, an indication is derived for the reliability of data.

b) Adults with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy and for whom 15 mg upadacitinib is the appropriate dose

The additional benefit is not proven for the treatment of moderate to severe atopic dermatitis in adults who are candidates for a continuous systemic therapy and for whom 15 mg is the appropriate dose.

Justification:

The pharmaceutical company does not provide suitable data for the patient population to be assessed, as the Heads Up study did not investigate the dose of 15 mg upadacitinib that is compliant with the marketing authorisation. The placebo-controlled marketing authorisation studies show a varying efficacy of upadacitinib depending on the dosage. In the European Public Assessment Report (EPAR), the European Medicines Agency (EMA) also points out that a dose dependency with differences in the responder rates is evident when considering the total populations of the Measure Up 1, Measure Up 2 and AD Up marketing authorisation studies. For this reason, no statement on the additional benefit of upadacitinib at a dose of 15 mg can be derived from the Heads Up study.

c) Adolescents 12 to 18 years of age with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy

The additional benefit is not proven for the treatment of moderate to severe atopic dermatitis in adolescents who are candidates for a continuous systemic therapy.

Justification:

The pharmaceutical company does not provide suitable data for the patient population to be assessed, as no patients under 18 years of age were enrolled in the Heads Up study. For adolescents 12 years and older, only the lower dose of 15 mg upadacitinib is approved. In the present data constellation, a transfer of the additional benefit from adults to adolescents is not possible, as no direct comparator data are available for the 15 mg dose in adults compared to dupilumab.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient upadacitinib.

The therapeutic indication assessed here is as follows: Rinvoq is indicated for the treatment of moderate to severe atopic dermatitis in adults and adolescents 12 years and older who are candidates for systemic therapy.

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

- a) Adults with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy and for whom 30 mg upadacitinib is the appropriate dose
- b) Adults with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy and for whom 15 mg upadacitinib is the appropriate dose
- c) Adolescents 12 to 18 years of age with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy

On patient population a)

The G-BA determined dupilumab (in combination with TCS and/or TCI if required) as the appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the randomised double-blind Heads Up study comparing 30 mg upadacitinib with dupilumab, each alone or in combination with topical TCS and/or TCI. The treatment duration was 24 weeks for all patients.

There are statistically significant advantages of upadacitinib over dupilumab in the endpoint category of morbidity. In the endpoint category of side effects, the overall rate of severe AEs (CTCAE grade ≥ 3) shows a disadvantage for upadacitinib, but this does not call into question the positive results. In detail, both advantages and disadvantages of upadacitinib compared to dupilumab are evident for the specific AEs.

The positive effects of upadacitinib, especially on itching, EASI 90 and remission (EASI 100) are assessed as considerable in extent. The risk of bias at the study level is rated as low.

In the overall assessment, an indication of a considerable additional benefit of upadacitinib over dupilumab is identified in adults with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy and for whom 30 mg is the appropriate dose.

On patient population b)

The G-BA determined dupilumab (in combination with TCS and/or TCI if required) as the appropriate comparator therapy.

The pharmaceutical company does not present suitable data for the patient population to be evaluated so that no statements on the additional benefit of upadacitinib compared to the appropriate comparator therapy can be derived.

In the overall assessment, no additional benefit of upadacitinib over the appropriate comparator therapy is identified in adults with moderate to severe atopic dermatitis who are candidates for a continuous systemic therapy and for whom 15 mg is the appropriate dose.

On patient population c)

The G-BA determined dupilumab (in combination with TCS and/or TCI if required) as the appropriate comparator therapy.

The pharmaceutical company does not present suitable data for the patient population to be evaluated so that no statements on the additional benefit of upadacitinib compared to the appropriate comparator therapy can be derived. For adolescents 12 years and older, only the lower dose of 15 mg upadacitinib is approved. In the present data constellation, a transfer of the additional benefit from adults to adolescents is not possible, as no direct comparator data are available for the 15 mg dose in adults compared to dupilumab.

In the overall assessment, no additional benefit of upadacitinib over the appropriate comparator therapy is identified in adolescents with moderate to severe atopic dermatitis who are candidates for continuous systemic therapy.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI). The information is based on the data from the resolutions of the G-BA on dupilumab in the therapeutic indication of moderate to severe atopic dermatitis in adults² and adolescents³ who are candidates for a systemic therapy.

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 RINVOQ (active ingredient: upadacitinib) at the following publicly accessible link (last access: 3 February 2022):

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

Treatment with upadacitinib should be initiated and supervised by a physician experienced in diagnosing and treating of conditions for which upadacitinib is indicated.

Discontinuation of upadacitinib should be considered for patients who do not show signs of therapeutic benefit after 12 weeks of treatment.

² Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V of 17 May 2018

³ Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V of 20 February 2020

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material includes instructions on how to manage the potential side effects associated with upadacitinib, particularly severe and opportunistic infections including tuberculosis and herpes zoster. It also points out the need for an effective contraceptive method.

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 February 2022).

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 is patient-individual 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.

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.

Upadacitinib is approved as such or in combination with topical corticosteroids and/or topical calcineurin inhibitors for the treatment of moderate to severe atopic dermatitis in adults. The active ingredient of the appropriate comparator therapy, dupilumab, can also be used both as part of a monotherapy and in combination with topical corticosteroids and/or topical calcineurin inhibitors. Thus, if applicable, the corresponding costs for the combination medicinal products are incurred both for the medicinal product under assessment and for the appropriate comparator therapy and are therefore not listed separately.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Upadacitinib	1 x daily	365	1	365
Appropriate comparator therapy				
Dupilumab	1 x every 14 days	26.1	1	26.1

Consumption:

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Upadacitinib	Adolescents aged between 12 and 17 years				
	15 mg	15 mg	1 x 15 mg	365	365 x 15 mg
	Adults				
	15 mg	15 mg	1 x 15 mg	365	365 x 15 mg
	or				
	30 mg	30 mg	1 x 30 mg	365	365 x 30 mg
Appropriate comparator therapy					
Dupilumab	Adolescents aged between 12 and 17 years < 60 kg bw				
	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
	Adolescents and adults > 60 kg bw				
	300 mg	300 mg	1 x 300 mg	26.1	26.1 x 300 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of usage. 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.

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					
Upadacitinib 15 mg	90 RET	€ 3,714.49	€ 1.77	€ 0.00	€ 3,712.72
Upadacitinib 30 mg	90 RET	€ 7,371.37	€ 1.77	€ 0.00	€ 7,369.60
Appropriate comparator therapy					
Dupilumab 200 mg	6 SFI	€ 4,337.25	€ 1.77	€ 244.41	€ 4,091.07
Dupilumab 300 mg	6 SFI	€ 4,337.25	€ 1.77	€ 244.41	€ 4,091.07
Abbreviations: SFI = solution for injection; RET = sustained-release tablets					

LAUER-TAXE® last revised: 1 February 2022

Costs for additionally required SHI services:

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

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

For the use of upadacitinib, costs are regularly incurred for examining for both active and inactive ("latent") tuberculosis infections. The costs presented 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)) and a chest radiograph. The tuberculin skin test is not presented due to lack of sensitivity and specificity as well as the possibility of "sensitisation".

In addition, patients receiving therapy with upadacitinib should be tested for the presence of HBV infection before initiating the respective treatment. For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required⁴. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If HBs antigen is positive, an active HBV infection is detected.

In deviation from this, additional necessary SHI services are required for the examination of suspected chronic hepatitis B, which usually differ between the drug to be evaluated and the appropriate comparator therapy and are consequently considered as additionally required SHI

⁴ "Update of the S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/11" https://www.awmf.org/uploads/tx_szleitlinien/021-011f_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf

services in the resolution.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs/ patient/ year
Medicinal product to be assessed				
Upadacitinib	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 BCG) (GOP 32670)	1	€ 58.00	€ 58.00
	Chest radiograph (GOP 34241)	1	€ 16.24	€ 16.24
	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 32823) ⁶	1	€ 89.50	€ 89.50

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 22 June 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 31 August 2021, the pharmaceutical company submitted a dossier for the benefit assessment of upadacitinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 1 September 2021 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 upadacitinib.

⁵ Only if HBs antigen negative and anti-HBc antibody positive.

⁶ Invoicing for GOP 32823 possible before or during antiviral therapy with interferon and/or nucleic acid analogues.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 November 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 01 December 2021. The deadline for submitting written statements was 22 December 2021.

The oral hearing was held on 10 January 2022.

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 08 February 2022, and the proposed resolution was approved.

At its session on 17 February 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	6 October 2020	Determination of the appropriate comparator therapy
Subcommittee Medicinal product	22 June 2021	New determination of the appropriate comparator therapy
Working group Section 35a	4 January 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	10 January 2022	Conduct of the oral hearing
Working group Section 35a	18 January 2022 1 February 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	8 February 2022	Concluding discussion of the draft resolution
Plenum	17 February 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 17 February 2022

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

Prof. Hecken