Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive:
Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V
Upadacitinib (new therapeutic indication: ulcerative colitis, pretreated)

of 16 February 2023

Contents

1. Legal basis

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

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

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

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published online 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 18 March 2022, the pharmaceutical company submitted an application for postponement of the date for the start of the benefit assessment procedure for upadacitinib in the therapeutic indication of moderate-to-severe active ulcerative colitis in accordance with Section 35a, paragraph 5b SGB V. In its session on 6 January 2022, the G-BA approved the application to postpone the relevant date in accordance with Section 35a paragraph 5b SGB V. The benefit assessment of upadacitinib in the therapeutic indication of moderate-to-severe active ulcerative colitis begins at the same time as the benefit assessment of upadacitinib in the therapeutic indication of active non-radiographic axial spondyloarthritis, at the latest

within four weeks after marketing authorisation of the therapeutic indication of active non-radiographic axial spondyloarthritis according to Chapter 5, Section 8, No. 2 VerfO, at the latest six months after the first relevant time point (4 weeks after marketing authorisation of the therapeutic indication of moderate-to-severe active ulcerative colitis).

On 22 July 2022, upadacitinib received an extension of the marketing authorisation for the therapeutic indication of moderate-to-severe active ulcerative colitis. The extension of the marketing authorisation for the therapeutic indication of active non-radiographic axial spondyloarthritis was granted on 27 July 2022. The extensions of the marketing authorisation are 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).

The pharmaceutical company submitted a dossier in accordance with Section 4,paragraph 3, No. 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the G-BA's Rules of Procedure (VerfO) on the active ingredient upadacitinib with the new therapeutic indication "moderately to severely active ulcerative colitis in adult patients who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent" in due time on 24 August 2022.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 December 2022 on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of 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 Methods[1] 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:

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

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 adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.

Therapeutic indication of the resolution (resolution of 16.02.2023):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

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

Appropriate comparator therapy for upadacitinib:

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

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

Appropriate comparator therapy for upadacitinib:

- A change of therapy to vedolizumab or tofacitinib or ustekinumab or a TNF-α antagonist (adalimumab or infliximab or golimumab), in each case taking into account the marketing authorisation and the previous therapy/ therapies

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

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. For the treatment of ulcerative colitis (UC), the medicinal products approved in the therapeutic indication are 5-aminosalicylates (mesalazine, sulfasalazine, olsalazine), glucocorticoids, azathioprine, TNF-α antagonists (infliximab, adalimumab, golimumab), the interleukin inhibitor ustekinumab, the integrin inhibitor vedolizumab, the JAK inhibitors tofacitinib and filgotinib as well as the sphingosine-1-phosphate receptor modulator ozanimod, depending on the severity grade of the disease. 6-mercaptopurine does not have a marketing authorisation in Germany for the treatment of UC.

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

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

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

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

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

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

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

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

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

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

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

When determining the appropriate comparator therapy for patients, extensive published data and guidelines are available.

a) After failure of a conventional therapy, three TNF-α antagonists (adalimumab or Infliximab or golimumab) whose efficacy and tolerability are equally supported by the current guidelines are available. A superiority or inferiority of a particular TNF-α antagonist could not be identified. The use of TNF-α antagonists, according to their marketing authorisation, requires that patients have an inadequate response to, or intolerance or contraindication to, conventional therapy, including corticosteroids and 6-mercaptopurine or azathioprine. The therapeutic indication of the integrin inhibitor vedolizumab and the monoclonal antibody against interleukin 12/13 ustekinumab presupposes that the patients have either responded inadequately to conventional therapy or a biologic agent or no longer respond to it.

According to the guideline, these treatment options are equally recommended for patients who respond inadequately to conventional therapy or who cannot tolerate it. A prioritisation of individual biologic agents is currently not given due to the lack of comprehensive head-to-head comparisons, so that current recommendations propose the TNF-alpha inhibitors infliximab, adalimumab, golimumab as well as vedolizumab or ustekinumab as equally appropriate therapy alternatives in the treatment setting after failure of a conventional therapy. Based on the generally recognised state of medical

knowledge and taking into account the German standard of care, the active ingredients tofacitinib, filgotinib and ozanimod are not determined as appropriate comparator therapy for the patient population a) in the present resolution.

b) After failure to respond to prior therapy with a biologic agent, the overall evidence is weak and the available evidence does not allow prioritisation within the eligible active ingredients. With regard to therapeutic efficacy, no evidence-based information was found that any of the active ingredients included in the appropriate comparator therapy is generally preferable in patients with moderately to severely active ulcerative colitis who have already failed to respond to a biologic agent. In this line of therapy, a change of product class or a change within the product class is considered appropriate.

Based on the generally recognised state of medical knowledge and taking into account the German standard of care, the active ingredients filgotinib and ozanimod are not determined as appropriate comparator therapy for patient population b) in the present resolution. Thus, the appropriate comparator therapy for this patient population includes the TNF-alpha inhibitors infliximab, adalimumab, golimumab, and vedolizumab or ustekinumab or tofacitinib. However, the authorisation status and previous therapy/therapies must be taken into account. The active ingredients in question are equally appropriate therapy alternatives in the treatment setting after failure of therapy with a biologic agent.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5, Section 6, paragraph 3 Rules of Procedure.

2.1.3 Extent and probability of the additional benefit

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

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

An additional benefit is not proven.

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

An additional benefit is not proven.

Justification:

For adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent., there are no direct comparator studies of upadacitinib versus the appropriate comparator therapy. The pharmaceutical company therefore presents an adjusted indirect comparison with ustekinumab via the bridge comparator placebo. For upadacitinib, it uses the U-ACHIEVE and U-ACCOMPLISH studies, and for ustekinumab, the UNIFI study.

The U-ACHIEVE and U-ACCOMPLISH studies are both double-blind RCTs comparing upadacitinib at different doses with placebo, and adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional or biological therapy. The U-ACHIEVE study includes a maximum 16-week induction phase and a 52-week maintenance phase for patients who had shown a clinical response after 8 weeks. Patients in the U-ACCOMPLISH study also switched to the maintenance phase of the U-ACHIEVE study after the 8-week induction phase in the event of a clinical response.

The UNIFI study is a double-blind RCT comparing ustekinumab with placebo in patients with moderate-to-severe ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional or biological therapy. The study is divided into an 8-week induction phase and a 44-week maintenance phase.

The therapeutic indication to be assessed is divided into the patient populations a (conventionally pretreated patients) and b (patients pretreated with biologic agents) depending on the pretreatment, for which, however, the pharmaceutical company does not submit separate evaluations according to pretreatment. Regardless of the lack of separate consideration of the two patient populations, the studies included by the pharmaceutical company for the indirect comparison do not show sufficient similarity. For the U-ACHIEVE and U-ACCOMPLISH studies, respectively, there are greater limitations in the prior and concomitant therapies of ulcerative colitis with immunosuppressants compared to the UNIFI study. At baseline in the maintenance phase of the UNIFI study, about 27% of patients were treated with immunosuppressants, whereas in the maintenance phase of the U-ACHIEVE study only 0.4% of patients received such therapy. In addition, uncertainties remain as to the extent to which patients differ in terms of the disease severity depicted by the Mayo score. There is evidence that the U-ACHIEVE study included more patients with higher disease severity. The existence of relevant differences between the study populations is also evident in the results presented for the respective bridge comparator arms. Thus, across several endpoints, significantly higher response rates are consistently observed in the placebo arm of the UNIFI study compared to the placebo arm of the U-ACHIEVE study.

The submitted indirect comparison is therefore not assessed as appropriate for deriving an additional benefit compared to the appropriate comparator therapy. Thus, there are no relevant data for the benefit assessment of upadacitinib.

In the overall assessment, this means that for a) adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional therapy and for b) adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to a biologic agent

(TNF-α antagonist or integrin inhibitor or interleukin inhibitor), an additional benefit of upadacitinib compared with the appropriate comparator therapy has not been proven in each case.

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of upadacitinib for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response or were intolerant to either conventional therapy or a biologic agent.

Due to the lack of direct comparator data, the pharmaceutical company submits an adjusted indirect comparison with ustekinumab via the bridge comparator placebo for the benefit assessment. For upadacitinib, it uses the U-ACHIEVE and U-ACCOMPLISH studies, and for ustekinumab, the UNIFI study.

Regardless of the lack of separate consideration of the two patient populations a (conventionally pretreated patients) and b (patients pretreated with biologic agents), the studies included by the pharmaceutical company for the indirect comparison do not show sufficient similarity. For the U-ACHIEVE and U-ACCOMPLISH studies, respectively, there are greater limitations in the prior and concomitant therapies of ulcerative colitis with immunosuppressants compared to the UNIFI study. There is also evidence that more patients with higher disease severity were enrolled in the U-ACHIEVE study. The existence of relevant differences between the study populations is also evident in the results presented for the respective bridge comparator arms.

The submitted indirect comparison is therefore not assessed as appropriate for deriving an additional benefit compared to the appropriate comparator therapy. Therefore, no data relevant for the benefit assessment of upadacitinib are available, so an additional benefit is not proven.

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

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

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

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

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

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Rinvoq (active ingredient: upadacitinib) at the following publicly accessible link (last access: 16 November 2022):

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

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

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. In particular, the training and information material contains instructions on how to deal with any side effects caused by upadacitinib, especially in serious and opportunistic infections, including TB and herpes zoster, as well as birth defects (pregnancy risk), MACE and VTE.

The product class of Janus kinase inhibitors (JAK) is currently undergoing a risk assessment procedure by the Pharmacovigilance Risk Assessment Committee (PRAC) of the European Medicines Agency (EMA)[2], which has not yet been concluded by a decision of the European Commission. The inclusion of new warnings and precautions in the product information is expected. These must then be observed accordingly.

[2] https://www.ema.europa.eu/en/documents/referral/rinvoq-epar-product-information-approved-chmp-23-january-2023-pending-endorsement-european_en.pdf

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 2023).

Treatment period:

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

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	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Patient population a)				
Adalimumab	Continuously, 1 x every 14 days	26.1	1	26.1
Golimumab	Continuously, 1 x every 28 days	13.0	1	13.0
Infliximab	Continuously, every 56 days	6.5	1	6.5
Ustekinumab	Continuously, every 84 days	4.3	1	4.3
Vedolizumab	Continuously, every 14 days	26.1	1	26.1

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	Continuously, 1 x daily	365	1	365
Appropriate comparator therapy				
Patient population b)				

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Adalimumab	Continuously, 1 x every 14 days	26.1	1	26.1
Golimumab	Continuously, 1 x every 28 days	13.0	1	13.0
Infliximab	Continuously, every 56 days	6.5	1	6.5
Tofacitinib	Continuously, 2 x daily	365	1	365
Ustekinumab	Continuously, every 84 days	4.3	1	4.3
Vedolizumab	Continuously, every 14 days	26.1	1	26.1

Consumption:

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

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

For the calculation of the consumption of medicinal products to be dosed according to weight, the G-BA generally uses non-indication-specific average weights as a basis. Therefore, an average body weight of 77 kg is assumed for the German population aged 18 years and older, according to the official representative statistics "Microcensus 2017"[3]. Consequently, patient-individual weight differences between women and men, which may be above or below the average value of 77 kg, are not taken into account for the cost calculation.

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	15 mg	15 mg	15 mg	365.0	365 x 15 mg
	30 mg	30 mg	30 mg	365.0	365 x 30 mg

3 Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Appropriate comparator therapy					
Patient population a					
Adalimumab	40 mg	40 mg	40 mg	26.1	26.1 x 40 mg
Golimumab	50 mg	50 mg	50 mg	13.0	13.0 x 50 mg
Infliximab	385 mg	5 mg/ kg BW	4 x 100 mg	6.5	26 x 100 mg
Ustekinumab	90 mg	90 mg	1 x 90 mg	4.3	4.3 x 90 mg
Vedolizumab	108 mg	108 mg	1 x 108 mg	26.1	26.1 x 108 mg

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	15 mg	15 mg	15 mg	365.0	365 x 15 mg
	30 mg	30 mg	30 mg	365.0	365 x 30 mg
Appropriate comparator therapy					
Patient population b					
Adalimumab	40 mg	40 mg	40 mg	26.1	26.1 x 40 mg
Golimumab	50 mg	50 mg	50 mg	13.0	13.0 x 50 mg
Infliximab	385 mg	5 mg/ kg BW	4 x 100 mg	6.5	26 x 100 mg
Tofacitinib	5 mg	10 mg	2 x 5 mg	365	730 x 5 mg
Ustekinumab	90 mg	90 mg	1 x 90 mg	4.3	4.3 x 90 mg
Vedolizumab	108 mg	108 mg	1 x 108 mg	26.1	26.1 x 108 mg

Costs:

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

of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. If a fixed reimbursement rate is available, this will be used as the basis for calculating the costs.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Upadacitinib 15 mg	90 RET	€ 3,714.49	€ 2.00	€ 149.18	€ 3,563.31
or					
Upadacitinib 30 mg	90 RET	€ 4,741.13	€ 2.00	€ 191.05	€ 4,548.08
Appropriate comparator therapy					
Adalimumab 40 mg[4]	6 SFI	€ 2,859.17	€ 2.00	€ 228.57	€ 2,628.60
Golimumab 50 mg[4]	3 SFI	€ 2,605.92	€ 2.00	€ 0.00	€ 2,603.60
Infliximab 100 mg[4]	5 PIC	€ 3,490.53	€ 2.00	€ 280.08	€ 3,208.45
Tofacitinib 5 mg	182 FCT	€ 2,982.07	€ 2.00	€ 119.30	€ 2,860.77
Ustekinumab 90 mg	1 IFE	€ 5,446.71	€ 2.00	€ 527.61	€ 4,917.10
Vedolizumab 108 mg	6 SFI	€ 3,769.65	€ 2.00	€ 363.42	€ 3,404.23
Abbreviations: FCT = film-coated tablets; IFE = solution for injection in a pre-filled syringe; SFI = solution for injection; PIC = powder for the preparation of an infusion solution concentrate; RET = retard tablets					

LAUER-TAXE® last revised: 1 February 2023

Costs for additionally required SHI services:

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

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

The additionally required SHI services for screening for tuberculosis infection are incurred equally for the medicinal product to be assessed and the appropriate comparator therapy, so

[4] Fixed reimbursement rate

that they are not presented.

Test for the presence of HBV infection prior to the administration of upadacitinib or the active ingredients of the appropriate comparator therapy (adalimumab, golimumab, infliximab and tofacitinib).

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Upadacitinib Adalimumab Golimumab Infliximab Tofacitinib	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)[5]	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32817)[6]	1	€ 89.50	€ 89.50

Other SHI services:

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

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 100 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 100 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

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

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

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

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

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

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 28 June 2022, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 24 August 2022, 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 25 August 2022 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient upadacitinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 November 2022, and the written statement procedure was initiated with publication on the G-BA website on 1 December 2022. The deadline for submitting written statements was 22 December 2022.

The oral hearing was held on 9 January 2023.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 7 February 2023, and the proposed resolution was approved.

At its session on 16 February 2023, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 June 2022	Determination of the appropriate comparator therapy
Working group Section 35a	4 January 2023	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	9 January 2023	Conduct of the oral hearing
Working group Section 35a	18 January 2023 1 February 2023	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	7 February 2023	Concluding discussion of the draft resolution
Plenum	16 February 2023	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 February 2023

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

Prof. Hecken