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: non-radiographic axial spondyloarthritis)

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 27 July 2022, upadacitinib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, sentence 7).

On 24 August 2022, i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 of the 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 "for the treatment of active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation, indicated by elevated C-reactive protein (CRP) and/or evidence by magnetic resonance imaging (MRI), who have responded inadequately to non-steroidal anti-inflammatory drugs (NSAIDs)".

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:

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 active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs).

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 active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)

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

Appropriate comparator therapy for upadacitinib:

- a TNF-α inhibitor (etanercept or adalimumab or golimumab or certolizumab pegol) or an IL-17 inhibitor (secukinumab or ixekizumab)

b) Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately or who are intolerant to previous biologic disease-modifying antirheumatic drug (bDMARD) therapy

Appropriate comparator therapy for upadacitinib:

- switching to a different biological disease-modifying antirheumatic drug: TNF-α inhibitor (etanercept or adalimumab or golimumab or certolizumab pegol) or an IL-17 inhibitor (secukinumab or ixekizumab)

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. In addition to non-steroidal anti-inflammatory drugs (NSAIDs) for the symptomatic treatment of pain and inflammation, glucocorticoids and biologic agents are approved for this therapeutic indication. The marketing authorisation covers biologic agents in the therapeutic indication following a failure to respond to conventional therapies (or in the case of a contraindication to NSAIDs). In the present therapeutic indication, these are the TNF-α inhibitors adalimumab, golimumab, certolizumab pegol, etanercept and the IL-17 inhibitors ixekizumab and secukinumab.

on 2. A non-medicinal treatment paid by the SHI is not considered as an appropriate comparator therapy in the therapeutic indication.

on 3. For the treatment of the non-radiographic form of axial spondyloarthritis, there are resolutions of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient ixekizumab dated 21 January 2021 and for the active ingredient secukinumab dated 18 February 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 therapeutic indication according to Section 35a, paragraph 7 SGB V.

Both the German S3 guideline[2] from 2019, as well as the current European ASAS-EULAR-Guideline[3] of 2022 provide for the evidence-based use of NSAIDs in conventional (first-line-) therapy of axSpA (symptomatic or continuous use). After the failure of therapy with NSAIDs or conventional therapy, the use of biologic agents (bDMARDs) is recommended on the basis of the available evidence. Conventional, classical DMARDs (e.g. MTX, sulfasalazine, leflunomide) are neither approved for the therapeutic indication axSpA nor is their use supported by the available evidence. The guidelines distinguish between the older TNF-α inhibitors and the newer biologic agents. Within the product classes of TNF-α inhibitors, however, no distinction is made in the therapy recommendation; within the TNF-α inhibitors approved in Germany, there is therefore no prioritisation. Furthermore, no head-to-head comparisons of the active ingredients would allow prioritisation; the evidence is mainly based on RCTs with placebo comparisons.

Overall, the treatment recommendations for axial spondyloarthritis after the failure of conventional therapy focus on the use of biologic agents. For the therapeutic indication, it is assumed that for patients after failure of a conventional therapy or NSAIDs, a continuation of the sole conventional therapy with NSAIDs or glucocorticoids is not (any longer) indicated according to the doctor's assessment. The recently updated EULAR-LL[3] does not explicitly differentiate between the radiographic and non-radiographic forms of axSpA in its treatment recommendations, as patients had been found to be largely similar in terms of clinical presentation, disease burden, including comorbidities, treatment received and response. According to the German S3 guideline[2], r-axSpA and nr-axSpA are also one clinical picture. A distinction by the severity grade of axSpA apparent in the underlying evidence is also not noticeable: Neither the German S3 guideline[2] nor the EULAR-LL[3] or the EMA guideline[4] distinguish between severity grade in their recommendations for axSpA. Rather, a treatment decision is made in everyday care depending on the disease manifestation (e.g. axial, peripheral), the failure to respond to previous therapies and the disease activity. After the failure of conventional therapy, biologic agents are also used for the treatment of the non-radiographic subtype of axSpA. The G-BA did not determine an additional benefit of ixekizumab and secukinumab because no suitable data were available for a comparison with the appropriate comparator therapy.

2 German Society for Rheumatology (DGRh). Axial spondyloarthritis including ankylosing spondylitis and early forms; S3 guideline [online]. AWMF register number 060-003. Version 2019. Berlin (GER): Association of the Scientific Medical Societies (AWMF); 2019. [Accessed: 07.04.2020].

3 ASAS-EULAR Recommendations: Ramiro S, Nikiphorou E, Sepriano A, Ortolan A, Webers C, Baraliakos X, et al. ASAS-EULAR recommendations for the management of axial spondyloarthritis: 2022 update. Ann Rheum Dis 2023;82(1):19-34.

4 EMA Guideline on the clinical investigation of medicinal products for the treatment of Axial Spondyloarthritis - Adopted guideline (CPMP/EWP/4891/03 Rev.1) 12 October 2017; EMA Draft Guideline on the clinical investigation of medicinal products for the treatment of Axial Spondyloarthritis - Draft (CPMP/EWP/4891/03 Rev.1) 2016.

Change of the appropriate comparator therapy:

Since the therapy recommendations in the recently updated EULAR-LL[3] in the therapeutic indication of axSpA - including nr-axSpA - are based in particular on the criterion of failure on prior therapies, the present therapeutic indication includes both patients who have responded inadequately to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) (so-called "second-line therapy") and patients who have responded inadequately to prior therapy with biologic antirheumatic drugs (so-called "third-line therapy"). As these two patient populations differ in the clinical course to date as well as in terms of therapy recommendations, a subdivision into two patient populations is now made. In addition, no distinguishing criteria can be derived between r-axSpA and nr-axSpA, so that a deviating procedure regarding a division or non-division of the patient population is no longer appropriate. Although this perspective has been indicated in the past, the updated EULAR-LL[3] manifests the clinical view that the patient population in the present therapeutic indication should be divided according to prior therapies. This patient division is in line with the statements of clinical experts.

To date, TNF-α inhibitors (etanercept or adalimumab or golimumab or certolizumab pegol) have been considered as an appropriate comparator therapy for adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs). Taking the statements into account, this does not correspond to the current medical treatment situation. In medical treatment practice, the IL-17 inhibitors secukinumab and ixekizumab have established themselves as equal-ranking treatment options alongside TNF-α inhibitors for the treatment of nr-axSpA after treatment failure on NSAIDs since their marketing authorisation in the therapeutic indication in April 2020 and June 2020, respectively. In the EULAR-LL[3] updated in January 2023, TNF-α inhibitors and IL-17 inhibitors are considered equal, even in the absence of head-to-head comparisons of the active ingredients. The G-BA therefore considers it appropriate to change the appropriate comparator therapy at this point in time and to adapt it to the current state of medical knowledge by adding the two active ingredients secukinumab and ixekizumab.

Thus, according to the current state of medical knowledge, the approved TNF-α inhibitors (etanercept or adalimumab or golimumab or certolizumab pegol) and the IL-17 inhibitors secukinumab and ixekizumab can be considered as equally appropriate treatment options for the "second-line therapy" (failure to respond to conventional therapies) of nr-axSpA.

For the "third-line therapy" of nr-axSpA after the failure of a first TNF-α inhibitor or IL-17 inhibitor, the evidence is overall weaker compared to "second-line therapy". Regardless of this, even after failure of a biologic agent, the available evidence does not allow prioritisation within the active ingredients of TNF-α inhibitors (etanercept or adalimumab or golimumab or certolizumab pegol) or the IL-17 inhibitors (secukinumab or ixekizumab) considered for "third-line therapy". Instead, it depends on comorbidities and patient-individual criteria as well as on the previous therapy to which further bDMARD is switched after the failure of a first therapy with a bDMARD. Against this background, in this line of therapy of active, non-radiographic axSpA, a switch to another approved bDMARD that is established in use is currently considered appropriate. Further differentiation of the patient population (e.g. also with regard to failure on 1 vs >1 bDMARD) is not made at this time due to the lack of uniform therapy recommendations.

Taking into account the respective authorisation status of the medicinal products in conjunction with the clinical course and against the background of the available body of evidence, TNF-α inhibitors (etanercept or adalimumab or golimumab or certolizumab pegol) or an IL-17 inhibitor (secukinumab or ixekizumab) are determined as appropriate comparator therapy for the treatment of adults with active non-radiographic axial spondyloarthritis who have responded inadequately to conventional therapy (patient group a); these active ingredients are equally appropriate treatment options.

For adults with active non-radiographic axial spondyloarthritis who have had an inadequate response or intolerance to previous therapy with biological disease-modifying antirheumatic drugs (bDMARD) (patient group b), a switch to another biological disease-modifying antirheumatic drug is determined to be an appropriate comparator therapy: switching to a TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab) or an IL-17 inhibitor (secukinumab or ixekizumab); the above active ingredients are considered equally appropriate treatment options.

Overall, the presently carried out adjustment of the patient populations and the addition of the appropriate comparator therapy has no influence on the outcome of the ongoing 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 active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)

Extent and probability of the additional benefit:

An additional benefit is not proven.

b) Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately or who are intolerant to previous biologic disease-modifying antirheumatic drug (bDMARD) therapy

Extent and probability of the additional benefit:

An additional benefit is not proven.

Justification:

In its dossier for the assessment of the additional benefit of upadacitinib, the pharmaceutical company does not present any direct comparative study versus the appropriate comparator

therapy. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment.

The results of the SELECT-AXIS 2 approval study are available for the early benefit assessment. The SELECT-AXIS 2 study is a placebo-controlled RCT. Adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation who have responded inadequately to a therapy with NSAIDs or for whom a therapy with NSAIDs is not indicated or unsuitable were enrolled in the study. Patients were randomised in a 1:1 ratio to treatment with upadacitinib 15 mg 1 time daily or placebo.

In the placebo-controlled approval study SELECT-AXIS 2, the appropriate comparator therapy is not implemented, so that no appropriate data are available for the early benefit assessment on the basis of this study.

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 active non-radiographic axial spondyloarthritis in adult patients with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)."

The following patient groups were distinguished for the benefit assessment:

a) Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately to nonsteroidal anti-inflammatory drugs (NSAIDs)

and

b) Adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI), who have responded inadequately or who are intolerant to previous biologic disease-modifying antirheumatic drug (bDMARD) therapy

Patient group a:

The G-BA determined a TNF-α inhibitor (etanercept or adalimumab or golimumab or certolizumab pegol) or an IL-17 inhibitor (secukinumab or ixekizumab) as an appropriate comparator therapy. The pharmaceutical company does not present any appropriate direct comparator data versus the appropriate comparator therapy with the dossier for the assessment of the additional benefit. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment. Thus, no appropriate data are available to assess the additional benefit of upadacitinib in the present therapeutic indication. In the overall assessment, the additional benefit of upadacitinib versus the appropriate comparator therapy is not proven for adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation, indicated by elevated C-reactive protein (CRP) and/or

evidence by magnetic resonance imaging (MRI), who have had an inadequate response to non-steroidal anti-inflammatory drugs (NSAIDs).

Patient group b:

The G-BA determined the change to another biological disease-modifying antirheumatic drug - to a TNF-α inhibitor (etanercept or adalimumab or golimumab or certolizumab pegol) or an IL-17 inhibitor (secukinumab or ixekizumab) - as an appropriate comparator therapy. The pharmaceutical company does not present any appropriate direct comparator data versus the appropriate comparator therapy with the dossier for the assessment of the additional benefit. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment. Thus, no appropriate data are available to assess the additional benefit of upadacitinib in the present therapeutic indication. In the overall assessment, the additional benefit of upadacitinib versus the appropriate comparator therapy is not proven for adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation, indicated by elevated C-reactive protein (CRP) and/or evidence by magnetic resonance imaging (MRI), who have had an inadequate response or intolerance to previous therapy with biologic disease-modifying antirheumatic drugs (bDMARD).

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 ixekizumab (resolution of 21.01.2021) 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 ixekizumab was also fraught with uncertainties and tends to be underestimated. Despite the uncertainties, the figures from the ixekizumab procedure are considered less uncertain than those from the pharmaceutical company in the present procedure.

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: 6 January 2023):

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 the therapy of axial spondyloarthritis.

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.

Consider discontinuing treatment in patients with axial spondyloarthritis who do not show a clinical response after 16 weeks of treatment. Some patients with an initial partial response may improve during the course of continued treatment beyond 16 weeks.

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)[5], 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.

2.4 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 populations a) and b)				
A TNF-α inhibitor				
Adalimumab	Continuously, 1 x every 14 days	26.1	1	26.1
Certolizumab pegol	Continuously	13	1	13

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

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
	1 x every 14 days Or 1 x every 28 days			
Etanercept	Continuously, 2 x within 7 days or 1 x every 7 days	52.1	1	52.1
Golimumab	1 x monthly always on the same day	12	1	12
IL-17 inhibitor				
Secukinumab	1 x monthly	12	1	12
Ixekizumab	1 x every 28 days	13	1	13

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	15 mg	15 mg	1 x 15 mg	365	365 x 15 mg
Appropriate comparator therapy					
Patient populations a) and b)					
A TNF-α inhibitor					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Certolizumab pegol	400 mg	400 mg	2 x 200 mg	13	26.0 x 200 mg
Etanercept	25 mg	25 mg	1 x 25 mg	104.2	104.2 x 25 mg
Golimumab	50 mg	50 mg	1 x 50 mg	12	12 x 50 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
IL-17 inhibitor					
Secukinumab	150 mg	150 mg	1 x 150 mg	12.0	12 x 150 mg
Ixekizumab	80 mg	80 mg	1 x 80 mg	13.0	13 x 80 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.

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	90 RET	€ 3,714.49	€ 2.00	€ 149.18	€ 3,563.31
Appropriate comparator therapy					
Adalimumab 40 mg[6]	6 SFI	€ 2,859.17	€ 2.00	€ 228.57	€ 2,628.60
Certolizumab pegol 200 mg[6]	6 SFI	€ 2,859.17	€ 2.00	€ 228.57	€ 2,628.60
Etanercept 25 mg[6]	24 SFI	€ 2,859.17	€ 2.00	€ 228.57	€ 2,628.60
Etanercept 50 mg[6]	12 SFI	€ 2,859.17	€ 2.00	€ 228.57	€ 2,628.60
Golimumab 50 mg[6]	3 SFI	€ 2,605.92	€ 2.00	€ 0.00	€ 2,063.92
Secukinumab 150 mg	6 PEN	€ 4,653.99	€ 2.00	€ 187.50	€ 4,464.49
Ixekizumab 80 mg	3 PEN	€ 3,989.28	€ 2.00	€ 160.38	€ 3,826.90
RET = retard tablets; SfI = solution for injection; PEN = solution for injection in a pre-filled pen					

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

[6] Fixed reimbursement rate

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.

Prior to the use of upadacitinib or the TNF-α inhibitor of the appropriate comparator therapy (adalimumab, certolizumab pegol, etanercept and golimumab), the patients must be examined for active and inactive ("latent") tuberculosis infections. In addition, patients must be tested for the presence of HBV infection before starting therapy with upadacitinib or the TNF-α inhibitor of the appropriate comparator therapy (adalimumab, certolizumab pegol, etanercept and golimumab).

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Upadacitinib Adalimumab Certolizumab pegol Etanercept Golimumab	Quantitative determination of an in vitro interferon-gamma release after ex vivo stimulation with antigens (at least ESAT-6 and CFP-10) specific for Mycobacterium tuberculosis-complex (except BCG) (GOP 32670)	1	€ 58.00	€ 58.00
	Chest radiograph (GOP 34241)	1	€ 16.78	€ 16.78
Upadacitinib Adalimumab Certolizumab pegol Etanercept Golimumab	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 32817)[8]	1	€ 89.50	€ 89.50

7 Only if HBs antigen negative and anti-HBc antibody positive.
8 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 6 November 2018, 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 1, sentence 2 VerfO.

By letter dated 29 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	6 November 2018	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