Gemeinsamer Bundesausschuss

Justification

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

of 15 July 2021

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1. Legal basis

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

marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

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

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

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

2. Key points of the resolution

The 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 22 January 2021, 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 December 2008, p. 7).

On 29 January 2021, i.e. at the latest within four weeks after the disclosure, the pharmaceutical company, on the approval of a new area of application, has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient upadacitinib with the new therapeutic indication (ankylosing spondylitis).

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 ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy.

Therapeutic indication of the resolution (resolution of 15 July 2021):

see new therapeutic indication according to marketing authorisation.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) Adults with active radiographic axial spondyloarthritis who have had an inadequate response to conventional therapy

Appropriate comparator therapy for upadacitinib:

- a TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL17 inhibitor (secukinumab)

a2) Adults with active radiographic axial spondyloarthritis who have had an inadequate response to, or intolerance to prior biologic antirheumatic drug (bDMARD) therapy

Appropriate comparator therapy for upadacitinib:

- switching to a different biological disease-modifying antirheumatic drug: TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL17 inhibitor (secukinumab)

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.

1 General Methods, version 6.0 from 5.11.2020. 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 benefit 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 biologics are approved for this therapeutic indication. The marketing authorisation covers biologics in the therapeutic indication following a failure to respond to conventional therapies (or in the case of a contraindication to NSAIDs). In the present indication area these are the active ingredients infliximab, adalimumab, golimumab, certolizumab pegol, etanercept as well as the IL17-inhibitors secukinumab and Ixekizumab.

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

on 3. There are two resolutions of the G-BA in the indication area of radiographic axial spondyloarthritis (ankylosing spondylitis): for secukinumab dated 2 June 2016 and for ixekizumab dated 21 January 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 § 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 2016/2017 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 biologics (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

2 German Society for Rheumatology (DGRh). Axial spondyloarthritis including ankylosing spondylitis and early forms; S3 guideline [online]. AWMF register number 060-003. 2019 Version. Berlin (GER): Association of the Scientific Medical Societies (AWMF); 2019. [Accessed: 7/4/2020):
3 ASAS-EULAR Recommendations: Van der Heide D et al, Ann Rheum Dis 2017;0:1-14.

inhibitors and the newer biologics. 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 biologics. 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 medical assessment. Treatment recommendations rarely explicitly distinguish between the radiographic and non-radiographic forms of axSpA. Nor is a distinction by the severity of axSpA evident in the underlying evidence: Neither the German S3 guidelinenor the EULAR-LL[3] or the EMA guideline[4] distinguish between severity in their recommendations for axSpA. Rather, a therapy 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, biologics are used for the treatment of the non-radiographic subtype of axSpA. The IL-17 inhibitor Ixekizumab was only recently granted marketing authorisation in axSpA so that it cannot yet be considered established in this indication.

The therapeutic indication "adults with active radiographic axial spondyloarthritis who have had an inadequate response to conventional therapy" includes both patients who have had an inadequate response to treatment with non-steroidal anti-inflammatory drugs (NSAIDs) (so-called "second-line therapy")and patients who have had an inadequate response to previous therapy with biologic antirheumatic drugs (so-called "third-line therapy"). Since these two patient populations differ in their clinical course to date and in terms of therapy recommendations, a subdivision of patient population a) into two subpopulations a1) and a2) is made, as is also done accordingly in the current guidelines.

<u>On a1)</u>

For the therapy of r-axSpA after the failure of NSAIDs, all approved TNFα inhibitors as well as the interleukin-17 inhibitor secukinumab, which has been approved since 2015, can be considered. The recommendations from the latest guidelines available in the indication unanimously see - especially for patients with certain comorbidities - the use of the IL17 inhibitor secukinumab as an equal alternative to the established TNFα inhibitors. Thus, according to the current state of medical knowledge, the approved TNFα inhibitors and secukinumab can be considered as equally appropriate comparator therapy for the "second-line therapy" of r-axSpA.

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.

On a2)

For "third-line therapy" of r-axSpA after the failure of a first TNFα inhibitor or IL17 inhibitor, the evidence is overall weaker compared to "second-line therapy". Regardless, even after a biologic failure, the available evidence does not allow prioritisation within the agents of TNFα inhibitors or the IL-17 inhibitor secukinumab 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, 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 one vs more than one bDMARDs) is not made at this time due to the lack of uniform therapy recommendations. Taking into account the respective authorisation status of the medicinal product in conjunction with the clinical course and against the background of the available body of evidence, TNFα inhibitors (etanercept or adalimumab or infliximab or golimumab or certolizumab pegol) or an IL17 inhibitor (secukinumab) are determined as the appropriate comparator therapy for the treatment of adult patients with active radiographic axial spondyloarthritis who have responded inadequately to conventional therapy (patient group a1). For adults with active radiographic axial spondyloarthritis who have had an inadequate response to, or intolerance to, previous biologic antirheumatic drug (bDMARD) therapy (patient group a2), switching to another biological disease-modifying antirheumatic drug: TNFα inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL17 inhibitor (secukinumab) is considered appropriate.

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:

a1) Adults with active radiographic axial spondyloarthritis who have had an inadequate response to conventional therapy

For adult patients with active radiographic axial spondyloarthritis who have had an inadequate response to conventional therapy, the additional benefit of upadacitinib compared with the appropriate comparator therapy is not proven.

Justification:

In his dossier for the assessment of the additional benefit of upadacitinib, the pharmaceutical company does not present any direct comparator studies regarding the appropriate comparator therapy. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment.

The SELECT-AXIS-1 study presented with the dossier is a placebo-controlled RCT. Adult patients with active ankylosing spondylitis were included in an inadequate response to or intolerance of therapy with non-steroidal anti-inflammatory drugs (NSAIDs). They were randomised 1:1 to treatment with upadacitinib 15 mg once daily or placebo. After 14 weeks, patients in the placebo arm continued to be treated with upadacitinib.

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

a2) Adults with active radiographic axial spondyloarthritis who have had an inadequate response to, or intolerance to prior biologic antirheumatic drug (bDMARD) therapy

For adult patients with active radiographic axial spondyloarthritis who have had an inadequate response to, or intolerance to previous therapy with biologic antirheumatic drugs (bDMARDs), the additional benefit of upadacitinib compared with the appropriate comparator therapy is not proven.

Justification:

In his dossier for the assessment of the additional benefit of upadacitinib, the pharmaceutical company does not present any direct comparator studies regarding the appropriate comparator therapy. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment.

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:
" treatment of active ankylosing spondylitis in adult patients who have responded inadequately to conventional therapy."

Two patient groups were distinguished for the benefit assessment:

a1) Adults with active radiographic axSpA who have had an inadequate response to conventional therapy;

a2) Adults with active radiographic axSpA who have had an inadequate response to, or intolerance to prior biologic antirheumatic drug (bDMARD) therapy;

Patient group a1)

The G-BA determined a TNFα inhibitor (etanercept or adalimumab or infliximab or golimumab or certolizumab pegol) or an IL17 inhibitor (secukinumab) as an appropriate comparator therapy. For this patient group, the pharmaceutical company does not submit any suitable direct comparator data regarding the appropriate comparator therapy in 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 adequate data are available to assess the additional benefit of upadacitinib. Overall, for adults with active radiographic axSpA who have had an inadequate response to conventional therapy, the additional benefit of upadacitinib compared with the appropriate comparator therapy is not proven.

Patient group a2)

The G-BA determined the change to another biological disease-modifying antirheumatic drug - to a TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL17 inhibitor (secukinumab) - as an appropriate comparator therapy. For this patient group, the pharmaceutical company does not submit any direct comparator data 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 adequate data are available to assess the additional benefit of upadacitinib. Overall, the additional benefit for adults with active radiographic axSpA who have had an inadequate response to, or intolerance to prior therapy with biologic antirheumatic drugs (bDMARDs) upadacitinib compared with the appropriate comparator therapy is not proven.

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

The information is based on the data provided by the pharmaceutical company in the dossier. The figures are based on prevalence and incidence data from diagnosed patients.
Overall, the calculation of the number of patients tends to be underestimated and subject to uncertainties. This results in the same number of patients as in the early benefit assessment of ixekizumab[5].

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: 11 March 2021):
https://www.ema.europa.eu/documents/product-information/rinvoq-epar-product-information_de.pdf

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

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material and a patient identification card. The training material for medical professionals includes

5 Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a SGB V of 21 January 2021.

instructions on how to manage the potential side effects associated with upadacitinib, particularly severe and opportunistic infections including TB and herpes zoster.

The use of the drug must also be carefully weighed against established therapies against the background of a comparatively new mode of action and the associated still existing uncertainties in the risk profile.

Consider discontinuing treatment in patients with ankylosing spondylitis 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.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 June 2021).

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.

Infliximab can also be used subcutaneously as a maintenance treatment. The presentation in the cost calculation is limited to the fixed-amount regulated intravenous infusion therapy.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Medicinal product to be assessed				
Upadacitinib	Continuously, once daily	365	1	365
Appropriate comparator therapy				
Patient populations a1) + a2)				
Adalimumab	Once every 14 days	26.1	1	26.1
Certolizumab pegol	Once every 14 days	26.1	1	26.1
Etanercept	Once every 7 days	52.1	1	52.1
Golimumab	Once a month	12	1	12

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Days of treatment/ patient/ year
Infliximab	1 x 56 -- 42 days	6,5. 8.7	1	6,5. 8.7
Secukinumab	Once a month	12	1	12

Consumption:

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg).[6]

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.

Designation of the therapy	Dosage/ Application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	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 a1) + a2)					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Certolizumab pegol	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Etanercept	50 mg	50 mg	1 x 50 mg	52.1	52.1 x 50 mg
Golimumab	50 mg	50 mg	50 mg	12	12 x 50 mg
Infliximab	5mg/kg	385 mg	4 x 100 mg	6,5. 8.7	26 x 400 mg - 34.8 x 400 mg

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

Designation of the therapy	Dosage/ Application	Dosage/ patient/ days of treatment	Usage by potency/ day of treatment	Treatment days/ patient/ year	Average annual consumption by potency
Secukinumab	150 mg). 300 mg	150 mg). 300 mg	1 x 150 mg - 2 x 150 mg	12	12 x 150 mg - 24 x 150 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. I 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 product:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate § 130 SGB V	Rebate § 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Upadacitinib	90 RET	€ 3,714.25	€ 1.77	€ 0.00	€ 3,712.48
Appropriate comparator therapy					
Adalimumab[7]	6 SFI	€ 2,858.93	€ 1.77	€ 228.57	€ 2,628.59
Certolizumab Pegol[7]	6 SFI	€ 2,858.93	€ 1.77	€ 0.00	€ 2 857.16
Etanercept[7]	12 SFI	€ 2,858.93	€ 1.77	€ 228.57	€ 2,628.59
Golimumab[7]	3 IFE	€ 2,605.68	€ 1.77	€ 0.00	€ 2,603.91
Infliximab[7]	5 PIC	€ 3,490.29	€ 1.77	€ 280.08	€ 3,208.44
Secukinumab	6 PEN	€ 5,173.49	€ 1.77	€ 0.00	€ 5,171.72
Abbreviations: IFE = solution for injection in a pre-filled syringe; SFI = solution for injection; PEN = solution for injection in a pre-filled pen, PIC = powder for the preparation of an infusion solution concentrate, RET = retard tablets					

Last revised LAUER-TAXE®: 15 June 2021

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

7Fixed reimbursement rate

other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

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

For some active ingredients of the appropriate comparator therapy (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and ustekinumab), costs are regularly incurred for testing for both active and inactive ("latent") tuberculosis infections. However, these studies are not required when using secukinumab as an appropriate comparator therapy. 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". These studies are also required when using upadacitinib.

In addition, patients must be tested for the presence of HBV infection before initiating treatment with adalimumab or certolizumab pegol or etanercept or golimumab or infliximab. These studies are not required for the use of secukinumab as appropriate comparator therapy but are regularly required for the use of upadacitinib as the medicinal product to be evaluated. For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required[8]. 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 diagnosis 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 services in the resolution.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Medicinal product to be assessed: Upadacitinib Appropriate comparator therapy for patient population a1) and a2)				
Upadacitinib adalimumab Certolizumab pegol Etanercept Golimumab Infliximab	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

8 "Update of the S3 guideline on prophylaxis, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011" https://www.awmf.org/uploads/tx_szleitlinien/021-011l_S3_Hepatitis_B_Virusinfektionen_Prophylaxe_Diagnostik_Therapie_2011-abgelaufen.pdf

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Upadacitinib adalimumab Certolizumab pegol Etanercept Golimumab Infliximab	X-ray thorax (GOP 34241)	1	€ 16.24	€ 16.24
Upadacitinib adalimumab Certolizumab pegol Etanercept Golimumab Infliximab	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	anti-HBs antibody (GOP 32617)[9]	1	€ 5.50	€ 5.50
	anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)[10]	1	€ 89.50	€ 89.50

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (contract on price formation for substances and preparation of substances) from 1.10.2009 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 € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy retail 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 sales 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.

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.

9 Only if HBs antigen negative and anti-HBc antibody positive.
10 Invoicing for GOP 32823 possible before or during antiviral therapy with interferon and/or nucleic acid analogues.

4. Process sequence

At its session on 28 July 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 29 January 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 29 January 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.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 April 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 3 May 2021. The deadline for submitting written statements was 25 May 2021.

The oral hearing was held on 8 June 2021.

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 the representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 22 June 2021, and the proposed resolution was approved.

At its session on 15 July 2021, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 July 2020	Determination of the appropriate comparator therapy
Working group Section 35a	2 June 2021	Information on written statement procedures received; preparation of the oral hearing
Subcommittee Medicinal products	8 June 2021	Conduct of the oral hearing
Working group Section 35a	15 June 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	22 June 2021	Concluding discussion of the draft resolution

Plenum	15 July 2021	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 July 2021

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

Prof. Hecken