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: Psoriatic Arthritis)

of 15 July 2021

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 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, the pharmaceutical company 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 in due time (psoriatic arthritis) (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

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, and the addenda to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional

benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of 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 psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. RINVOQ may be used as monotherapy or in combination with methotrexate.

Therapeutic indication of the resolution (resolution of 15.07.2021):

see approved [new] therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARD).

- a TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if necessary in combination with methotrexate

b) Adult patients with active psoriatic arthritis Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more biologic disease-modifying anti-rheumatic drugs (bDMARDs).

- switching to another biological disease-modifying antirheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or ustekinumab), if necessary in combination with methotrexate

1 General Methods, version 6.0 from 5.11.2020. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. In the indication area of psoriatic arthritis, the following active ingredient of different medicinal product classes are approved:

- steroidal antirheumatic drugs: prednisolone, prednisone, triamcinolone
- non-steroidal anti-inflammatory drugs (NSAIDs): e.g. acemetacin
- conventional synthetic disease-modifying antirheumatic drugs (csDMARDs): methotrexate, leflunomide
- biological disease-modifying anti-rheumatic drugs (bDMARDs):
  - TNF-alpha inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab
  - Interleukin inhibitors: guselkumab, ixekizumab, secukinumab, ustekinumab
  - Inhibitor of T-cell activation: abatacept
- targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs):
  - JAK inhibitors: tofacitinib, upadacitinib
  - Phosphodiesterase-4 inhibitor: apremilast

on 2. Non-drug measures as sole appropriate comparator therapy are not considered in the present therapeutic indication.

on 3. In the therapeutic indication under consideration here, the following resolutions of the G-BA are available:

- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient apremilast from the 6 August 2015.

- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient ixekizumab from the 16 August 2018.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient tofacitinib from the 21 February 2019.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient secukinumab from 18 February 2021.
- Resolution on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for the active ingredient guselkumab from 20 May 2021.

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

Upadacitinib is approved for patients who have had an inadequate response or who have been intolerant to a prior disease-modifying anti-rheumatic drug. Treatment with non-steroidal anti-inflammatory drugs or glucocorticoids alone is no longer an adequate therapeutic option for these patients. Even if the local injection of glucocorticoids, in particular, may be used as add-on therapy in some patients, non-steroidal anti-inflammatory drugs and glucocorticoids do not represent an appropriate therapy option in the present therapeutic indication, which is why both product classes are not considered further in the determination of the appropriate comparator therapy.

On a) <u>Adult patients with active psoriatic arthritis who have had an inadequate response or have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy.</u>

For patients who have had an inadequate response or intolerance to previous conventional disease-modifying anti-rheumatic (csDMARD) therapy, initial treatment with a bDMARD is indicated. For these patients, therapy with a TNF-alpha inhibitor (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), an interleukin-17 inhibitor (ixekizumab and secukinumab) or an interleukin-12/23 inhibitor (ustekinumab) is recommended according to the current therapy recommendations of the European League Against Rheumatism (EULAR 2020)[2].

For adults who have had an inadequate response or have been intolerant to a prior disease-modifying anti-rheumatic drug (DMARD) therapy, the TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the interleukin-17 inhibitors ixekizumab and secukinumab and the interleukin-12/23 inhibitor ustekinumab, possibly in combination with methotrexate, are therefore determined to be equally appropriate therapeutic options.

2Gossec L, et al. European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis 2020;79:700712.

On b) Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more biologic disease-modifying anti-rheumatic drugs (bDMARDs).

For adults who have responded inadequately to, or who are intolerant to a biologic disease-modifying anti-rheumatic drug treatment (bDMARDs), switching to another bDMARD (TNF-alpha inhibitor, interleukin inhibitor) is recommended.

For adults who have responded inadequately to, or who are intolerant to a biologic disease-modifying anti-rheumatic drug treatment (bDMARDs), TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab and infliximab), the interleukin-17 inhibitors ixekizumab and secukinumab and the interleukin-12/23 inhibitor ustekinumab, possibly in combination with methotrexate, were determined to be equally appropriate therapy options. Continuation of an inadequate therapy does not correspond to the implementation of the appropriate comparator therapy.

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

2.1.3 Extent and probability of the additional benefit

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

a) Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs).

Hint of a considerable additional benefit

Justification:

For the benefit assessment, the pharmaceutical company submits the randomised controlled study SELECT-PsA 1, in which upadacitinib is compared with adalimumab, in each case in monotherapy or in combination with methotrexate.

A total of 2 doses of upadacitinib (15 mg and 30 mg, each once daily), adalimumab, and placebo were studied in this study. The 1,705 adults were randomised in a 2:2:2:1:1 ratio to 2 upadacitinib arms, 1 adalimumab arm, and 2 placebo arms. The arm with 30 mg upadacitinib and the two placebo arms are not relevant for the present benefit assessment and are therefore not considered.

The study population includes adults with active moderate to severe psoriatic arthritis who had an inadequate response to prior treatment with at least one conventional synthetic disease-modifying antirheumatic drug (csDMARD) of at least 12 weeks. Adults were required to have ≥ 3 swollen and ≥ 3 pressure-sensitive joints, active plaque psoriasis (or a documented history of it), and a high-sensitivity C-reactive protein value above the upper normal limit or ≥ 1 radiographically visible bone erosion.

Patients could receive up to two additional non-biological DMARDs concomitant to the study medication. However, upadacitinib is only approved as monotherapy or in combination with methotrexate. The pharmaceutical company, therefore, defines a subpopulation that exclusively comprises patients who have received upadacitinib or adalimumab as

monotherapy or in combination with methotrexate. This leaves 355 adults in the upadacitinib arm and 352 in the adalimumab arm.

In addition to methotrexate, concomitant treatment with non-steroidal anti-inflammatory drugs (NSAIDs) and oral corticosteroids, among others, was also possible. Patients who did not show a response to therapy at week 16 of treatment could have their concomitant therapy adjusted at this time (initiation or adjustment of methotrexate treatment, NSAIDs, analgesics, or oral corticosteroids). Injection of corticosteroids into a peripheral joint, trigger point, tender point, bursa, or enthesis was also possible.

The results presented are based on the most recent data cut-off. At this point, all patients had been treated for at least 56 weeks.

The primary endpoint of the study was response according to the American College of Rheumatology (ACR) criteria with an improvement of at least 20% at week 12 (ACR20).

Extent and probability of the additional benefit

Mortality

In the SELECT-PsA 1 study, no deaths occurred during the study period.

Morbidity

Minimal disease activity (MDA and DAPSA)

For the endpoint minimal disease activity results from two operationalisations (minimal disease activity [MDA] and DAPSA) are available. In contrast to the MDA, the calculation of the minimum disease activity based on the DAPSA includes the collection of an inflammatory parameter (C-reactive protein). The assessment of the endpoint minimal disease activity is therefore primarily based on the MDA.
For the minimal disease activity measured by MDA, there is a statistically significant difference in the benefit of upadacitinib compared to adalimumab. This effect is confirmed in statistical significance in only one of the three sensitivity analyses conducted using alternative replacement strategies (NRI with variance correction).
There was no statistically significant difference between the treatment groups for the minimum disease activity measured by DAPSA (≤ 15).

Remission (DAPSA ≤ 3.3)

For the endpoint remission assessed with the DAPSA ≤ 3.3, there is a statistically significant difference in the benefit of upadacitinib over adalimumab.

Pressure pain sensitive joints (TJC68 ≤ 1)

For the endpoint pressure pain sensitive joints no statistically significant difference was detected between the treatment groups.

Swollen joints (SJC66 ≤ 1)

For the endpoint swollen joints no statistically significant difference was detected between the treatment groups.

Enthesitis (LEI and SPARCC)

For the endpoint enthesitis, results from two operationalisations are available (LEI and SPARCC). The LEI was developed for the indication of psoriatic arthritis and the SPARCC for the indication of spondyloarthritis. Therefore, the assessment of the enthesitis endpoint is primarily based on the LEI.
For enthesitis assessed by LEI, there is a statistically significant difference in the benefit of upadacitinib over adalimumab.
There was no statistically significant difference between the treatment groups for enthesitis as measured by the SPARCC

Dactylitis (LDI)

For the endpoint dactylitis assessed by LDI, no statistically significant difference was detected between the treatment groups.

Fatigue (FACIT-Fatigue)

According to IQWiG's current methodological approach (Methods 6.0, published on 5.11.2021), IQWiG considers a response threshold for responder analyses of at least 15% of the scale range of an instrument (for post hoc analyses of precisely 15% of the scale range) to be necessary for patient-reported endpoints to represent a noticeable change with sufficient certainty.
The G-BA has already recognised a response threshold of ≥ 4 points as a clinically relevant change in FACIT-Fatigue in the present indication. Therefore, against the background of the current methodological discussion, both the responder analysis with a response threshold of 15% and the responder analysis with a response threshold of ≥ 4 points are used to assess the additional benefit. The methodological discussion on the further procedure in the G-BA has not yet been concluded.
For the endpoint fatigue assessed with the FACIT-Fatigue, there was no statistically significant difference between treatment groups for the proportion of adults with an improvement of ≥ 7.8 points (equivalent to 15% of the scale range) or the proportion of adults with an improvement of ≥ 4 points.

Skin symptoms (PASI 100-response, PASI 90- and PASI 75-response)

For the endpoint skin symptoms measured with the PASI, there was no statistically significant difference between the treatment groups, neither in the remission of skin symptoms (PASI 100) nor in the PASI 90 and PASI 75 response.

Physical functional status (HAQ-DI)

For the endpoint physical functional status, the G-BA has recognised a response threshold of ≥ 0.35 points as a clinically relevant change in HAQ-DI in the present indication. Analogous to the procedure for FACIT-Fatigue, against the background of the current methodological discussion, this responder analysis is therefore also used in the present evaluation and the responder analysis with a response threshold of 15% of the scale range.
For the endpoint physical functional status assessed with the HAQ-DI, there was a statistically significant difference in the benefit of upadacitinib over adalimumab for both the proportion of adults with an improvement of ≥ 0.45 points (representing 15% of the scale range) and the proportion of adults with an improvement of ≥ 0.35 points.

Health status (EQ-5D VAS)

For the endpoint health status measured with the EQ-5D VAS, a statistically significant difference to the advantage of upadacitinib over adalimumab was shown based on the responder analyses at the response threshold of 15% of the scale range.

Morning stiffness (severity and duration)

Data on the severity and duration of the symptom Morning stiffness were collected. For both endpoints, there was a statistically significant difference in the benefit of Upadacitinib. The relevance of the results was checked in each case through Hedges' g. The 95% confidence intervals include the irrelevance threshold of -0.20. Thus, it cannot be inferred that the effect is relevant.

Axial involvement (BASDAI)

For axial involvement assessed by the BASDAI, a statically significant difference to the advantage of upadacitinib is shown. The relevance of this result was verified through Hedges' g. The 95% confidence interval includes the irrelevance threshold of -0.20. Thus, it cannot be inferred that the effect is relevant.

Pain (Pain NRS)

For the endpoint pain no statistically significant difference was detected between the treatment groups.

Patient-reported global disease activity (PtGADA)

For the endpoint PtGADA, there is a statistically significant difference to the benefit of upadacitinib. The relevance of this result was verified through Hedges'g. The 95% confidence interval includes the irrelevance threshold of -0.20. Thus, it cannot be inferred that the effect is relevant.

Quality of life

Short Form 36 Health Survey (SF-36)

For the endpoint health-related quality of life assessed by the SF-36, the physical sum score (PCS) and the mental sum score (MCS) are considered separately.
Therefore, against the background of the current methodological discussion, both the responder analysis with a response threshold of 15% and the responder analysis with a response threshold of ≥ 5 points are used to assess the additional benefit.
The pharmaceutical company submits data on a response threshold of 9.4 points for the PCS and 9.6 points for the MCS for the response threshold of 15% of the scale range.
For the physical and mental sum score of the SF-36, a statistically significant difference to the advantage of upadacitinib over adalimumab is shown both based on the responder analyses for the response threshold of 15% of the scale range and the proportion of adults with an improvement of ≥ 5 points.

Side effects

Overall rates of SAEs and discontinuations due to AEs

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

Infections and infestations (SOC, AEs)

For the endpoint infections and infestations no statistically significant difference was detected between the treatment arms.

Overall assessment

The benefit assessment is based on the randomised controlled SELECT-PsA 1 study, in which upadacitinib is compared with adalimumab, in each case alone or in combination with methotrexate. The study population includes adults with active moderate to severe psoriatic arthritis who had an inadequate response to prior treatment with at least one conventional synthetic disease-modifying antirheumatic drug (csDMARD) of at least 12 weeks. The results of a subpopulation of the study in which adults received upadacitinib or adalimumab exclusively as monotherapy or in combination with methotrexate were used for the present assessment. Results are based on the most recent data cut-off; at this point, all adults had been treated for at least 56 weeks.

In the endpoint category morbidity, there was a statistically significant difference in favour of upadacitinib compared to adalimumab in each of the endpoints minimal disease activity (MDA), remission (DAPSA), enthesitis (LEI), physical functional status (HAQ-DI) and health status (EQ-5D VAS).

In the endpoint category of health-related quality of life, the SF-36 showed a statistically significant difference in the benefit of upadacitinib over adalimumab for both the physical and mental sum scores.

In the endpoint category side effects, there is neither an advantage nor a disadvantage for treatment with upadacitinib compared to therapy with adalimumab.
In the overall assessment, in particular, the positive effects of upadacitinib on minimal disease activity (MDA), remission (DAPSA), physical functional status (HAQ-DI) and health status (EQ-5D VAS) as well as on the health-related quality of life (physical and mental component score

of the SF-36) compared with the appropriate comparator therapy are assessed as a previously unachieved significant improvement of the therapy-relevant benefit, and the extent of the additional benefit is classified as considerable.

Thus, overall, a considerable additional benefit of upadacitinib over adalimumab in adults with active psoriatic arthritis who have had an inadequate response to, or have been intolerant of, previous disease-modifying antirheumatic (DMARD) therapy can be inferred.

Reliability of data (probability of additional benefit)

The assessment of the additional benefit is based on a randomised and head-to-head comparator study. At the data cut-off point used, all adults had been treated for at least 56 weeks. The cross-endpoint risk of bias is rated as low for the study.

However, the risk of bias of many results at the endpoint level, especially where a statistically significant difference was observed, is to be considered high due to a high proportion of patients considered non-responders due to missing values (>10% in both treatment arms). This also applies to the HAQ-DI because of the high proportion of patients (> 10%) who were not included in the evaluation.

Overall, therefore, a hint is derived for the reliability of data.

b) Adult patients with active psoriatic arthritis Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more biologic disease-modifying anti-rheumatic drugs (bDMARDs).

An additional benefit is not proven.

Justification:

The pharmaceutical company submits results of a placebo-controlled RCT (SELECT-PsA 2) for the patient population to be evaluated. As upadacitinib was not compared with the appropriate comparator therapy in this study, no conclusions on the additional benefit of upadacitinib compared with the appropriate comparator therapy can be derived from these data. An additional benefit is not proven.

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 psoriatic arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more DMARDs. RINVOQ may be used as monotherapy or in combination with methotrexate.

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

a) Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs)

b) Adult patients with active psoriatic arthritis who have responded inadequately to, or who are intolerant to one or more biologic disease-modifying anti-rheumatic drugs (bDMARDs).

Patient population a)

The G-BA determined a TNF-alpha antagonist (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an interleukin inhibitor (ixekizumab or secukinumab or ustekinumab), if necessary in combination with methotrexate, as an appropriate comparator therapy.

For this patient group, the pharmaceutical company presents the RCT SELECT-PsA 1, in which upadacitinib is compared with adalimumab, in each case as monotherapy or in combination with methotrexate. At the data cut-off point used, all adults had been treated for at least 56 weeks.

There are statistically significant benefits in favour of upadacitinib over adalimumab in both the morbidity and quality of life endpoint categories. There were no statistically significant differences in the endpoint category of side effects.

The positive effects of upadacitinib, particularly on minimal disease activity, remission, physical functional status and health status, and health-related quality of life are judged to be considerable.
Overall, however, uncertainties remain, as the risk of bias in many outcomes at the endpoint level is considered high.

Overall, a hint for a substantial additional benefit of upadacitinib over adalimumab in adults with active psoriatic arthritis who have had an inadequate response to, or have been intolerant of, previous disease-modifying antirheumatic (DMARD) therapy is identified.

Patient population b)

The G-BA determined the change to another biological disease-modifying antirheumatic drug (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab or ixekizumab or secukinumab or ustekinumab), possibly in combination with methotrexate, as an appropriate comparator therapy.

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

Overall, no additional benefit of upadacitinib compared with the appropriate comparator therapy in adults with active psoriatic arthritis who have had an inadequate response to or are intolerant of prior therapy with disease-modifying biological antirheumatic drugs (bDMARDs) is identified.

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

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

Therefore, the data from the G-BA resolution on ixekizumab of 2018[3] and the resolution on secukinumab[4] and guselkumab of 2021[5] are used as a basis.

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 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.

3 Benefit assessment resolution of the G-BA on ixekizumab dated 16 August 2018.
4 Benefit assessment resolution of the G-BA on secukinumab dated 18 February 2021.
5 Benefit assessment resolution of the G-BA on guselkumab dated 20 May 2021.

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.

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or co-morbidities) 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.

Upadacitinib is approved alone or in combination with methotrexate for the treatment of adult patients with active psoriatic arthritis. The active ingredients of the appropriate comparator therapy for both patient groups can also be used both as part of monotherapy and in combination with methotrexate. Thus, if applicable, the corresponding costs for methotrexate are incurred both for the medicinal product under assessment and for the appropriate comparator therapy and are therefore not listed separately.

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	Once daily	365	1	365
Appropriate comparator therapy				
Patient population a) and b)				
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
Infliximab	Once every 56 days	6.5	1	6.5
Ixekizumab	Once every 28 days	13	1	13
Secukinumab	Once a month	12	1	12
Ustekinumab	Once every 84 days	4.3	1	4.3

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]

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 population a) and b)					
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	1 x 50 mg	12	12 x 50 mg
Infliximab	5mg/kg	385 mg	4 x 100 mg	6.5	26 x 100 mg
Ixekizumab	80 mg	80 mg	1 x 80 mg	13	13 x 80 mg
Secukinumab	150 mg - 300 mg	150 mg - 300 mg	1 x 150 mg - 1 x 300 mg	12	12 x 150 mg - 12 x 300 mg
Ustekinumab	45 mg	45 mg	1 x 45 mg	4.3	4.3 x 45 mg

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

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 product:

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	€ 3,714.25	€ 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
Ixekizumab	3 IFE	€ 4,175.73	€ 1.77	€ 0.00	€ 4,173.96
Secukinumab 150 mg	6 SFI	€ 5,173.49	€ 1.77	€ 0.00	€ 5,171.72
Secukinumab 300 mg	3 SFI	€ 5,173.49	€ 1.77	€ 0.00	€ 5,171.72
Ustekinumab	1 SFI	€ 5,258.42	€ 1.77	€ 297.03	€ 4,959.62
Abbreviations: 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					

Last revised LAUER-TAXE®: 15 June 2021

7 Fixed reimbursement rate

Costs for additionally required SHI services:

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

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

For the use of upadacitinib and 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. The costs presented are a blood test (quantitative determination of an in vitro interferon-gamma release after ex vivo stimulation with antigens specific for Mycobacterium tuberculosis-complex (except BCG)) and a chest radiograph. The tuberculin skin test is not presented due to lack of sensitivity and specificity as well as the possibility of "sensitisation".

In addition, patients receiving therapy with upadacitinib, and adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab should be tested for the presence of HBV infection before initiating the respective treatment. For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are 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.

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
Medicinal product to be assessed				
Upadacitinib	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
	X-ray thorax (GOP 34241)	1	€ 16.24	€ 16.24
	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
Appropriate comparator therapy				
Adalimumab Certolizumab pegol Etanercept Golimumab Infliximab Ustekinumab	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
	X-ray thorax (GOP 34241)	1	€ 16.24	€ 16.24
Adalimumab Certolizumab pegol Etanercept	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	anti-HBs antibody (GOP 32617)[9]	1	€ 5.50	€ 5.50

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.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Golimumab Infliximab	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.

4. Process sequence

At its session on 9 June 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.

By letter dated 08 June 2021, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addenda prepared by IQWiG was submitted to the G-BA on 22 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 6 July 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	9 June 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, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	16 June 2021 30 June 2021	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal products	6 July 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