Gemeinsamer Bundesausschuss

Justification

to 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: giant cell arteritis)

of 6 November 2025

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all 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 studies the pharmaceutical company have 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,
7. number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

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 decide on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

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

On 4 April 2025, 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 5 May 2025, 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 "RINVOQ is indicated for the treatment of giant cell arteritis in adult patients" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 15 August 2025 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, and the addenda to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA have 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 giant cell arteritis in adult patients.

Therapeutic indication of the resolution (resolution of 6 November 2025):

See the approved therapeutic indication.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with giant cell arteritis who are eligible for treatment with glucocorticoids alone

Appropriate comparator therapy for upadacitinib:

- a therapy with systemic glucocorticoids

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

b) Adults with giant cell arteritis who are not eligible for treatment with glucocorticoids alone

Appropriate comparator therapy for upadacitinib:

- a therapy with systemic glucocorticoids in combination with tocilizumab

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:

On 1. In addition to the medicinal product to be assessed, systemic glucocorticoids, including the active ingredients methylprednisolone, prednisolone, prednisone and triamcinolone are explicitly approved for the treatment of giant cell arteritis. The biologic agent tocilizumab (interleukin-6 inhibitor) has also been approved for the field of indication of giant cell arteritis.

On 2. A sole non-medicinal treatment cannot be considered in the therapeutic indication.

On 3. For the treatment of giant cell arteritis, there are no resolutions from the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

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.

The guidelines[2,3,4,5] recommend systemic glucocorticoids as standard therapy for the treatment of giant cell arteritis. However, glucocorticoid-sparing therapy with tocilizumab should be additionally carried out after individual assessment of certain patients with giant cell arteritis, particularly those with refractory or relapsed disease, or subjects who suffer from or are at increased risk of glucocorticoid-associated secondary damage. The active ingredient methotrexate is mentioned in the guidelines as a therapeutic alternative. In contrast to glucocorticoids and tocilizumab, this is however not approved for the treatment of giant cell arteritis.

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[2] **German Society for Rheumatology (DGRh).** Management of large vessel vasculitis; S2k guideline; long version [online]. AWMF registry number 060-007. Berlin (GER): Association of the Scientific-Medical Societies (AWMF); 2020. [Accessed: 11.06.2024]. https://www.awmf.org

[3] **Hellmich B, et al.** 2018 update of the EULAR recommendations for the management of large vessel vasculitis. Ann Rheum Dis 2020;79(1):19-30.

[4] **Mackie SL, et al.** British Society for Rheumatology guideline on diagnosis and treatment of giant cell arteritis. Rheumatology (Oxford) 2020;59(3):e1-e23.

[5] **Maz M, et al.** 2021 American College of Rheumatology/Vasculitis Foundation guideline for the management of giant cell arteritis and takayasu arteritis. Arthritis Rheumatol 2021;73(8):1349-1365

When giant cell arteritis occurs for the first time, it is started with a high initial dose of systemic glucocorticoids, which is gradually reduced once remission has been achieved. A faster reduction of the glucocorticoid dose is recommended during therapy with tocilizumab compared to glucocorticoid monotherapy.

In summary, based on the recommendations of the guidelines and taking into account the statements, the target population is divided into two patient groups, depending on the suitability for the use of glucocorticoid monotherapy. The G-BA consider a therapy with systemic glucocorticoids to be appropriate for adults with giant cell arteritis who are eligible for treatment with glucocorticoids alone. A therapy with systemic glucocorticoids in combination with tocilizumab is considered appropriate for adults with giant cell arteritis who are not eligible for glucocorticoid therapy alone.

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

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

2.1.3 Extent and probability of the additional benefit

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

a) There is a hint for a minor additional benefit of upadacitinib for adults with giant cell arteritis who are eligible for glucocorticoid therapy alone.

b) An additional benefit is not proven for adults with giant cell arteritis who are not eligible for glucocorticoid therapy alone.

Justification:

<u>Patient population a)</u>

The pharmaceutical company presented the results of a sub-population of the SELECT-GCA study for adults with giant cell arteritis (GCA) who are eligible for glucocorticoid therapy alone.

The SELECT-GCA study is a completed, double-blind, multicentre, 3-arm randomised controlled trial comparing upadacitinib at doses of 15 mg and 7.5 mg with placebo in adults with new-onset or recurrent active giant cell arteritis. In all study arms, the subjects receive glucocorticoids (GC), which are tapered off according to a defined regimen.

At the start of the study, patients had to have received a treatment with at least 20 mg prednisone or prednisolone and be sufficiently clinically stable for the GC tapering regimen specified in the study protocol. Patients with infectious diseases specified in the study protocol, uncontrolled arterial hypertension or cardiovascular events within the last 6 months were excluded from the study.

A total of 428 patients were enrolled in the study: 209 in the intervention arm with 15 mg upadacitinib and 112 in the control arm. The study arm with a dosage of 7.5 mg upadacitinib

is not considered for the present benefit assessment as the dosage is not covered by the marketing authorisation.

In the two relevant study arms, GC was tapered off according to a predetermined regimen. Depending on the starting dose, a first unblinded phase-out period of varying duration up to a daily dose of 20 mg took place. Subsequently, GC was completely tapered off in a blinded regimen by week 26 at the latest in the intervention arm and week 52 in the comparator arm. In order to maintain blinding after complete taper, the patients received a placebo from this point onwards. In the event of a relapse or if the study participants were unable to follow the tapering regimen, the taper was interrupted and prednisone/ prednisolone was administered unblinded as emergency therapy so that the GC dose was at least 20 mg per day.

At the end of the 52-week double-blind phase, patients who met the criteria for sustained remission from week 24 or had no symptoms or signs of giant cell arteritis at week 52 and were GC-free were able to participate in a blinded 52-week extension phase. For this, patients were either treated in the arm already allocated or randomised again. The results of this extension phase are not relevant for the present benefit assessment due to the renewed randomisation and associated selection of patients.

The primary endpoint of the study was sustained remission from week 12 to week 52, defined as the absence of signs or symptoms of giant cell arteritis and adherence to the GC tapering regimen specified in the study protocol. In addition, endpoints in the categories of morbidity, health-related quality of life and adverse events (AEs) were assessed.

Relevant sub-population

The sub-population of the SELCT-GCA study presented by the pharmaceutical company in the dossier was used for the assessment of the additional benefit of upadacitinib for patient group a). This sub-population exclusively includes study participants with new-onset giant cell arteritis. Subjects with relapse were excluded because they can also be assigned to patient group b), i.e. adults with giant cell arteritis who are not eligible for glucocorticoid therapy alone.

The relevant sub-population includes 148 patients in the intervention arm and 76 in the comparator arm. Of these subjects, 29% and 36%, respectively, had at least one comorbidity associated with an increased risk of GC-induced side effects. Despite the lack of effect modifications by the comorbidities characteristic (yes vs no), there is thus uncertainty as to whether all patients in this sub-population are eligible for treatment with GC alone.

Extent and probability of the additional benefit

Mortality

For the endpoint of overall survival, there was no statistically significant difference between the treatment groups.

Morbidity

For the morbidity endpoint category, both the endpoint of remission and the patient-reported endpoints of fatigue, health status and pain are used for the benefit assessment. For these endpoints, the pharmaceutical company presented several evaluation and substitution strategies in the dossier and as part of the written statement procedure for dealing with intercurrent events and missing values.

For the present benefit assessment, the treatment policy strategy, which does not consider the intercurrent event "use of emergency therapy", is taken into account for the patient-reported endpoints, thus all patient-reported values at week 52 being included in the evaluation. With regard to the substitution of missing values, multiple imputation (MI) is taken into account here. This is however subject to uncertainties. The background to this is the high percentage of missing values without information on the reasons.

Responder analyses are used for both evaluations since both an improvement and a deterioration are possible for the patient-reported endpoints in the analysed study population of the present therapeutic indication.

For the remission endpoint, the evaluation strategy of the treatment policy and the substitution by means of non-responder imputation (NRI)-MI are used. The substitution of missing values using NRI-MI is subject to uncertainty, partly because study dropouts can also be responders. In addition, it remains unclear how many patients were replaced as responders if they were categorised as responders both before and after a missed visit.

Remission

Achieving and maintaining remission is a key therapeutic goal in this therapeutic indication. This presupposes remission and non-recurrence of the symptoms. In addition, glucocorticoid-induced side effects should be avoided as far as possible.

In the dossier, the pharmaceutical company presented various evaluations on the composite endpoint of remission, which differ in the individual components included on the one hand and in the considered evaluation time point on the other.

For an evaluation as a responder, no signs and symptoms of GCA were allowed to be present in all submitted operationalisations, and the GC tapering regimen specified in the study protocol had to have been adhered to during the course of the study.

However, it is considered critical that the remission endpoint could not be achieved if the GC therapy was adjusted in the sense of emergency therapy. This operationalisation potentially disadvantages the comparator arm in particular, in which patients were particularly dependent on optimally selected, flexible GC therapy due to the lack of a standardised additional therapy (such as upadacitinib). In principle, the classification as a non-responder due to an adjustment of the glucocorticoids in the sense of emergency medication means that subjects who achieved a remission after deviating from the fixed tapering regimen could no longer be included in the analysis as responders at a later point in time. As a result, the number of responders is underestimated in the comparator arm in particular, and it is not possible to deduce how many patients ultimately achieved remission when applying a patient-individually adjustable tapering regimen. The operationalisations presented in the dossier are therefore not suitable for derivation of the additional benefit.

As part of the written statement procedure, the pharmaceutical company submitted further evaluations on the remission endpoint, in which the reduction in glucocorticoid requirement was operationalised as steroid avoidance (0 mg/day GC) at week 52 or as reaching or falling below a daily GC dose of 5 mg from week 36 to 52.

The operationalisation with the GC threshold value ≤ 5 mg/day is used for the benefit assessment. According to the guidelines, reaching or falling below this threshold value represents a target value after one year. This should minimise the risk of glucocorticoid-induced side effects. The selected operationalisation takes into account a period of 16 weeks, in which both the absence of signs and symptoms of giant cell arteritis is assumed and the GC threshold value criterion had to be met throughout. This endpoint is defined as "sustained

remission". On the contrary, the achievement of steroid avoidance was only assessed at a single point in time, so that the operationalisation "steroid-free remission" is presented additionally.

For the considered remission endpoint "sustained remission", there was a statistically significant difference to the advantage of upadacitinib + GC compared to placebo + GC.

Further operationalisations submitted by the pharmaceutical company for the remission endpoint also include the individual components "normalisation of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)". As part of the written statement procedure, the scientific-medical society and the clinical expert emphasised that the inclusion of inflammation values in medical healthcare plays an important role in the classification of the occurring signs and symptoms of giant cell arteritis and is therefore also important for therapy management. When looking at the results on the operationalisation "sustained remission", which also includes the criterion of normalisation of CRP and ESR ("complete sustained remission"), there was a statistically significant advantage of upadacitinib over the control arm (RR = 2.32; 95% confidence interval [1.43; 3.75]). However, the inflammation parameters CRP and ESR are laboratory parameters that are not patient-relevant per se. There is also evidence that acute-phase proteins such as CRP react independently of clinical improvement when JAK inhibitors are used. The inclusion of laboratory parameters in the remission definition can therefore potentially lead to an unfair comparison in favour of the intervention arm. Overall, the operationalisations are therefore not used for the present benefit assessment.

Fatigue

The endpoint of fatigue was assessed in the present study using the "Functional Assessment of Chronic Illness Therapy-Fatigue" (FACIT-Fatigue) questionnaire. There was no statistically significant difference between the treatment arms for the percentage of patients with clinically relevant improvement or deterioration in the FACIT-Fatigue by ≥ 8 points (of 52 points).

Health status

For the endpoint of health status, assessed using the VAS of the European Quality of Life Questionnaire 5 Dimensions (EQ-5D), there was no statistically significant difference between the treatment arms for the percentage of patients with a clinically relevant improvement or deterioration by ≥ 15 points (of 100 points).

Pain (PGIC)

In the SELECT-GCA study, GCA-related symptomatology was assessed via the pain endpoint using the Patient Global Impression of Change (PGIC). The PGIC consists of a single question asking the study participants to rate the change in GCA-related symptomatology since the start of treatment on a 7-point scale (from "very much improved" to "very much deteriorated").

In the dossier and as part of the written statement procedure, the pharmaceutical company submitted various evaluations on any and strong improvement/ deterioration ("very much improved/ deteriorated" and "much improved/ deteriorated"). Based on the predefinition, the significant improvement or significant deterioration is used for the benefit assessment.

However, no data with the evaluation strategy of the multiple imputation treatment policy considered here was submitted or subsequently submitted for the significant improvement.

For the operationalisation of significant deterioration, there were no statistically significant differences between the treatment groups.

Quality of life

Health-related quality of life was assessed using the physical component and mental component summary scores of the generic Short Form 36-Item Health Survey questionnaire. Analogous to the patient-reported morbidity endpoints, the analyses of improvement and deterioration with the evaluation strategy of the multiple imputation treatment policy are used (see above).

The responder analyses on the clinically relevant improvement or deterioration by ≥ 10 points show no statistically significant differences between the treatment arms for either summary score.

Side effects

For the endpoints of serious adverse events (AEs), severe AEs and discontinuation due to AEs, as well as the specific AEs of infections and serious infections, there were no statistically significant differences between the treatment arms.

Overall assessment

The results of the randomised controlled trial SELECT-GCA on the sub-population of study participants with new-onset giant cell arteritis are available for the assessment of the additional benefit of upadacitinib for the treatment of adults with giant cell arteritis who are eligible for glucocorticoid therapy alone.

For the endpoint categories of mortality, health-related quality of life and side effects, there were neither advantages nor disadvantages of upadacitinib + GC compared to placebo + GC.

For the morbidity endpoint category, there was a statistically significant difference in favour of upadacitinib for the remission endpoint - operationalised by the absence of signs and symptoms of giant cell arteritis and reaching or falling below a daily GC dose of 5 mg from week 36 to 52. For the assessed patient-reported endpoints of fatigue, health status and pain, there were no statistically significant differences between the treatment groups.

Achieving and maintaining absence of symptoms while avoiding glucocorticoid-induced side effects is a key therapeutic goal in this therapeutic indication. Against this background, the overall analysis of the available results shows an additional benefit of upadacitinib compared with the appropriate comparator therapy for the treatment of adults with giant cell arteritis in patient group a), based on the statistically significant advantage in the endpoint "sustained remission". The additional benefit is assessed as low due to the moderate effect.

Reliability of data (probability of additional benefit)

The SELECT-GCA study is a randomised, double-blind study with low risk of bias for the assessment of the additional benefit.
However, the reliability of data is limited across all endpoints as there is uncertainty due to the high percentage of study participants with certain comorbidities as to whether all patients in the sub-population analysed are eligible for a therapy with GC alone.

In addition, there is a high risk of bias for all endpoints on quality of life and morbidity, including sustained remission, due to uncertainties in the substitution strategy. With the exception of the endpoint "discontinuation due to AEs", there is also a high risk of bias in the

endpoints of mortality and side effects due to the overall high percentage of therapy dropouts and due to the existing difference in the percentages of therapy dropouts between the treatment arms.

Therefore, a hint for an additional benefit is assumed in the overall assessment.

Patient population b)

No data are available for the assessment of the additional benefit of upadacitinib compared with the appropriate comparator therapy for adults with giant cell arteritis who are not eligible for glucocorticoid therapy alone. An additional benefit is therefore 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 giant cell arteritis in adult patients."

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

a) Adults with giant cell arteritis who are eligible for treatment with glucocorticoids alone
b) Adults with giant cell arteritis who are not eligible for treatment with glucocorticoids alone

On patient population a)

The G-BA determined the appropriate comparator therapy to be a therapy with systemic glucocorticoids. The results of the randomised controlled trial SELECT-GCA on the sub-population of study participants with new-onset giant cell arteritis are available for the benefit assessment. The comparison of placebo with 15 mg upadacitinib is taken into account. In both study arms, the subjects receive glucocorticoids (GC), which are tapered off according to a defined regimen.

For the endpoint categories of mortality, health-related quality of life and side effects, there were neither advantages nor disadvantages of upadacitinib + GC compared to placebo + GC.

For the morbidity endpoint category, there was a statistically significant difference in favour of upadacitinib for the remission endpoint - operationalised by the absence of signs and symptoms of giant cell arteritis and reaching or falling below a daily GC dose of 5 mg from week 36 to 52. For the assessed patient-reported endpoints of fatigue, health status and pain, there were no statistically significant differences between the treatment groups.

Achieving and maintaining absence of symptoms while avoiding glucocorticoid-induced side effects is a key therapeutic goal in this therapeutic indication. Against this background, the overall analysis of the available results shows a minor additional benefit of upadacitinib compared with the appropriate comparator therapy for the treatment of adults with giant cell arteritis in patient group a), based on the moderate advantage in the endpoint "sustained remission".

The reliability of data is rated as a "hint". On the one hand, there are uncertainties as to whether all patients in the sub-population analysed are eligible for a therapy with GC alone. On the other, there is a high risk of bias for all endpoints except for the endpoint "discontinuation due to adverse events". The reason for this is the high percentage of therapy

dropouts, which also differs between the treatment arms, as well as uncertainties regarding the chosen substitution strategies.

On patient population b)

No data are available for the assessment of the additional benefit of upadacitinib compared with the appropriate comparator therapy for adults with giant cell arteritis who are not eligible for glucocorticoid therapy alone. An additional benefit is therefore not proven.

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

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

The resolution is based on the information from the dossier assessment of the IQWiG (mandate A25-66). In deviation from the pharmaceutical company's approach, the number of patients, whose more recent data available from Herlyn et al.[6] from 2006 was used to calculate the prevalence of patients with giant cell arteritis, is used. However, transferability to the whole of Germany is fraught with uncertainty due to regional differences. Furthermore, it cannot be ruled out that the prevalence has continued to rise since 2006.

Further uncertainties arise in relation to the division of patients into the two patient populations, with percentages of 20% for patient group a) and 80% for patient group b). The percentages may tend to shift in favour of patient group b).

In addition, when deriving the size of the SHI-target population, the pharmaceutical company did not take into account the limitations of the target population in the therapeutic indication defined in the product information for upadacitinib (section 4.4.). This means that the stated patient numbers are overestimated.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Rinvoq (active ingredient: upadacitinib) at the following publicly accessible link (last access: 16 September 2025):

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 specialists experienced in treating giant cell arteritis.

In accordance with the EMA requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients (including patient card). 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 tuberculosis and

[6] Herlyn K, et al. Doubled prevalence rates of ANCA-associated vasculitides and giant cell arteritis between 1994 and 2006 in northern Germany. Rheumatology (Oxford) 2014; 53(5): 882-889.

herpes zoster, as well as birth defects (pregnancy risk), serious adverse cardiac events, venous thromboembolisms and malignancies.

Prior to initiation of therapy with upadacitinib, it is recommended checking the vaccination status of the patients.

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 September 2025). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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.

The daily doses recommended in the product information were used as the calculation basis.

According to the product information for Rinvoq, upadacitinib is used in combination with a tapered therapy with systemic glucocorticoids, after which upadacitinib can be continued as monotherapy in the chronic course of giant cell arteritis. Glucocorticoids which are tapered off over time are also used as part of the appropriate comparator therapy.

Prednisolone is used as an example for the group of oral glucocorticoids. The initial daily dose of 10 – 40 mg is followed by a daily dose of 5 – 15 mg in the phase-out period.
Other potencies of 1 and 2 mg are available.

a) Adults with giant cell arteritis who are eligible for treatment with glucocorticoids alone

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Upadacitinib	Continuously, 1 x daily	365.0	1	365.0
Prednisolone	Different from patient to patient			
Appropriate comparator therapy				
A therapy with systemic glucocorticoids				
Prednisolone	Different from patient to patient			

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	365.0	365 x 15 mg
Prednisolone	Different from patient to patient				
Appropriate comparator therapy					
A therapy with systemic glucocorticoids					
Prednisolone	Different from patient to patient				

b) Adults with giant cell arteritis who are not eligible for treatment with glucocorticoids alone

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Upadacitinib	Continuously, 1 x daily	365.0	1	365.0
Prednisolone	Different from patient to patient			
Appropriate comparator therapy				
A therapy with systemic glucocorticoids in combination with tocilizumab				
Tocilizumab	Continuously, 1 x every 7 days	52.1	1	52.1
Prednisolone	Different from patient to patient			

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	365.0	365 x 15 mg
Prednisolone	Different from patient to patient				
Appropriate comparator therapy					
A therapy with systemic glucocorticoids in combination with tocilizumab					
Tocilizumab	162 mg	162 mg	1 x 162 mg	52.1	52.1 x 162 mg
Prednisolone	Different from patient to patient				

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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

Patient populations a) and b)

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Upadacitinib 15 mg	90 SRT	€ 3,494.84	€ 1.77	€ 0.00	€ 3,493.07
Appropriate comparator therapy					
Prednisolone 5 mg[7]	100 TAB	€ 15.43	€ 1.77	€ 0.33	€ 13.33
Prednisolone 10 mg[7]	100 TAB	€ 17.81	€ 1.77	€ 0.51	€ 15.53
Prednisolone 20 mg[7]	100 TAB	€ 21.62	€ 1.77	€ 0.81	€ 19.04
Tocilizumab 162 mg	12 PEN	€ 5,135.91	€ 1.77	€ 290.02	€ 4,844.12
Abbreviations: PEN = solution for injection in a pre-filled pen; SRT = sustained release tablet; TAB = tablet					

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Costs for additionally required SHI services:

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

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

Prior to administration of the active ingredient upadacitinib, patients must be examined for active and inactive ("latent") tuberculosis infections as well as viral hepatitis.

Diagnostics to rule out chronic hepatitis B requires sensibly coordinated steps. 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. In certain case constellations, further steps may be necessary in accordance with current guideline recommendations[8].

Diagnostics to rule out hepatitis C requires sensibly coordinated steps. HCV screening is based on the determination of anti-HCV antibodies. In certain case constellations, it may be necessary to verify the positive anti-HCV antibody findings in parallel or subsequently by HCV-

[7] Fixed reimbursement rate

[8] S3 guideline on prevention, diagnosis and therapy of hepatitis B virus infection AWMF registry no.: 021/011 https://register.awmf.org/assets/guidelines/021-011l_S3_Prophylaxe-Diagnostik-Therapie-der-Hepatitis-B-Virusinfektion_2021-07.pdf].

RNA detection to confirm the diagnosis of an HCV infection[9].

Additionally required SHI services for the active ingredient tocilizumab of the appropriate comparator therapy in patient group b) are equally necessary for screening for tuberculosis infection, so that the annual treatment costs are not shown for the medicinal product to be assessed and the appropriate comparator therapy for this patient group.

Designation of the therapy	Designation of the service	Number	Costs per unit	Costs per patient per year
Upadacitinib, tocilizumab	Quantitative determination of an in vitro IFN-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	€ 53.36	€ 53.36
	Chest radiograph (GOP 34241)	1	€ 18.09	€ 18.09
Upadacitinib	HBV test Hepatitis B surface antigen status (GOP 32781)	1	€ 5.06	€ 5.06
	Anti-HBc antibody (GOP 32614)	1	€ 5.43	€ 5.43
	HCV antibody status (GOP 32618)	1	€ 9.02	€ 9.02

2.5 Designation of 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 the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA 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.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it

[9] S3 guideline on prevention, diagnosis and therapy of hepatitis C virus (HCV) infection; AWMF registry no.: 021/012 https://register.awmf.org/assets/guidelines/021-012l_S3_Hepatitis-C-Virus_HCV-Infektion_2018-07.pdf].

is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph

1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the

combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

a) Adults with giant cell arteritis who are eligible for treatment with glucocorticoids alone

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for upadacitinib (RINVOQ); RINVOQ® 15 mg/ 30 mg/ 45 mg sustained-release tablets; last revised: June 2025

b) Adults with giant cell arteritis who are not eligible for treatment with glucocorticoids alone

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for upadacitinib (RINVOQ); RINVOQ® 15 mg/ 30 mg/ 45 mg sustained-release tablets; last revised: June 2025

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 their session on 6 August 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 5 May 2025, 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 15 May 2025 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 12 August 2025, and the written statement procedure was initiated with publication on the G-BA website on 15 August 2025. The deadline for submitting statements was 5 September 2025.

The oral hearing was held on 22 September 2025.

By letter dated 23 September 2025, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 10 October 2025.

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 28 October 2025, and the proposed draft resolution was approved.

At their session on 6 November 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	6 August 2024	Determination of the appropriate comparator therapy
Working group Section 35a	16 September 2025	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	22 September 2025	Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	30 September 2025 14 October 2025	Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure
Subcommittee on Medicinal Products	28 October 2025	Concluding discussion of the draft resolution
Plenum	6 November 2025	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 6 November 2025

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

Prof. Hecken