Justification

Gemeinsamer Bundesausschuss

to 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 (Rheumatoid Arthritis)

of 16 July 2020

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 relevant date for the first placing on the market of the active ingredient upadacitinib in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 February 2020. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 16 January 2020.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 4 May 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of upadacitinib compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has assessed 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 arrived at 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 moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ may be used as monotherapy or in combination with methotrexate.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adult patients with moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors[2] and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventionalDMARDs, including methotrexate (MTX)) or did not tolerate it

- Alternative conventional DMARDs (e.g. MTX, leflunomide) provided that they are suitable as mono- or combination therapy

b) Adult patients with moderate to severe active rheumatoid arthritis for whom first-line therapy with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated

- bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability)

c) Adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

[2] Unfavourable prognostic factors:
- Detection of auto-antibodies (e.g. rheumatoid factors, high levels of antibodies against citrullinated peptide antigens)
- High disease activity (demonstrated by DAS or DAS28 assessment system, swollen joints, and parameters of the acute phase reaction such as C-reactive protein and erythrocyte sedimentation rate)
- Early occurrence of joint erosion

- Change of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability; or in patients with severe rheumatoid arthritis rituximab, taking into account the marketing authorisation) depending on the previous therapy.

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 according to 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.

Many approved medicinal products are available for the treatment of rheumatoid arthritis. These includes medicinal products of the following active ingredient classes and the following active ingredients:

- non-steroidal anti-inflammatory drugs/anti-rheumatic drugs (NSAIDs/NSAR), whereby these are used purely symptomatically
- Steroidal anti-inflammatory drugs (glucocorticoids) such as prednisolone and methylprednisolone
- conventional synthetic disease-modifying anti-rheumatic drugs (“basic therapeutics”, cDMARDs) such as MTX, leflunomide, and sulfasalazine
- Other active ingredients: D-penicillamine, parenteral gold, ciclosporin, and azathioprine
- Biological disease-modifying anti-rheumatic drugs (“biologics”, bDMARDs): TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab, and golimumab), abatacept, anakinra, rituximab, tocilizumab, sarilumab
- targeted synthetic DMARDs (tsDMARDs): the JAK inhibitors baricitinib and tofacitinib

Some active ingredients are used only for severe forms of rheumatoid arthritis (e.g. rituximab, ciclosporin, or azathioprine) in accordance with marketing authorisation. These active ingredients are therefore suitable for only a part of the patients and do not represent an appropriate comparator therapy for a large part of the patient population covered by the therapeutic indication.

On 2.

For the treatment of rheumatoid arthritis, non-pharmaceutical measures alone cannot be considered as appropriate comparator therapy

On 3.

There are three resolutions of G-BA in the indication area rheumatoid arthritis: for baricitinib on 21 September 2017, for tofacitinib on 19 October 2017 and 1 November 2018, and for sarilumab on 15 February 2018. Furthermore, a final report of the Institute for Quality and Efficiency in Health Care (IQWiG) on a comparative benefit assessment of biologic medicinal products in second-line therapy of rheumatoid arthritis for the active ingredients rituximab, abatacept, etanercept, infliximab, adalimumab, certolizumab pegol, golimumab, anakinra, and tocilizumab dated 28 June 2013 is available. Furthermore, a final report of the Institute for Quality and Efficiency in Health Care (IQWiG) on biologic active ingredients for rheumatoid arthritis dated 23 July 2019 is available. In addition, the therapeutic guidelines in accordance with Section 92, para. 2, sentence 7 SGB V in conjunction with Section 17 of the Pharmaceuticals Directive (AM-RL) on the cost-effective prescription of medicinal products must be taken into account for the active ingredient leflunomide. The therapeutic indications for adalimumab and infliximab will be legally repealed after publication of the corresponding resolutions in the Federal Gazette.

On 4.

The generally accepted state of medical knowledge was illustrated by research for guidelines as well as systematic reviews of clinical studies in this indication.

The approved therapeutic indication and the approval population of the medicinal product under evaluation are decisive for determining the appropriate comparator therapy
Because of different therapeutic situations, the population in the present therapeutic indication can be divided into

a) Patients for whom there are no unfavourable prognostic factors[2] and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventionalDMARDs, including methotrexate) or did not tolerate it,
b) Patients for whom first-line therapy with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated
c) Patients who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these

According to the current state of scientific knowledge, MTX is considered the agent of choice in first-line therapy and is also established in combination therapy.

Because of their strong anti-inflammatory effect, glucocorticoids are generally used only for a limited period of time as high-dose therapy or orally in low doses as “bridge therapy” at the beginning of treatment until the basic therapy has responded. They also represent an important therapeutic option for malignant disease progression but cannot replace a basic therapy.

On a)

In second-line therapy (patient group a), patients are first differentiated according to the presence or absence of unfavourable prognostic factors . If there are no unfavourable prognostic factors and patients have not responded adequately to previous therapy with a conventional DMARD (cDMARD) or have not tolerated it, the current guideline of the European League Against Rheumatism[3] (EULAR) as well as the S2-e guideline of the DGRh from 2018[4] recommends the use of an alternative conventionalDMARD (e.g. MTX, leflunomide) provided that it is suitable as mono- or combination therapy. Other active ingredients such as D-penicillamine, parenteral gold, ciclosporin, and azathioprine play a subordinate role in this therapy situation because of their poorer risk-benefit ratio. They are therefore not included in the appropriate comparator therapy. In individual cases, patient population a may also include patients with unfavourable prognostic factors who did not respond adequately to initial treatment with a cDMARD or did not tolerate such treatment but who are eligible for a second conventional DMARD based on individual criteria in medical practice before initial bDMARD therapy is initiated.

On b)

After failure or intolerance of treatment with a conventionaldisease-modifying anti-rheumatic agent, the use of a biologic agent or tsDMARD is recommended in the case of unfavourable prognosis factors. The use of a biologic is also recommended for patients who have already had an inadequate response to several cDMARDs or have not tolerated them. Thus, the first-time use of a bDMARD or tsDMARD is equally suitable as an appropriate comparator therapy for these two patient groups, although they differ in terms of their previous therapy and the course of the disease to date. The combining into a patient group is considered justified because the presence of negative prognostic markers and the number of previous therapies in this therapy situation no longer have any predictive value for the course of therapy. Thus, the group of patients for whom initial therapy with bDMARDs or tsDMARDs (patient group b) includes both patients with unfavourable prognostic factors[2] who did not respond adequately to or did not tolerate previous treatment with one disease-modifying anti-rheumatic drug (conventional DMARDs, including MTX) and patients who did not respond adequately to or did not tolerate previous treatment with several disease-modifying anti-rheumatic drugs (conventional DMARDs, including MTX).

The use of the interleukin(IL)-1 receptor antagonist anakinra is not recommended because of its weaker efficacy compared with other biologics based on the IQWiG final report from 2019. After the failure of conventional DMARDs in the recommendations of the EULAR[3] as well as in other guidelines included (including the S2-e guideline of the DGRh from 2018[4]) bDMARDs or tsDMARDs, including TNF-alpha inhibitors in combination with MTX, the CTLA-4 analogue abatacept, the IL-6 inhibitors tocilizumab and sarilumab, and the JAK inhibitors tofacitinib and baricitinib, are the agents of choice. In the early benefit assessment according to Section 35a SGB V, no inferiority or equivalence to the TNF-α inhibitor adalimumab was found for both tofacitinib and baricitinib. There was also an additional benefit for sarilumab compared with the TNF-α inhibitor adalimumab.

Based on the final report of the IQWiG on bDMARDs from 2013, the previously seen inferiority of the TNF-α inhibitor infliximab compared with the other active ingredients in its class because of an increased side effect profile is no longer seen based on the current, aggregated

[3] Smolen JS, et al. Ann Rheum Dis. 2020 June;79(6): 685–699.

[4] Fiehn C, Holle J, Iking-Konert C, Leipe J, Weseloh C, Frerix M, et al. Therapie der rheumatoiden Arthritis mit krankheitsmodifizierenden Medikamenten; S2e-Leitlinie [online]. AWMF register number 060-004. Berlin (GER): Working Group of the Scientific Medical Societies (AWMF; Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften); 2018.

evidence*. Against this background, and because that even in the current guidelines[3, 4], there are no recommendations within the class of bDMARDs that would substantiate the superiority or subordination of individual active ingredients at this point in time, infliximab will be included as a further TNF-α inhibitor in the appropriate comparator therapy.
The G-BA thus comes to the conclusion that, in the overall view, in addition to the TNF-α inhibitors (adalimumab, certolizumab-pegol, etanercept, golimumab, and infliximab), other bDMARDs and tsDMARDs, including abatacept, the IL-6 inhibitors tocilizumab and sarilumab, and the JAK inhibitors tofacitinib and baricitinib – each in combination with MTX are equally suitable as an appropriate comparator therapy.
Consequently, for patients for whom initial therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated, bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability) are equally appropriate comparator therapies. bDMARDs or tsDMARDs should always be used in combination with MTX because this improves the efficacy and reduces the formation of neutralising “anti-drug-antibodies” in the case of bDMARDs. Only patients who cannot tolerate MTX or who have an MTX contraindication are eligible for monotherapy with a bDMARD or tsDMARD as appropriate comparator therapy. The data basis on monotherapy with the anti-IL-6 receptor antibody tocilizumab for MTX intolerance is currently not considered sufficient to allow the use of the TNF-α inhibitors adalimumab, etanercept, and certolizumab pegol, which are also approved as monotherapy, or the tsDMARDs tofacitinib or baricitinib or the bDMARD sarilumab in this situation (patient population b1) as less appropriate alternatives. All approved bDMARD or tsDMARDs can thus also be considered as an equally effective appropriate comparator therapy in this case. Abatacept and golimumab and infliximab are approved only in combination with MTX and therefore only for patient population b2.

On c):
For the therapy situation “after failure of at least one bDMARD or tsDMARD therapy” (after failure of a TNF-α inhibitor therapy), the active ingredients tocilizumab, abatacept, and rituximab (in combination with MTX) are explicitly approved. However, the marketing authorisation of TNF-α inhibitors does not exclude their use even after failure of a previous TNF-α inhibitor therapy (in a “later therapy line”) provided that the prerequisite for use (i.e. the failure of DMARDs) is fulfilled. Thus, in the therapy situation “after failure of at least one bDMARD or tsDMARD therapy”, various TNF-alpha inhibitors, the CTLA-4 analogue abatacept, IL inhibitors, JAK inhibitors and, for severe rheumatoid arthritis, rituximab are approved.

Since the marketing authorisation of the TNF-α inhibitors, the IL inhibitors, and the JAK inhibitors, a growing body of evidence with proof of the efficacy of these active ingredients following the failure of a first bDMARD or tsDMARD has been established. Compared with the therapy situation in patient group b, the aggregated evidence is altogether more limited. However, there are some recommendations from German[4] and European guidelines[3] as well as results from early benefit assessments according to Section 35a SGB V on the treatment situation “after failure of at least one bDMARD or tsDMARD therapy”. Thus, depending on the previous therapy of a patient in the aforementioned therapy stage, the change to a TNF-α inhibitor (adalimumab, certolizumab-pegol, etanercept, golimumab, infliximab) as well as to a therapy with a principle of action deviating from TNF-α inhibition (CTLA-4 analogue, IL-6 inhibitor, or JAK inhibitor), in each case in combination with MTX, can be regarded as

appropriate. Rituximab is also suitable and useful for patients with severe active rheumatoid arthritis who do not respond adequately to other DMARDs, including one or more TNF-alpha inhibitors. For infliximab as well as anakinra, please refer to patient population b.

As in patient group b, bDMARDs and tsDMARDs should always be used in combination with MTX according to the recommendations of professional associations because this improves the efficacy and reduces the formation of neutralising “anti-drug antibodies” in the case of bDMARDs. Only patients who cannot tolerate MTX or who have an MTX contraindication are eligible for monotherapy with a bDMARD or tsDMARD.

In summary, for patients who did not respond adequately to a previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these, depending on the previous therapy, a change in bDMARD or tsDMARD therapy, taking into account the active ingredients abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib (or, in patients with severe rheumatoid arthritis, rituximab), in each case in combination with MTX or possibly as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability is appropriate. Depending on the previous therapy, a change in the principle of action should be considered. A further differentiation of the patient population c (e.g. also with regard to failure of two vs more than two bDMARDs/tsDMARDs) will not be made at this time because of the lack of uniform therapy recommendations.

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

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 moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors[2] and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventional DMARDs, including methotrexate (MTX)) or did not tolerate it

For adult patients with moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors[2] and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventional DMARDs, including methotrexate (MTX)) or did not tolerate it, the additional benefit of upadacitinib (as monotherapy or in combination with MTX) compared with the appropriate comparator therapy is not proven.

Justification for patient population a1:

For the assessment of the additional benefit of treatment with upadacitinib as monotherapy compared with the appropriate comparator therapy, no data were submitted with the dossier.

Justification for patient population a2:

For the assessment of the additional benefit of treatment with upadacitinib in combination with MTX compared with the appropriate comparator therapy, no data were submitted with the dossier.

b) Adult patients with moderate to severe active rheumatoid arthritis for whom first-line therapy with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated

For adult patients with moderate to severe active rheumatoid arthritis for whom first-line therapy with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated, the additional benefit of upadacitinib as monotherapy compared with the appropriate comparator therapy in not proven. However, for upadacitinib in combination with MTX, a hint for a considerable additional benefit compared with the appropriate comparator therapy adalimumab + MTX can be derived.

Justification for patient population b1:

In the relevant patient population b1 for the assessment of the additional benefit of treatment with upadacitinib as monotherapy compared with the appropriate comparator therapy, no data were submitted with the dossier.

Justification for patient population b2:

The benefit assessment is based on the SELECT COMPARE Phase III study presented by the pharmaceutical company. This is a three-arm, randomised, double-blind study comparing upadacitinib with adalimumab and placebo, each in combination with MTX. The study included a total of 1,629 adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to MTX. The patients were randomised to the three treatment arms upadacitinib + MTX (N = 651), adalimumab + MTX (N = 327), and placebo + MTX (N = 651) at a ratio of 2:1:2. Patients were stratified by region in addition to pre-treatment with bDMARD (yes/no). Only the study arms upadacitinib + MTX and adalimumab + MTX are relevant for the present benefit assessment. The planned double-blind, randomised treatment period was 48 weeks. In the subsequent extension phase, which is still ongoing, the treatment of the patients is continued openly. For ≥ 3 months, patients had to have received continuous MTX treatment administered in a stable dosage within the last 4 weeks before the first administration of the study medication. This dosage was continued as concomitant treatment during the study. A concomitant treatment with further csDMARDs – apart from MTX – was not allowed within the study until week 26. In the study, therapy adjustments were made at predefined points in time if certain criteria for response to treatment were not met. At week 14, 18, or 22, patients with < 20% improvement in the number of swollen and pressure-painful joints compared with the start of study switched to the other treatment arm. Blinding was maintained as part of a rescue therapy. At week 26, such a change occurred for patients who had not achieved a low disease activity, which was defined as a Clinical Disease Activity Index (CDAI) ≤ 10. From week 26, adjustments of concomitant medication (e.g. with corticosteroids or non-steroidal anti-rheumatic drugs (NSAIDs) according to local guidelines) and concomitant treatment with additional csDMARDs in addition to MTX were permitted.

The primary endpoint of the study was defined as the proportion of patients with a Disease Activity Score (DAS) based on 28 joints (DAS28) < 2.6 or the proportion of patients with a 20% improvement in ACR criteria (ACR 20), both at week 12. In addition, patient-relevant endpoints on morbidity, health-related quality of life, and adverse events (AEs) were surveyed.

Evaluations for week 26 and week 48 were submitted in the dossier. By week 26, one quarter of the patients had already switched from the comparator therapy adalimumab + MTX to the rescue therapy upadacitinib + MTX. At predefined points in time (e.g. week 14, 18, or 22), while

maintaining blinding as part of a rescue therapy, patients were switched to treatment in the other study arm if certain criteria for non-response were met. At week 26, 19.4% of patients had already moved from the upadacitinib arm to the adalimumab arm and 25.1% from the adalimumab arm to the upadacitinib arm. At week 48, this was true for almost half of the patients in the comparator arm. The difference in patients with rescue therapy between the treatment arms increased from about 6% at week 26 to about 10% points at week 48. When considering the patients with change of therapy of therapy and -discontinuation together, it becomes clear that in the study at week 48 only about 39% of the patients randomised to the comparator therapy were treated with adalimumab + MTX. In the present situation, the potential bias is more pronounced at week 48 than at week 26 because of the significantly higher proportion of patients with such a change. The proportion of patients who, contrary to the marketing authorisation of upadacitinib and adalimumab, received therapy adjustments from week 26 onwards through the addition of further csDMARDs is also unclear. Evaluations for week 26 are therefore used for the present benefit assessment.

For the present benefit assessment, for endpoints in the morbidity and health-related quality of life categories, evaluations using non-responder imputation (NRI) after change to rescue therapy (RNRI) are used as the primary analysis for binary endpoints, and evaluations using rescue last observation carried forward (RLOCF) as a replacement strategy for patients with change of therapy or discontinuation of therapy for continuous endpoints. For endpoints with a high risk of bias for which statistically significant and clinically relevant results are available in addition to a high risk of bias, the sensitivity analyses with NRI or LOCF replacement in which values of patients with a change of therapy are not replaced are also used to check the reliability of data. For endpoints in the categories mortality and side effects, the IQWiG's own calculations with the effect measure relative risk (RR) are based on the naïve rates at which patients were censored after change of therapy. There are no sensitivity analyses for this endpoint.

Extent and probability of the additional benefit

Mortality

For the endpoint overall mortality, there was a statistically significant difference to the advantage of upadacitinib + MTX compared with adalimumab + MTX at week 26. Against the background of the few events that occurred at week 26 and beyond and taking into account the fact that there are no significant differences in mortality at week 48, the effect on overall mortality is not considered sufficiently proven.

Morbidity

The pharmaceutical company assesses morbidity by means of remission, low disease activity, disease-specific symptoms, patient-reported disease activity, physical functional status, health status.

Remission (CDAI ≤ 2.8; SDAI ≤ 3.3; Boolean definition according to ACR/EULAR)

A remission – measured by the Clinical Disease Activity Index (CDAI) – is considered patient-relevant. The CDAI is a clinical construct that comprises information on pressure-painful and swollen joints as well as disease activity reported on a VAS by both the patient and the examiner. Inflammation parameters such as CRP or ESR are not included in the calculation of

the CDAI. The survey of effects via CDAI is thus considered to be more appropriate than constructs that include inflammation parameters, especially for active ingredients with direct influence on inflammation parameters.

A remission is operationalised by the achievement of a CDAI ≤ 2.8. At week 26, statistically significantly more patients achieved remission with upadacitinib + MTX compared with treatment with adalimumab + MTX.

The endpoint remission was also assessed in the study using the Simplified Disease Activity Index (SDAI) and the Boolean definition according to ACR/EULAR. For the endpoint remission, both the operationalisation as SDAI ≤ 3,3 and the operationalisation via the Boolean definition according to ACR-EULAR confirm the statistically significant advantage of upadacitinib + MTX compared with adalimumab + MTX for the operationalisation as CDAI ≤ 2.8 at week 26. In the overall view, an advantage for upadacitinib + MTX compared with adalimumab + MTX can be derived for the endpoint disease remission.

Low disease activity (CDAI ≤ 10; SDAI ≤ 11; DAS28 ESR ≤ 3.2; DAS28 CRP ≤ 3.2)

A low disease activity – measured by the Clinical Disease Activity Index (CDAI) – represents a patient-relevant endpoint. The CDAI is a clinical construct that comprises information on pressure-painful and swollen joints and disease activity reported on a VAS by both the patient and the examiner. A low disease activity by achieving a CDAI ≤ 10 represents a patient-relevant therapeutic goal. Similar to the remission endpoint, inflammation parameters such as CRP or ESR are not included in the calculation of the CDAI.

For the endpoint low disease activity (CDAI ≤ 10), the SELECT COMPARE study at week 26 showed a statistically significant effect in favour of the intervention arm upadacitinib + MTX compared with the control arm adalimumab + MTX.

The endpoint “low disease activity” was also assessed by the DAS28 CRP, the DAS28 ERR, and the SDAI. If the further operationalisations DAS28 CRP ≤ 3.2, DAS28 ESR ≤ 3.2, and SDAI ≤ 11 are used to support the endpoint low disease activity, the advantage observed for upadacitinib + MTX compared with the comparative intervention adalimumab + MTX for the operationalisation via CDAI ≤ 10is confirmed by all evaluations with respect to order of magnitude. In addition, for the operationalisations CDAI ≤ 10 and SDAI ≤ 11, the sensitivity analyses without replacement of patients with change of therapy confirm the effect with regard to statistical significance.

Regardless of the chosen operationalisation, at week 26 in the SELECT COMPARE study, a statistically significantly higher proportion of patients treated with upadacitinib + MTX achieved low disease activity than those treated with adalimumab + MTX. In the overall view, an advantage for upadacitinib + MTX compared with adalimumab + MTX can be derived for the endpoint low disease activity.

Physical functional status (improvement of HAQ-DI by ≥ 0.22 points)

The patient questionnaire Health Assessment Questionnaire - Disability Index (HAQ-DI) surveys the physical functional status, including activities of daily life. It consists of 8 domains (dressing/undressing, personal hygiene, standing up, eating, walking, hygiene, reachability of objects, gripping, and general daily activities). The items for these 8 domains are each answered on a 4-point Likert scale. A value of 0 corresponds to “without difficulty” and a value

of 3 to “unable to perform”. The functional status is calculated using the mean values of the individual domains. For the patient-relevant endpoint of physical functional status (improvement of HAQ-DI by ≥ 0.22 points), the treatment groups revealed a statistically significant advantage in favour of upadacitinib + MTX at week 26 of the SELECT COMPARE study. In the sensitivity analysis, the statistical significance of the effect cannot be confirmed.

Fatigue (improvement of FACIT-F by ≥ 4 points)

The FACIT Fatigue Scale is a validated self-assessment tool designed to measure fatigue in patients with chronic disease. The tool consists of 13 items that measure the intensity of fatigue as well as weakness and difficulty in performing daily activities because of fatigue within the last seven days. The items are answered on a numerical 5-point scale (0 = not at all; 4 = very much). For the patient-relevant endpoint fatigue, there was a statistically significant effect to the advantage of upadacitinib + MTX compared with adalimumab + MTX for the proportion of patients with an improvement of ≥ 4 points at week 26 of the SELECT COMPARE study.

Number of pressure-painful joints

In the studies, 68 joints were examined for pressure pain. By means of a 2-point scale, the degree of pressure pain of the joints was determined, and the evaluation was carried out on the basis of 28 joints, among others. The responder analyses presented for the response threshold of ≤ 1 joint are not used. For the endpoint “pressure-painful joints”, a statistically significant difference to the benefit of upadacitinib + MTX was found at week 26 based on the mean differences. The associated 95%-confidence interval (CI) of the mean change includes a difference of < 1 joint. Thus, it cannot be concluded that the effect is clinically relevant. This is confirmed by the sensitivity analysis, which also shows no statistically significant difference between the treatment arms.

Number of swollen joints

In the studies, 66 joints were examined for swelling. The degree of swelling of the joints was determined using a 2-point scale. For the evaluation based on 28 joints, no statistically significant effect of upadacitinib + MTX compared with adalimumab + MTX was determined at week 26 based on the mean differences.

Pain (VAS)

The symptom pain is reported by the patient using a visual analogue scale. This comprises a scale from 0 mm (no pain) to 100 mm (strongest pain imaginable). Pain intensity measured by VAS is a patient-relevant endpoint. The SELECT COMPARE study showed a statistically significant benefit of upadacitinib + MTX for the mean change to week 26. To assess the relevance of the findings, the standardised mean difference (SMD) in the form of Hedges’ g was considered. However, the 95% CI of the SMD is not completely outside the irrelevance range of −0.2 to 0.2. Thus, it cannot be concluded that the effect is clinically relevant.

Patient-reported assessment of disease activity (VAS)

Patient reported disease activity represents a patient-relevant endpoint for the benefit assessment. In the study, the estimation of disease activity was reported by patients with the

help of a visual analogue scale. Patients were asked to assess the severity of their current impairment from their rheumatoid arthritis on a scale from 0 (no impairment) to 100 mm (maximum impairment). For the endpoint, there was a statistically significant difference to the advantage of upadacitinib + MTX. To assess the relevance of the findings the study calculated an SMD as a Hedges' g. Because the 95% CI does not lie completely outside of the irrelevant range of −0.2 to 0.2, it is not possible to derive whether this effect is clinically relevant.

Morning stiffness: Severity [NRS] and duration

Morning stiffness describes a restriction in the mobility of the joints noticed by the patient immediately after waking up. In the SELECT COMPARE study, the severity of morning stiffness was assessed by the patients themselves on a scale (NRS) of 0 (no morning stiffness) to 10 (worst morning stiffness imaginable) within the last 7 days. In addition, the duration up to the maximum possible mobility was queried. The pharmaceutical company presented evaluations of the mean change in the severity and duration of morning stiffness compared with the start of study.
For the severity (NRS) of morning stiffness, there was a statistically significant effect in favour of upadacitinib + MTX compared with adalimumab + MTX at week 26. However, the 95% CI of the SMD in the form of Hedges' g is not completely outside of the irrelevant range of −0.2 to 0.2. It is therefore not possible to derive whether the effect is clinically relevant. For the duration of morning stiffness, there was no statistically significant difference between the treatment groups.

Health status (EQ-5D VAS)

Health status is recorded in a patient report by means of a visual analogue scale on which the patient assesses his/her health status at the time of measurement. Here, 0 mm stands for the worst imaginable health status and 100 mm for the best imaginable health status. For the mean change in EQ-5D VAS, the SELECT COMPARE study showed no statistically significant advantage or disadvantage for upadacitinib + MTX compared with adalimumab + MTX.

Quality of life

Health Survey Short Form 36 (SF-36) (improvement of SF-36 by ≥ 5 points)

The Health Survey Short Form 36 (SF-36) is a generic instrument for measuring health-related quality of life. It consists of 8 domains and a total of 36 questions. The assessment was based on the physical component scale (PCS) as well as the mental component scale (MCS) of the generic quality-of-life questionnaire SF-36 v2akut. The responder analyses submitted by the pharmaceutical company on the basis of a relevance threshold of ≥ 5 are considered valid for the benefit assessment in the indication rheumatoid arthritis.
For the physical component score of SF-36v2, the evaluation of the proportion of patients with an improvement of ≥ 5 points shows a statistically significant difference to the benefit of upadacitinib + MTX. In the sensitivity analysis, the statistical significance of the effect cannot be confirmed. On the other hand, for the SF-36v2 component score, there was no statistically significant difference between treatment groups.

Side effects

SAE, discontinuation because of AE

For the endpoints SAE as well as discontinuation because of AE, no statistically significant advantages or disadvantages of upadacitinib + MTX compared with adalimumab + MTX were shown at week 26 in the SELECT COMPARE study.

Infections, serious infections

For the patient-relevant endpoints infections and serious infections, there was no statistically significant difference between upadacitinib + MTX and adalimumab + MTX in the SELECT COMPARE study at week 26.

Overall assessment/conclusion

For adult patients with moderate to severe active rheumatoid arthritis for whom initial therapy with bDMARDs or tsDMARDs is indicated, the comparison of upadacitinib + MTX with adalimumab + MTX is based on the results of the directly comparative SELECT COMPARE study at week 26.

In summary, in the endpoint category morbidity, upadacitinib + MTX has statistically significant advantages compared with adalimumab + MTX for both remission and low disease activity; these are confirmed across all operationalisations. For the endpoints remission and low disease activity in particular, the effects of upadacitinib + MTX compared with adalimumab + MTX are assessed to be considerable. A statistically significant, clinically relevant advantage of upadacitinib + MTX compared with adalimumab + MTX can also be derived for the morbidity endpoint fatigue. For the physical functional status (HAQ-DI), there is a statistically significant advantage for upadacitinib + MTX compared with adalimumab + MTX; this is not confirmed in the sensitivity analysis. For the morbidity endpoints number of pressure-painful joints, pain, patient-reported disease activity, and severity of morning stiffness, there are statistically significant effects in favour of upadacitinib + MTX. For the endpoints health status, number of swollen joints and duration of morning stiffness, there were no statistically significant differences between upadacitinib + MTX and the appropriate comparator therapy adalimumab + MTX.

In the quality of life category, there was a statistically significant advantage for upadacitinib + MTX in the physical component score of the SF-36v2; this was not confirmed in the sensitivity analysis. With respect to the mental component score of SF-36v2 at week 26, there are no differences between the treatment groups.

In the side effects category, no advantages or disadvantages can be deduced for upadacitinib + MTX compared with the appropriate comparator therapy adalimumab + MTX at week 26.

At week 26, the advantages of upadacitinib + MTX in terms of morbidity and health-related quality of life (SF-36 physical component score) without disadvantages in terms of side effects compared with the appropriate comparator therapy are assessed as a significant improvement of the therapy-relevant benefit. Based on these considerations, the information in the dossier, and the results of the benefit assessment, the extent of additional benefit for upadacitinib in combination with MTX compared with the appropriate comparator therapy adalimumab + MTX for the treatment of adult patients with moderate to severe rheumatoid arthritis who are candidates for bDMARD or tsDMARD therapy for the first time is classified as considerable.

Reliability of data (probability of additional benefit)

The SELECT COMPARE study is a randomised, double-blind Phase III study for the assessment of the additional benefit.
Because of the high proportion of patients with change of therapy or discontinuation, the risk of bias is considered high for all endpoints on mortality, morbidity (excluding clinical remission), health-related quality of life, and side effects. For the endpoint clinical remission there is a low risk of bias.
Furthermore, the study design chosen in the SELECT COMPARE study results in uncertainties for the assessment of the additional benefit. Even the replacement strategies and sensitivity analyses presented for the benefit assessment cannot eliminate the uncertainties regarding the reliability of data with sufficient certainty. This is particularly the case for the morbidity endpoint physical functional status (HAQ-DI) as well as for the questionnaire on quality of life (SF-36 physical component score) for which the sensitivity analyses have not confirmed the result.

In the overall view, the uncertainties described justify a downgrading of the reliability of data to a hint for an additional benefit.

c) Adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these

For adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these, the additional benefit of upadacitinib as monotherapy compared with the appropriate comparator therapy is not proven. For adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these, for upadacitinib in combination with MTX, compared with the appropriate comparator therapy abatacept + MTX for patients with high disease activity at the start of study (DAS28 [CRP] > 5.1), a hint for a minor additional benefit can be derived, although this is not proven for patients without high disease activity at the start of study (DAS28 [CRP] ≤ 5.1).

Justification for patient population c1:

In the relevant patient population c1 for the assessment of the additional benefit of treatment with upadacitinib as monotherapy compared with the appropriate comparator therapy, no data were submitted with the dossier.

Justification for patient population c2:

The benefit assessment is based on the SELECT CHOICE Phase III study presented by the pharmaceutical company. This is a randomised, double-blind study comparing upadacitinib with abatacept, each in combination with a csDMARD treatment.

The study included adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to or tolerate pre-treatment with ≥ 1 bDMARD (except abatacept) for at least 3 months. Patients also had to have received treatment with csDMARD(s) in stable doses within the last 4 weeks before the first administration of the study medication and had to continue this treatment as concomitant treatment during the study. A total of 657 patients were randomised to upadacitinib + csDMARD(s) (N = 304) and abatacept + csDMARD(s) (N

= 309) at a ratio of 1:1. In addition to pre-treatment with bDMARD (failure on 1 or 2 bDMARDs with the same mechanism of action/failure on different mechanisms of action or ≥ 3 bDMARDs with the same mechanism of action), patients were stratified by geographic region. The planned double-blind, randomised treatment phase of the SELECT CHOICE study was 24 weeks. In the subsequent, still ongoing extension phase, all patients were switched to open treatment with upadacitinib. For the study, evaluations are available at the end of the randomised treatment phase of 24 weeks.

The primary endpoint of the study is the change in DAS28 (CRP) at week 12. In addition, patient-relevant endpoints on morbidity, health-related quality of life, and AEs were surveyed.

The analyses for the benefit assessment did not include those patients randomised up to and including protocol amendment 3 who received a non-approved daily dose of 30 mg upadacitinib in the intervention arm (N = 21 for upadacitinib, N = 23 for abatacept). Moreover, only a sub-population of the SELECT CHOICE study is relevant for answering the question of the benefit assessment. In the SELECT CHOICE study, the csDMARD treatment administered in stable doses within the last 4 weeks before study inclusion was continued. However, the concomitant treatment with csDMARDs allowed in the trial only corresponds to the marketing authorisation for a sub-population of the study because upadacitinib is approved only in combination with MTX or as monotherapy and abatacept only in combination with MTX. Therefore, for the present benefit assessment, only the sub-population receiving treatment with upadacitinib or abatacept in combination with MTX is relevant. These are 223 patients in the intervention arm and 215 in the comparator arm. During the study, predefined therapy adjustments were made from week 12 onwards if certain criteria for treatment response were not met. For the relevant sub-population, the pharmaceutical company does not provide information on how many patients received additional csDMARDs as a therapy adjustment from week 12 onwards. However, the data on the total population show that such an adjustment was made in only a few patients. For the present benefit assessment, it is therefore assumed that most patients in the relevant sub-population were also treated in accordance with the marketing authorisation of upadacitinib or abatacept during the course of the study.

Overall, evaluations of the relevant sub-population at week 24 are used for the present benefit assessment for patient population c2.

Extent and probability of the additional benefit

Mortality

The overall mortality for the relevant sub-population of the SELECT CHOICE study does not differ significantly between the two treatment groups at week 24.

Morbidity

The pharmaceutical company assesses morbidity by means of remission, low disease activity, disease-specific symptoms, patient-reported disease activity, physical functional status, health status.

Remission (CDAI ≤ 2.8; SDAI ≤ 3.3; Boolean definition according to ACR/EULAR)

A remission – measured by the Clinical Disease Activity Index (CDAI) – is considered patient-relevant. The CDAI is a clinical construct that comprises information on pressure-painful and swollen joints and disease activity reported on a VAS by both the patient and the examiner. Inflammation parameters such as CRP or ESR are not included in the calculation of the CDAI. The survey of effects via CDAI is thus considered to be more appropriate than constructs that include inflammation parameters, especially for active ingredients with direct influence on inflammation parameters.
A remission is operationalised by the achievement of a CDAI ≤ 2.8. At week 24, there was no statistically significant difference between the treatment groups in the SELECT CHOICE study based on a CDAI ≤ 2.8.

In the Boolean definition, there is also no statistically significant advantage or disadvantage for upadacitinib + MTX compared with abatacept + MTX at week 24.

However, for clinical remission operationalised via a SDAI ≤ 3.3, a statistically significant difference to the advantage of upadacitinib + MTX is shown.

In the overall view, no advantage can be derived for the endpoint remission for upadacitinib + MTX compared with abatacept + MTX because there are no consistent results across all operationalisations.

Low disease activity (CDAI ≤ 10; SDAI ≤ 11; DAS28 ESR ≤ 3.2; DAS28 CRP ≤ 3.2)

A low disease activity – measured by the Clinical Disease Activity Index (CDAI) – represents a patient-relevant endpoint. The CDAI is a clinical construct that comprises information on pressure-painful and swollen joints and disease activity reported on a VAS by both the patient and the examiner. A low disease activity by achieving a CDAI ≤ 10 represents a patient-relevant therapeutic goal. Similar to the remission endpoint, inflammation parameters such as CRP or ESR are not included in the calculation of the CDAI.

For the endpoint “low disease activity” (CDAI ≤ 10), the SELECT CHOICE study at week 24 showed no statistically significant difference between the intervention arm upadacitinib + MTX and the comparator arm abatacept + MTX when considering the entire sub-population. However, for CDAI ≤ 10, there is an effect modification by the characteristic disease activity at the start of study for high disease activity. This is defined by the threshold value of the DAS28 CRP. For patients with high disease activity at the start of study (DAS28 [CRP] > 5.1), there is a statistically significant advantage of upadacitinib + MTX compared with abatacept + MTX. However, for patients without high disease activity at the start of study (DAS28 [CRP] ≤ 5.1), there are no differences between treatment groups. The effect is confirmed with regard to statistical significance in the sensitivity analyses using alternative replacement strategies.

The endpoint low disease activity was also assessed at week 24 of the SELECT CHOICE study using the SDAI, the DAS28 CR, and the DAS28 ESR.
For SDAI ≤ 11, there is also an effect modification by the characteristic disease activity at the start of study for high disease activity. This is defined by the threshold value of the DAS28 CRP. For patients with high disease activity at the start of study (DAS28 [CRP] > 5.1), at week 24, there is a statistically significant advantage of upadacitinib + MTX compared with abatacept + MTX. However, for patients without high disease activity at the start of study (DAS28 [CRP] ≤ 5.1), there are no differences between treatment groups. This supports the results available for the “low disease activity” operationalised via the CDAI.

The further operationalisations via DAS28 CRP ≤ 3.2 and DAS28 ESR ≤ 3.2 each show statistically significant, comparable benefits for upadacitinib + MTX compared with the comparative intervention abatacept + MTX at week 24 independent of disease activity at the start of study.

Against the background of the effect modification shown by the characteristic disease activity in the two operationalisations CDAI and SDAI, it is appropriate to differentiate between two patient groups when deriving the additional benefit. For patients with high disease activity at the start of study (DAS28 [CRP] > 5.1), an advantage for upadacitinib + MTX compared with abatacept + MTX can be derived for the endpoint "low disease activity". However, no advantage can be derived for patients without high disease activity at the start of study (DAS28 [CRP] ≤ 5.1).

Physical functional status (improvement of HAQ-DI by ≥ 0.22 points)

For the patient-relevant endpoint of physical functional status (improvement of HAQ-DI by ≥ 0.22 points), there was no statistically significant difference between the treatment groups in at week 24 of the SELECT CHOICE study.

Fatigue (improvement of FACIT-F by ≥ 4 points)

For the patient-relevant endpoint fatigue, there was no statistically significant difference between upadacitinib + MTX and abatacept + MTX for the proportion of patients with an improvement of ≥ 4 points at week 24 of the SELECT CHOICE study.

Number of pressure-painful joints

For the endpoint "pressure-painful joints", no statistically significant difference between upadacitinib + MTX and abatacept + MTX was found at week 24 based on mean differences.

Number of swollen joints

For the evaluation based on 28 joints, no statistically significant advantage or disadvantage upadacitinib + MTX compared was abatacept + MTX was determined at week 24 based on the mean differences.

Pain (VAS)

The SELECT COMPARE study showed no statistically significant difference between upadacitinib + MTX and abatacept + MTX for the mean change at week 26.

Patient-reported assessment of disease activity (VAS)

For this endpoint, there was no statistically significant difference between the treatment groups.

Morning stiffness: Severity [NRS] and duration

For the severity (NRS) of morning stiffness, there was a statistically significant effect in favour of upadacitinib + MTX compared with abatacept + MTX at week 24. However, the 95% CI of the SMD in the form of Hedges' g is not completely outside of the irrelevant range of −0.2 to 0.2. It is therefore not possible to derive whether the effect is clinically relevant. For the duration of morning stiffness, there was no statistically significant difference between the treatment groups.

Health status (EQ-5D VAS)

For the mean change in EQ-5D VAS, the SELECT CHOICE study showed a statistically significant benefit in favour of upadacitinib + MTX at week 24. To assess the relevance of the findings, the standardised mean difference (SMD) in the form of Hedges' g was considered. However, the 95% CI of the SMD is not completely outside the irrelevance range of −0.2 to 0.2. Thus, it cannot be concluded that the effect is clinically relevant.

Quality of life

Health Survey Short Form 36 (SF-36) (improvement of SF-36 by ≥ 5 points)

Neither the physical component score nor the mental component score of SF-36v2 showed a statistically significant difference between upadacitinib + MTX and Abatacept + MTX in the evaluation of the proportion of patients with an improvement of ≥ 5 points in the SELECT CHOICE study.

Side effects

SAE, discontinuation because of AE

For the endpoints SAE as well as discontinuation because of AE, no statistically significant advantages or disadvantages of upadacitinib + MTX compared with abatacept + MTX were shown at week 24 in the SELECT CHOICE study.

Infections, serious infections

For the patient-relevant endpoints infections and serious infections, there was no statistically significant difference between upadacitinib + MTX and abatacept + MTX in the SELECT CHOICE study at week 24.

Overall assessment/conclusion

For adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these; evaluations are available for the comparison of upadacitinib + MTX with abatacept + MTX in a sub-population of the directly comparative SELECT CHOICE study at week 24.

In summary, there is no difference in mortality at week 24 between the treatment groups.

In the morbidity category, for remission at week 24 (operationalised via SDAI ≤ 3.3), there was consistent advantage for upadacitinib + MTX compared with abatacept + MTX across all operationalisations presented. In the endpoint low disease activity, operationalisations via CDAI and SDAI show an effect modification by the characteristic "disease activity at the start of study"; this justifies a separate consideration of the patient groups. Because there is a statistically significant advantage of upadacitinib + MTX compared with abatacept + MTX for patients with high disease activity at the start of study (DAS28 [CRP] > 5.1), especially for operationalisation via CDAI, an advantage can be derived in this patient group. However, no overall advantage in this endpoint can be derived for patients without high disease activity at the start of study (DAS28 [CRP] ≤ 5.1). For the endpoints severity of morning stiffness and health status, there are effects in favour of upadacitinib + MTX compared with abatacept + MTX are available. However, the clinical relevance of these cannot be assessed with sufficient certainty. On the other hand, in the other morbidity endpoints fatigue, physical functional status (HAQ-DI), number of pressure-painful and swollen joints, pain, patient-reported disease activity, and the duration of morning stiffness, there were no statistically significant differences between upadacitinib + MTX and the appropriate comparator therapy abatacept + MTX.

In the quality of life category, there is no statistically significant difference between the treatment groups upadacitinib + MTX and abatacept + MTX.

In the side effects category, no advantages or disadvantages can be deduced for upadacitinib + MTX compared with abatacept + MTX at week 24.

In the overall view, the effect modification for the characteristic disease activity at the start of study – defined via the threshold value of the DAS28 (CRP) – is used to derive the additional benefit in the sub-population relevant here. Based on the SELECT CHOICE study, at week 24, for patients with high disease activity at the start of study (DAS28 [CRP] > 5.1), for the endpoint low disease activity, there was an overall advantage for upadacitinib + MTX compared with abatacept + MTX, while there were no disadvantages seen. The positive effects of upadacitinib + MTX in the low disease activity compared with the appropriate comparator therapy are assessed as a moderate improvement of the therapy-relevant benefit that has not been achieved so far. Despite the lack of clinically relevant benefits in symptomatology and quality of life, there was an advantage for upadacitinib + MTX compared with abatacept + MTX, particularly in the endpoint low disease activity. In contrast, at week 24, based on the SELECT CHOICE study for patients without high disease activity at the start of study (DAS28 [CRP] ≤ 5,1), upadacitinib + MTX showed neither advantages nor disadvantages compared with abatacept + MTX in all categories.

Based on these considerations, the information in the dossier, and the results of the benefit assessment, the extent of additional benefit for upadacitinib in combination with MTX is considered low for patients with high disease activity at the start of study (DAS28 [CRP] > 5.1) compared with the appropriate comparator therapy abatacept + MTX for the treatment adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these. For patients without high disease activity at the start of study (DAS28 [CRP] ≤ 5.1), the additional benefit is not proven.

Reliability of data (probability of additional benefit)

Patient population c2A (patients with high disease activity (DAS28 [CRP] > 5.1))
The SELECT CHOICE study is a randomised, double-blind Phase III study for the assessment of the additional benefit.

The risk of bias at the study level is classified as low across all endpoints. At the endpoint level, there is a high risk of bias for the endpoints remission and low disease activity as well as total mortality and side effects. The bias for the other endpoints is estimated to be low. The high risk of bias for the endpoints remission and low disease activity is based on the high proportion of patients evaluated as non-responders because of missing values. Despite sensitivity analyses, for the endpoints remission and low disease activity, the existing uncertainties for the benefit assessment cannot be fully addressed. There are also uncertainties regarding the reliability of data on overall mortality and side effects because of the different follow-up times between the therapy arms.

In the overall view, the uncertainties described justify a downgrading of the reliability of data to a hint for an additional benefit.

Patient population c2B (patients without high disease activity (DAS28 [CRP] ≤ 5.1))

Not applicable

2.1.4 Summary of the assessment

The present assessment refers to the benefit assessment of the medicinal product Rinvoq® with the active ingredient upadacitinib. The therapeutic indication assessed here is as follows: "for the treatment of moderate to severe active rheumatoid arthritis in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying anti-rheumatic drugs (DMARDs). RINVOQ may be used as monotherapy or in combination with methotrexate".

For the benefit assessment, the following patient groups were distinguished:

a) Adult patients with moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors[2] and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventional DMARDs, including methotrexate (MTX)) or did not tolerate it
   a1) Upadacitinib as monotherapy
   a2) Upadacitinib in combination with MTX

b) Adult patients with moderate to severe active rheumatoid arthritis for whom first-line therapy with biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated
   b1) Upadacitinib as monotherapy
   b2) Upadacitinib in combination with MTX

c) Adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these
   c1) Upadacitinib as monotherapy
   c2A) Upadacitinib in combination with MTX; patients with high disease activity [DAS28 CRP ≤ 5.1]
   c2B) Upadacitinib in combination with MTX; patients without high disease activity [DAS28 CRP ≤ 5.1]

Patient group a1)

The G-BA determined alternative conventional DMARDs (e.g. MTX, leflunomide) as an appropriate comparator therapy provided that they are suitable as mono- or combination therapy For this patient group, the pharmaceutical company does not provide any data with the dossier for the assessment of the additional benefit. For adult patients with moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors[2] and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventional DMARDs, including methotrexate (MTX)) or did not tolerate it, the additional benefit of upadacitinib as monotherapy compared with the appropriate comparator therapy is not proven.

Patient group a2)

The G-BA determined alternative conventional DMARDs (e.g. MTX, leflunomide) as an appropriate comparator therapy provided that they are suitable as mono- or combination therapy For this patient group, the pharmaceutical company does not provide any data with the dossier for the assessment of the additional benefit. For adult patients with moderate to severe active rheumatoid arthritis for whom there are no unfavourable prognostic factors[2] and who did not respond adequately to previous treatment with a disease-modifying anti-rheumatic agent (conventional DMARDs, including methotrexate (MTX)) or did not tolerate it, the additional benefit of upadacitinib in combination with MTX compared with the appropriate comparator therapy is not proven.

Patient group b1)

The G-BA determined the appropriate comparator therapy to be bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability). For this patient group, the pharmaceutical company does not provide any data with the dossier for the assessment of the additional benefit of upadacitinib as monotherapy. For adult patients with moderate to severe active rheumatoid arthritis for whom first-line therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated, the additional benefit of upadacitinib as monotherapy compared with the appropriate comparator therapy in not proven.

Patient group b2)

The G-BA determined the appropriate comparator therapy to be bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability).

For this patient group, for the comparison of upadacitinib + MTX with adalimumab + MTX at week 26 of the directly comparative SELECT COMPARE study are available.

In summary, the data presented show statistically significant advantages for upadacitinib + MTX compared with adalimumab + MTX in the morbidity category for remission, low disease activity, and fatigue. For the physical functional status (HAQ-DI), there is a statistically significant advantage for upadacitinib + MTX compared with adalimumab + MTX; this is not confirmed in the sensitivity analysis. For the morbidity endpoints number of pressure-painful joints, pain, patient-reported disease activity, and severity of morning stiffness, there are statistically significant effects in favour of upadacitinib + MTX. However, the clinical relevance of these cannot be assessed with sufficient certainty. For the endpoints health status, number of swollen joints and duration of morning stiffness, there were no statistically significant differences between upadacitinib + MTX and the appropriate comparator therapy adalimumab + MTX. In the quality of life category, there was a statistically significant advantage for

upadacitinib + MTX in the physical component score of the SF-36v2; this was not confirmed in the sensitivity analysis. With respect to the psychological component score of the Sf-36v2, there was neither an advantage nor a disadvantage for upadacitinib + MTX compared with adalimumab + MTX at week 26. In the side effects category, no advantages or disadvantages can be deduced for upadacitinib + MTX compared with adalimumab + MTX at week 26.

In the overall view, for upadacitinib + MTX at week 26, there are advantages in morbidity and health-related quality of life (SF-36 physical component score); these are not offset by disadvantages in other categories. Consequently, for adult patients with moderate to severe rheumatoid arthritis who are candidates for bDMARD or tsDMARD therapy for the first time, for upadacitinib in combination with MTX, there is a hint for a considerable additional benefit compared with the appropriate comparator therapy adalimumab + MTX.

Patient group c1)

The G-BA determined the appropriate comparator therapy to be the change of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability; or in patients with severe rheumatoid arthritis rituximab, taking into account the marketing authorisation) depending on the previous therapy. For this patient group, the pharmaceutical company does not provide any data with the dossier for the assessment of the additional benefit of upadacitinib as Monotherapy. For adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these, the additional benefit of upadacitinib as monotherapy compared with the appropriate comparator therapy is not proven.

Patient group c2A)

The G-BA determined the appropriate comparator therapy to be the change of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability; or in patients with severe rheumatoid arthritis rituximab, taking into account the marketing authorisation) depending on the previous therapy.

For this patient group, the pharmaceutical company presents the results of a sub-population of the directly comparative SELECT CHOICE Phase III study to compare upadacitinib with abatacept, each in combination with MTX.

In summary, there is no difference in mortality at week 24 between the treatment groups. In the morbidity category, at week 24, for patients with high disease activity at the start of study [DAS28 CRP > 5.1], there were statistically significant advantages for upadacitinib + MTX compared with abatacept + MTX in the endpoint low disease activity across all operationalisations, especially for the operationalisation via the CDAI. For the endpoints severity of morning stiffness and health status, there are effects in favour of upadacitinib + MTX compared with abatacept + MTX available. However, the clinical relevance of these cannot be assessed with sufficient certainty. In the other morbidity endpoints fatigue, physical functional status (HAQ-DI), number of pressure-painful and swollen joints, pain, patient-reported disease activity, and the duration of morning stiffness, there were no statistically significant differences between upadacitinib + MTX and the appropriate comparator therapy abatacept + MTX. No benefit can be derived from the statistically significant difference of upadacitinib + MTX compared with abatacept + MTX in the endpoint remission operationalised via the SDAI ≤ 3.3 because this is not confirmed in other operationalisations. At week 24, there were no statistically significant differences between upadacitinib + MTX and abatacept + MTX in the categories quality of life and side effects.

In the overall view, in the relevant sub-population at week 24, there are exclusively positive effects for upadacitinib + MTX compared with abatacept + MTX with no disadvantages. Consequently, for adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these, for upadacitinib in combination with MTX for patients with high disease activity at the start of study (DAS28 [CRP] > 5.1), a hint for a minor additional benefit compared with the appropriate comparator therapy abatacept + MTX can be derived.

Patient group c2B)

The G-BA determined the appropriate comparator therapy to be the change of bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab-pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib, in combination with MTX; if necessary as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability; or in patients with severe rheumatoid arthritis rituximab, taking into account the marketing authorisation) depending on the previous therapy.

For this patient group, the pharmaceutical company presents the results of a sub-population of the directly comparative SELECT CHOICE Phase III study to compare upadacitinib with abatacept, each in combination with MTX.

In summary, there is no difference in mortality at week 24 between the treatment groups. In the endpoint low disease activity, no overall benefit can be derived for patients without high disease activity at the start of study (DAS28 [CRP] ≤ 5.1). For the endpoints severity of morning stiffness and health status, there are effects in favour of upadacitinib + MTX compared with abatacept + MTX are available. However, the clinical relevance of these cannot be assessed with sufficient certainty. In the other morbidity endpoints fatigue, physical functional status (HAQ-DI), number of pressure-painful and swollen joints, pain, patient-reported disease activity, and the duration of morning stiffness, there were no statistically significant differences between upadacitinib + MTX and the appropriate comparator therapy abatacept + MTX. No benefit can be derived from the statistically significant difference of upadacitinib + MTX compared with abatacept + MTX in the endpoint remission operationalised via the SDAI ≤ 3.3 because this is not confirmed in other operationalisations. At week 24, there were no statistically significant differences between upadacitinib + MTX and abatacept + MTX in the categories quality of life and side effects.

In the overall view, in the relevant sub-population at week 24, for patients without high disease activity at the start of study (DAS28 [CRP] ≤ 5.1), there were neither advantages nor disadvantages for upadacitinib + MTX compared with abatacept + MTX in all categories. For adult patients with moderate to severe active rheumatoid arthritis who did not respond adequately to previous treatment with one or more bDMARDs and/or tsDMARDs or did not tolerate these, the additional benefit of upadacitinib + MTX compared with the appropriate comparator therapy abatacept + MTX for patients without high disease activity at the start of study (DAS28 [CRP] ≤ 5.1) is not proven.

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

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

The data are based on patient numbers. For patient population a, these are based on the information of the pharmaceutical company from the dossier, taking into account more recent sources on prevalence. For patient populations b and c, the patient numbers from the previous resolution of the G-BA in the indication area rheumatoid arthritis from 2017 and 2018[5] are

[5] Resolution of 21.September 2017 on baricitinib; resolution 19 October 2017 and 1 November 2018 on tofacitinib; resolution of 15 February 2018 on sarilumab.

taken into account. The number of patients in the SHI target population is of a plausible order of magnitude even if these figures are subject to uncertainties for the individual questions.

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: 30 June 2020):

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

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training material as well as a patient identification card. The training material for healthcare professionals includes instructions on how to deal with the possible side effects of upadacitinib, in particular severe and opportunistic infections, including TB and shingles.

Treatment should be started by a doctor experienced in the diagnosis and treatment of rheumatoid arthritis.

The use of the medicinal product must also be carefully considered against the background of a comparatively new principle of action and the associated remaining uncertainties in the risk profile compared with established therapies.

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 2020).

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 between individual treatments, and for the maximum treatment duration if specified in the product information.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments per patient per year	Treatment duration per treatment (days)	Treatment days per patient per year
Medicinal product to be assessed				

Designation of the therapy	Treatment mode	Number of treatments per patient per year	Treatment duration per treatment (days)	Treatment days per patient per year
Upadacitinib	continuously, 1 × daily	365	1	365
possible methotrexate	continuously; 1 × every 7 days	52.1	1	52.1
Appropriate comparator therapy for patient population a				
Methotrexate	continuously; 1 × every 7 days	52.1	1	52.1
Leflunomide	continuously, 1 × daily	365	1	365
Sulfasalazine	continuously, 2–3 × daily	365	1	365
Chloroquine phosphate	continuously, 1 × daily	322	1	322[6]
Hydroxychloroquine sulphate	continuously, 2 × daily[7]	365	1	365
Appropriate comparator therapy for patient population b				
Methotrexate	continuously; 1 × every 7 days	52.1	1	52.1
Adalimumab	continuously, every 14 days	26.1	1	26.1
Etanercept	continuously, every 14 days	26.1	1	26.1
Certolizumab pegol	continuously, every 14 days	26.1	1	26.1
Golimumab	continuously, 1 × monthly	12	1	12.0

[6] According to the product information, cumulative total doses of 1 g chloroquine per kilogram body weight or 50–100 g total dose can lead to retinal damage. A cumulative total dose of 50 g chloroquine should therefore not be exceeded. As a result, with a daily intake of 250 mg chloroquine phosphate, the cumulative total dose of 50 g chloroquine is reached after 322 therapy days. Thus, a maximum of 322 treatment days per year are included in the annual treatment costs.

[7] For hydroxychloroquine sulphate, the product information for the treatment of rheumatoid arthritis recommends a maintenance dose of one film-coated tablet 1–2 times daily, which corresponds to a dosage of 200–400 mg/day; the dosage must be adjusted according to weight. For an assumed weight of 76.3 kg, the recommended daily dosage is 2 tablets of 200 mg each. The initial dose of 400–600 mg 2–3 times a day is not considered for the cost calculation.

Designation of the therapy	Treatment mode	Number of treatments per patient per year	Treatment duration per treatment (days)	Treatment days per patient per year
Abatacept	continuously; 1 × every 7 days	52.1	1	52.1
Tocilizumab	continuously; 1 × every 7 days	52.1	1	52.1
Baricitinib	continuously, 1 × daily	365	1	365
Sarilumab	continuously; 1 × every 14 days	26.1	1	26.1
Tofacitinib	continuously, 1–2 × daily	365	1	365
Infliximab[8]	continuously, every 56 days	6.5	1	6.5
Appropriate comparator therapy for patient population c				
Methotrexate	continuously; 1 × every 7 days	52.1	1	52.1
Adalimumab	continuously, every 14 days	26.1	1	26.1
Etanercept	continuously, every 14 days	26.1	1	26.1
Certolizumab pegol	continuously, every 14 days	26.1	1	26.1
Golimumab	continuously, 1 × monthly	12	1	12.0
Abatacept	continuously; 1 × every 7 days	52.1	1	52.1
Tocilizumab	continuously; 1 × every 7 days	52.1	1	52.1
Rituximab	1 × on Day 1 and 15 of an at least 182-day cycle[9]	2	1–2	2–4

[8] Infliximab can also be used subcutaneously as maintenance treatment. The presentation in the cost calculation is limited to the fixed-price intravenous infusion therapy.

[9] The need for further treatment cycles should be assessed 24 weeks after the previous cycle. At this time, further treatment should be given if residual disease activity is still present. Otherwise, further treatment should be delayed until the disease activity increases again. This results in a maximum of 2 cycles within one year.

Designation of the therapy	Treatment mode	Number of treatments per patient per year	Treatment duration per treatment (days)	Treatment days per patient per year
Baricitinib	continuously, 1 × daily	365	1	365
Sarilumab	continuously; 1 × every 14 days	26.1	1	26.1
Tofacitinib	continuously, 1–2 × daily	365	1	365
Infliximab[8]	continuously, every 56 days	6.5	1	6.5

Usage and consumption:

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 Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates. If a fixed reimbursement rate is available, this will be used as the basis for the cost calculation.

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

For the calculation of the dosages as a function of body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average body weight): 77.0 kg)[10].

Designation of the therapy	Dosage/use	Dose/ patient/ Treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Medicinal product to be assessed					
Upadacitinib	15 mg	15 mg	1 × 15 mg	365	365 × 15 mg
possible methotrexate	7.5 mg – 20 mg	7.5 mg –	1 × 7.5 mg – 2 × 10 mg	52.1	52.1 × 7.5 mg – 104.2 × 10 mg

[10] German Federal Office For Statistics, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/use	Dose/ patient/ Treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
		20 mg			
Appropriate comparator therapy for patient populations a1 + a2					
Methotrexate	7.5 mg – 20 mg	7.5 mg – 20 mg	1 × 7.5 mg – 2 × 10 mg	52.1	52.1 × 7.5 mg – 104.2 × 10 mg
Leflunomide	10 mg – 20 mg	10 mg – 20 mg	1 × 10 mg – 1 × 20 mg	365	365 × 10 mg – 365 × 20 mg
Sulfasalazine	1,000 mg – 1,500 mg	2,000 mg – 3,000 mg	4 × 500 mg – 6 × 500 mg	365	1,460 × 500 mg – 2,190 × 500 mg
Chloroquine phosphate	250 mg	250 mg	1 × 250 mg	322	322 × 250 mg
Hydroxychloroquine sulphate	200 mg	400 mg	2 × 200 mg	365	730 × 200 mg
Appropriate comparator therapy for patient populations b1 + b2					
Monotherapies					
Adalimumab	40 mg	40 mg	1 × 40 mg	26.1	26.1 × 40 mg
Etanercept	50 mg	50 mg	50 mg	26.1	26.1 × 50 mg
Certolizumab pegol	200 mg	200 mg	1 × 200 mg	26.1	26.1 × 200 mg
Tocilizumab	162 mg	162 mg	1 × 162 mg	52.1	52.1 × 162 mg
Baricitinib	4 mg	4 mg	1 × 4 mg	365	365 × 4 mg
Sarilumab	200 mg	200 mg	200 mg	26.1	26.1 × 200 mg
Tofacitinib	5 mg	10 mg	2 × 5 mg	365	730 × 5 mg
	or				
	11 mg	11 mg	1 × 11 mg	365	365 × 11 mg
Combination therapies with methotrexate					
Methotrexate	7.5 mg – 20 mg	7.5 mg – 20 mg	1 × 7.5 mg – 2 × 10 mg	52.1	52.1 × 7.5 mg – 104.2 × 10 mg

Designation of the therapy	Dosage/use	Dose/ patient/ Treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Adalimumab	40 mg	40 mg	1 × 40 mg	26.1	26.1 × 40 mg
Etanercept	50 mg	50 mg	50 mg	26.1	26.1 × 50 mg
Certolizumab pegol	200 mg	200 mg	1 × 200 mg	26.1	26.1 × 200 mg
Golimumab	50 mg	50 mg	1 × 50 mg	12	12 × 50 mg
Abatacept	125 mg	125 mg	1 × 125 mg	52.1	52.1 × 125 mg
Tocilizumab	162 mg	162 mg	1 × 162 mg	52.1	52.1 × 162 mg
Baricitinib	4 mg	4 mg	1 × 4 mg	365	365 × 4 mg
Sarilumab	200 mg	200 mg	200 mg	26.1	26.1 × 200 mg
Tofacitinib	5 mg	10 mg	2 × 5 mg	365	730 × 5 mg
	or				
	11 mg	11 mg	1 × 11 mg	365	365 × 11 mg
Infliximab	3 mg/kg BW (231 mg) – 7.5 mg/kg BW (577.5 mg)	231 mg – 577.5 mg	3 × 100 mg – 6 × 100 mg	6.5	19.5 × 100 mg – 39 × 100 mg
Appropriate comparator therapy for patient populations c1 + c2					
Monotherapies					
Adalimumab	40 mg	40 mg	1 × 40 mg	26.1	26.1 × 40 mg
Etanercept	50 mg	50 mg	50 mg	26.1	26.1 × 50 mg
Certolizumab pegol	200 mg	200 mg	1 × 200 mg	26.1	26.1 × 200 mg
Tocilizumab	162 mg	162 mg	1 × 162 mg	52.1	52.1 × 162 mg
Baricitinib	4 mg	4 mg	1 × 4 mg	365	365 × 4 mg
Sarilumab	200 mg	200 mg	200 mg	26.1	26.1 × 200 mg
Tofacitinib	5 mg	10 mg	2 × 5 mg	365	730 × 5 mg
	or				
	11 mg	11 mg	1 × 11 mg	365	365 × 11 mg
Combination therapies with methotrexate					

Designation of the therapy	Dosage/use	Dose/ patient/ Treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Annual average consumption by potency
Methotrexate	7.5 mg – 20 mg	7.5 mg – 20 mg	1 × 7.5 mg – 2 × 10 mg	52.1	52.1 × 7.5 mg – 104.2 × 10 mg
Adalimumab	40 mg	40 mg	1 × 40 mg	26.1	26.1 × 40 mg
Etanercept	50 mg	50 mg	50 mg	26.1	26.1 × 50 mg
Certolizumab pegol	200 mg	200 mg	1 × 200 mg	26.1	26.1 × 200 mg
Golimumab	50 mg	50 mg	1 × 50 mg	12	12 × 50 mg
Abatacept	125 mg	125 mg	1 × 125 mg	52.1	52.1 × 125 mg
Tocilizumab	162 mg	162 mg	1 × 162 mg	52.1	52.1 × 162 mg
Baricitinib	4 mg	4 mg	1 × 4 mg	365	365 × 4 mg
Sarilumab	200 mg	200 mg	200 mg	26.1	26.1 × 200 mg
Tofacitinib	5 mg	10 mg	2 × 5 mg	365	730 × 5 mg
	or				
	11 mg	11 mg	1 × 11 mg	365	365 × 11 mg
Rituximab	1,000 mg	1,000 mg	2 × 500 mg	2–4	4–8 × 500 mg
Infliximab	3 mg/kg BW (231 mg) –	231 mg –	3 × 100 mg –	6.5	19.5 × 100 mg –
	7.5 mg/kg BW (577.5 mg)	577.5 mg	6 × 100 mg		39 × 100 mg

Costs of the medicinal product:

Designation of the therapy	Package 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	€ 4,088.49	€ 1.77	€ 230.22	€ 3,856.50

Designation of the therapy	Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Methotrexate 7.5 mg[11]	30 TAB	€ 33.47	€ 1.77	€ 1.77	€ 29.93
Methotrexate 10 mg[11]	30 TAB	€ 41.35	€ 1.77	€ 2.40	€ 37.18
Appropriate comparator therapy					
Abatacept 125 mg	12 PEN	€ 4,559.56	€ 1.77	€ 257.12	€ 4,300.67
Adalimumab 40 mg	6 SFI	€ 2,804.69	€ 1.77	€ 156.90	€ 2,646.02
Baricitinib 4 mg	98 FCT	€ 4,078.46	€ 1.77	€ 229.65	€ 3,847.04
Certolizumab pegol 200 mg	6 SFI	€ 4,761.98	€ 1.77	€ 268.68	€ 4,491.53
Chloroquine phosphate 250 mg[11, 12]	100 TAB	€ 27.97	€ 1.77	€ 1.34	€ 24.86
Etanercept 50 mg[11]	12 SFI	€ 4,231.41	€ 1.77	€ 340.54	€ 3,889.10
Golimumab 50 mg	3 SFI	€ 5,483.76	€ 1.77	€ 309.90	€ 5,172.09
Hydroxychloroquine 200 mg[11]	100 FCT	€ 27.97	€ 1.77	€ 1.34	€ 24.86
Infliximab 100 mg[11]	5 PIS	€ 3,490.29	€ 1.77	€ 280.08	€ 3,208.44
Leflunomide 10 mg[11]	100 FCT	€ 179.90	€ 1.77	€ 13.36	€ 164.77
Leflunomide 20 mg[11]	100 FCT	€ 280.35	€ 1.77	€ 21.30	€ 257.28
Methotrexate 7.5 mg[11]	30 TAB	€ 33.47	€ 1.77	€ 1.77	€ 29.93
Methotrexate 10 mg[11]	30 TAB	€ 41.35	€ 1.77	€ 2.40	€ 37.18
Rituximab 500 mg	1 CIS	€ 1,777.06	€ 1.77	€ 98.21	€ 1,677.08
Sarilumab 200 mg	6 SFI	€ 4,216.13	€ 1.77	€ 237.51	€ 3,976.85
Sulfasalazine 500 mg	400 TMR	€ 98.58	€ 1.77	€ 6.92	€ 89.89
Tocilizumab 162 mg	12 SFI	€ 5,403.56	€ 1.77	€ 305.32	€ 5,096.47
Tofacitinib 11 mg	91 RET	€ 3,296.59	€ 1.77	€ 0.00	€ 3,294.82
Tofacitinib 5mg	182 FCT	€ 3,296.59	€ 1.77	€ 0.00	€ 3,294.82
Abbreviations: FCT = film-coated tablets; CIS = concentrate for the preparation of an infusion solution; SFI = solution for injection; PEN = injection solution in a prefabricated pen; PIS = powder for the preparation of an infusion solution; SRT = sustained-release tablets; TAB = tablets; TMR = tablets magnesia resistant.					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 June 2020

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 assessed 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

[11] Fixed reimbursement rate
[12] Chloroquine is currently available only as an imported medicinal product on the German market.

(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 active ingredients of the appropriate comparator therapy of the patient populations b and c (abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab, and tofacitinib), costs are regularly incurred for testing both active and inactive (latent) tuberculosis infections. The costs shown 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)) as well as a thoracic X-ray. The tuberculin skin test is not mapped because of lack of sensitivity and specificity as well as the possibility of "sensitisation". These studies are also required for the use of upadacitinib.

In addition, patients must be tested for the presence of HBV infection before treatment with abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or rituximab, or tofacitinib is initiated. These studies are not required for the use of sarilumab and tocilizumab as an appropriate comparator therapy but are regularly required for the use of upadacitinib as the medicinal product to be assessed. For the diagnosis of a suspected chronic hepatitis B, well coordinated steps are necessary[13]. A serological step-by-step diagnostic initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If the HBs antigen is positive, an active HBV infection has been detected.

Overall, for the patient populations b and c, there is no regular difference between the medicinal product to be evaluated and the appropriate comparator therapy with regard to examinations for tuberculosis infections. The presentation of the costs for additionally required SHI services in the resolution on examinations for tuberculosis infections is thus omitted. Deviating from this, additionally required SHI services for the diagnosis of suspected chronic hepatitis B are incurred. These regularly differ between the medicinal product to be assessed and the appropriate comparator therapy and are therefore considered additionally required SHI services in the resolution.

Designation of the therapy	Description of the service	Number	Costs per unit	Costs per patient per year
Medicinal product to be assessed: Upadacitinib Appropriate comparator therapy for patient population b and c				
Upadacitinib Abatacept Adalimumab Baricitinib Certolizumab pegol Etanercept Golimumab Infliximab Rituximab Sarilumab Tocilizumab	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 for BCG)	1	€ 58.00	€ 58.00

[13] "Update of the S3 guideline on prophylaxis, diagnosis and therapy of hepatitis B virus infection; AWMF register no.: 021/011" http://www.dgvs.de/fileadmin/user_upload/Leitlinien/Hepatitis_B/Leitlinie_Hepatitis_B.pdf

Designation of the therapy	Description of the service	Number	Costs per unit	Costs per patient per year
Tofacitinib	(GOP 32670)			
Upadacitinib Abatacept Adalimumab Baricitinib Certolizumab pegol Etanercept Golimumab Infliximab Rituximab Sarilumab Tocilizumab Tofacitinib	Chest radiograph (GOP 34241)	1	€ 16.04	€ 16.04
Upadacitinib Abatacept Adalimumab Baricitinib Certolizumab pegol Etanercept Golimumab Infliximab Rituximab Tofacitinib	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	anti-HBs antibody (GOP 32617)[14]	1	€ 5.50	€ 5.50
	anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)[15]	1	€ 89.50	€ 89.50

Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 11. Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

[14] Only if HBs antigen negative and anti-HBc antibody positive
[15] Settlement of GOP 32823 possible before or during antiviral therapy with interferon and/or nucleic acid analogues.

3. Bureaucratic costs

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 26 March 2019.

On 16 January 2020, the pharmaceutical company submitted a dossier for the benefit assessment of upadacitinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 16 January 2020 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient upadacitinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 April 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 4 May 2020. The deadline for submitting written statements was 25 May 2020.

The oral hearing was held on 8 June 2020.

On 17 June 2020, IQWiG submitted a new version of the IQWiG dossier evaluation to the G-BA. Version 1.1 of 17 June 2020 replaces version 1.0 of the dossier evaluation of 29 April 2020. The evaluation result was not affected by the changes in version 1.1 compared with version 1.0.

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 were discussed at the session of the subcommittee on 7 July 2020, and the proposed resolution was approved.

At its session on 16 July 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	26 March 2019	Determination of the appropriate comparator therapy
Working group Section 35a	3 June 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	8 June 2020	Conduct of the oral hearing

Working group Section 35a	16 June 2020 30 June 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	7 July 2020	Concluding discussion of the draft resolution
Plenum	16 July 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 16 July 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken