Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Tofacitinib (new scientific knowledge (Section 13): rheumatoid arthritis, pretreated patients, monotherapy or combination with methotrexate)

of 17 February 2022

Contents

1. Legal basis

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

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

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

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

2. Key points of the resolution

The active ingredient tofacitinib (Xeljanz) was first marketed on 1 May 2017. By resolution of 18 March 2021, the G-BA, at the request of its members, initiated a new benefit assessment pursuant to Section 35a (1) SGB V in conjunction with Section 3 (1) No. 4 AM-NutzenV and Chapter 5 Section 13 of the Rules of Procedure (VerfO) for the active ingredient tofacitinib. The new benefit assessment was initiated on the basis of new scientific knowledge including the A3921133 study (ORAL SURVEILLANCE; NCT number NCT02092467).

The relevant date for active ingredient tofacitinib in accordance with Chapter 5, Section 8, paragraph 1, number 6 of the Rules of Procedure of the G-BA (VerfO) is 1 September 2021. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 4 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 6 VerfO on 31 August 2021.

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 1 December 2021, 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 tofacitinib 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, the statements submitted in the written statement and oral hearing procedure, and the addendum to the benefit assessment prepared by IQWiG. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of tofacitinib.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Tofacitinib (Xeljanz) according to product information

Tofacitinib in combination with methotrexate (MTX) is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs) (see section 5.1). Tofacitinib can be given as monotherapy in case of intolerance to MTX or when treatment with MTX is unsuited (see sections 4.4 and 4.5).

Therapeutic indication of the resolution (resolution of 17.02.2022):

Treatment of moderate to severe active rheumatoid arthritis (RA) in adults who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs and are eligible for treatment with tofacitinib.

Relevant patient population

According to a review of the safety profile of tofacitinib under the EMA's PRAC procedure, given the increased risk of serious infections, myocardial infarction and malignancies associated with tofacitinib in patients 65 years and older and due to major adverse cardiovascular events (MACE), tofacitinib should only be used in adults 65 years and older, former smokers, patients with cardiovascular risk factors and patients with other risk factors for malignancies if no appropriate treatment alternatives are available. In this context, reference is also made to the product information of tofacitinib[2] under 4.4. Overall, for the reassessment of tofacitinib the scientific knowledge therefore results in an assessment-relevant patient population that differs from the initial assessment and from the formally

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.
[2] FI Xeljanz: Tofacitinib 5 mg/10 mg film-coated tablets as of 11/2021 and 11 mg sustained-release tablets as of 09/2021.

approved population of adults with moderate to severe active rheumatoid arthritis (RA), who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs, particularly with regard to age, smoking status, presence of cardiovascular risk factors and risk factors for malignancies.

Specifically, the product information for tofacitinib[2] provides the following relevant limitations for patients with rheumatoid arthritis under 4.4:

Use in patients over 65 years of age
Considering the increased risk of serious infections, myocardial infarction, and malignancies with tofacitinib in patients over 65 years of age, tofacitinib should only be used in these patients if no suitable treatment alternatives are available.

Venous thromboembolism (VTE)
[...] Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage. [...] VTE risk factors include previous VTE, patients undergoing major surgery, immobilisation, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy. Additional VTE risk factors such as age, obesity (BMI ≥30), diabetes, hypertension, smoking status should also be considered. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk. For patients with RA with known risk factors for VTE, consider testing D-dimer levels after approximately 12 months of treatment. If D-dimer test result is ≥ 2× ULN, confirm that clinical benefits outweigh risks prior to a decision on treatment continuation with tofacitinib. Promptly evaluate patients with signs and symptoms of VTE. Tofacitinib should be discontinued in patients with suspected VTE, regardless of dose or indication.

Major adverse cardiovascular events (including myocardial infarction)
[...] In patients over 65 years of age, patients who are current or past smokers, and patients with other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.

Malignancy and lymphoproliferative disorder
[...] In patients over 65 years of age, patients who are current or past smokers, and patients with other malignancy risk factors (e.g., current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available.

Against this background, it is considered appropriate for the reassessment of tofacitinib in rheumatoid arthritis to specify the patient population of the resolution in this regard as well, and to further restrict the reassessment within adults with moderate to severe active rheumatoid arthritis (RA) in adults, who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs to patients, who are eligible for a treatment with tofacitinib.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adults with moderate to severe active rheumatoid arthritis, who do not have poor prognostic factors[3] and who have responded inadequately to, or have been intolerant to a prior disease-modifying antirheumatic drug therapy [classical DMARDs, including methotrexate (MTX)] and are eligible for a treatment with Tofacitinib

Appropriate comparator therapy for tofacitinib:

- Alternative classical DMARDs, if suitable (MTX, leflunomide, sulfasalazine) as mono or combination therapy

b) Adults with moderate to severe active rheumatoid arthritis for whom first-time therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated and who are eligible for a treatment with tofacitinib

Appropriate comparator therapy for tofacitinib:

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

c) Adults with moderate to severe active rheumatoid arthritis who have responded inadequately to, or have been intolerant to prior treatment with one or more bDMARDs and/or tsDMARDs and are eligible for a treatment with tofacitinib

Appropriate comparator therapy for tofacitinib:

- 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 upadacitinib, 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 in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven

[3] Poor prognostic factors:
- Detection of autoantibodies (e.g., rheumatoid factors, high levels of antibodies against citrullinated peptide antigens)
- High disease activity (detected by DAS or DAS28 score, swollen joints, acute phase reaction parameters such as C-reactive protein, erythrocyte sedimentation rate)
- Early occurrence of joint erosions

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 Federal Joint Committee has already determined the patient-relevant advantage 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.

A variety of approved medicinal products are available for the treatment of rheumatoid arthritis. These include medicinal products belonging to the following product classes and the following active ingredients:

- Non-steroidal anti-inflammatory drugs/ non-steroidal antirheumatic drugs (NSAIDs/NSARs), whereby these are used purely on the basis of symptomatology
- Steroidal anti-inflammatory drugs (glucocorticoids), e.g., prednisolone, methylprednisolone
- Conventional synthetic disease-modifying antirheumatic drugs ("basic therapeutics", cDMARDs), e.g., MTX, leflunomide, sulfasalazine
- Other active ingredients: D-penicillamine, parenteral gold, ciclosporin and azathioprine
- Biological disease-modifying antirheumatic drugs ("biologics", bDMARDs): TNF-alpha inhibitors (adalimumab, certolizumab pegol, etanercept, infliximab and golimumab), abatacept, anakinra, rituximab, tocilizumab, sarilumab. It is to be noted that abatacept, golimumab and infliximab are only approved in combination with MTX.
- Targeted synthetic DMARDs ("tsDMARDs"): the JAK inhibitors baricitinib, tofacitinib and upadacitinib

According to the marketing authorisation, some active ingredients are only used for severe forms of rheumatoid arthritis, e.g., rituximab, ciclosporin or azathioprine. These active ingredients are therefore only considered for a proportion of patients and do not represent an appropriate comparator therapy for a large proportion of the patient population covered by the therapeutic indication.

on 2.

For the treatment of rheumatoid arthritis, no non-medical measures can be considered as the sole appropriate comparator therapy.

on 3.

There are four resolutions of the G-BA in the indication rheumatoid arthritis, for baricitinib dated 21 September 2017, for tofacitinib dated 19 October 2017 and 1 November 2018 respectively, for sarilumab dated 15 February 2018 and for upadacitinib dated 16 July 2020. Furthermore, a final report by the Institute for Quality and Efficiency in Health Care (IQWiG) of 28 June 2013 is available on a comparative benefit assessment of biologic medicinal products in the second-line therapy of rheumatoid arthritis on the active ingredients rituximab, abatacept, etanercept, infliximab, adalimumab, certolizumab pegol, golimumab, anakinra and tocilizumab. Furthermore, a final report by the Institute for Quality and Efficiency in Health Care (IQWiG) dated 23 July 2019, on bioengineered active ingredients for rheumatoid arthritis is available. In addition, the therapeutic informations according to Section 92, paragraph 2, sentence 7 SGB V in conjunction with Section 17 Pharmaceuticals Directive (AM-RL) on the economic prescription of medicinal product for the active ingredient leflunomide are to be taken into account.

on 4.

The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present therapeutic indication. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.
The approved therapeutic indication and the thereby described marketing authorisation population of the medicinal product to be assessed are decisive for the determination of the appropriate comparator therapy.

Due to different therapy situations, the population in the present therapeutic indication is to be subdivided into:

a) Patients who do not have poor prognostic factors[3] and who have inadequately responded to, or have been intolerant to a prior disease-modifying antirheumatic drug therapy (classical DMARDs, including methotrexate),
b) Patients for whom initial therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated, and
c) Patients who have inadequately responded to, or have been intolerant to previous treatment with one or more bDMARDs and/or tsDMARDs.

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

Due to their strong antiphlogistic quality of action, the glucocorticoids group of active ingredients is usually used for a limited time as high-dose therapy or orally in low doses as "bridge therapy" at the beginning of treatment until the response of the basic therapy. They also represent an important therapy option in 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 poor prognostic factors[3]. If no poor prognostic factors are present and patients have responded inadequately to or have not tolerated prior therapy with a classical DMARD (cDMARD), the current guideline from the European League Against Rheumatism[4] (EULAR) as well as the S2-e guideline of the DGRh from 2018 recommends[5] the use of an alternative classical DMARD, if suitable (MTX, leflunomide, sulfasalazine) as monotherapy or combination therapy. Parenteral gold has no relevant value in this treatment situation compared to the available alternatives. Thus, parenteral gold is neither mentioned in the current guidelines nor is parenteral gold currently available on the German market. D-penicillamine is also neither mentioned nor recommended in the current guidelines. In addition, other active ingredients such as ciclosporin and azathioprine play a subordinate role in this treatment setting due to their poorer risk-benefit ratio and are not included in the appropriate comparator therapy. In individual cases, patient population A may also include patients with unfavourable prognostic factors who have responded inadequately to initial treatment with a cDMARD or who are intolerant to this treatment but who, in medical care practice, on the basis of individual criteria, may first be considered for a second classical DMARD before initial bDMARD therapy is started.

On b)

After failure or intolerance of treatment with a classical disease-modifying antirheumatic drug, the use of a biologic or tsDMARD is recommended if poor prognostic factors are present. For patients who have already responded inadequately to several cDMARDs or who are intolerant to them, the use of a biologic is also recommended. Thus, the first use of a bDMARD or tsDMARD is equally suitable as an appropriate comparator therapy for these two patient groups, although they differ with regard to their previous therapy and the previous course of the disease. A grouping of patients is considered justified, since the presence of negative prognostic markers and the number of previous therapies in this treatment setting no longer have predictive value for the course of therapy. Thus, the patient group of patients for whom initial therapy with bDMARDs or tsDMARDs (patient group b) includes both patients with poor prognostic factors[3], who have responded inadequately to, or have been intolerant to a prior therapy with one disease-modifying antirheumatic drug (classical DMARDs, including MTX) and patients who have responded inadequately to, or have been intolerant to a prior therapy with multiple disease-modifying antirheumatic drugs (classical DMARDs, including MTX).

[4] Smolen JS, et al. Ann Rheum Dis. 2020 Jun;79(6):685-699.
[5] Fiehn C, Holle J, Iking-Konert C, Leipe J, Weseloh C, Frerix M, et al. Therapy of rheumatoid arthritis with disease-modifying drugs; S2e guideline [online]. AWMF register number 060-004. Berlin (GER): Association of the Scientific Medical Societies (AWMF); 2018.

The use of the interleukin (IL)-1 receptor antagonist anakinra is not recommended due to weaker efficacy compared to other biologics based on the IQWiG final report from 2019. Means of choice after failure of classical DMARDs are bDMARDs or tsDMARDs, including TNF-alpha inhibitors in combination with MTX, the CTLA-4 analogue abatacept, the IL-6 inhibitors tocilizumab and sarilumab, the JAK inhibitors tofacitinib and baricitinib, both in the recommendations of the EULAR[4], as well as in other included guidelines (including, among others, the S2-e guideline of the DGRh from 2018[5]).

The subordination of the TNF-α inhibitor infliximab to the other active ingredient in its class due to an increased side effect profile, which was previously seen on the basis of the IQWiG final report on bDMARDs from 2013, is no longer seen on the basis of the current, aggregated evidence. Against this background and due to the fact that also in the current guidelines[4,5] no recommendations are derived within the class of bDMARDs that would justify a priority or subordination of individual active ingredients at the present time, infliximab is included as a further TNF-α inhibitor in the appropriate comparator therapy.
Thus, the G-BA comes to the conclusion that in the overall assessment, in addition to the TNF-α inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab), other bDMARDs and tsDMARDs, including abatacept, the IL-6 inhibitors tocilizumab and sarilumab as well as the JAK inhibitors baricitinib, tofacitinib and upadacitinib - in each case in combination with MTX - are equally suitable as appropriate comparator therapy.
Consequently, bDMARDs or tsDMARDs [abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or tofacitinib or upadacitinib, in combination with MTX (if necessary as monotherapy, taking into account the respective authorisation status in case of MTX intolerance or unsuitability)] are determined as equally appropriate comparator therapies for patients for whom first-time therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated, as monotherapy, taking into account the respective approval status in the case of MTX intolerance or unsuitability)) as equally appropriate comparator therapies. bDMARDs or tsDMARDs should generally be used in combination with MTX, as this improves efficacy and, in the case of bDMARDs, reduces the formation of neutralising "anti-drug antibodies". Only for patients who are intolerant to MTX or who have an MTX contraindication, monotherapy with a bDMARD or tsDMARD can be considered as an appropriate comparator therapy. The data basis for monotherapy with the anti-IL-6 receptor antibody tocilizumab in MTX intolerance is currently assessed as inadequate, also in view of the safety profile of tocilizumab, to consider the TNF-α inhibitors adalimumab, etanercept and certolizumab pegol or tsDMARDs baricitinib or tofacitinib or upadacitinib or the bDMARD sarilumab as less appropriate alternatives in this situation (patient population b1), so that also in this case all approved bDMARDs or tsDMARDs can be considered as equally appropriate comparator therapy. Abatacept, golimumab and infliximab are only approved in combination with MTX.

On c)
For the treatment setting "after failure of at least one bDMARD or tsDMARD therapy", the active ingredients tocilizumab, abatacept and rituximab (in combination with MTX) are explicitly approved (after failure of a TNF-α inhibitor therapy). 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 line of therapy"), provided that the application

requirement, failure of DMARDs, is met. Thus, in the treatment setting "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 also rituximab are approved.

Since the marketing authorisation of TNF-α inhibitors, IL inhibitors, and JAK inhibitors, a growing body of evidence has been found supporting the efficacy of these active ingredients after failure of a first bDMARD or tsDMARD. The aggregated evidence is overall more limited compared to the treatment setting in patient group b, but some recommendations from German[5] and European[4] guidelines as well as results from previous benefit assessments according to Section 35a SGB V are available for this therapy situation "after failure of at least one bDMARD or tsDMARD therapy". Thus, in the overall assessment, depending on the previous therapy of a patient in the above-mentioned therapy stage, both the change to a TNF-alpha inhibitor (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab) and to a therapy with a different mode of action from TNF-α inhibition (CTLA-4 analogue, IL-6 inhibitor or JAK inhibitor), in each case in combination with MTX, is considered appropriate. Rituximab is also suitable and appropriate for patients with severe active rheumatoid arthritis who respond inadequately to other DMARDs including one or more TNF-alpha inhibitors. For anakinra, please refer to the comments under patient population b.

Analogous to patient group b, according to the respective guidelines of scientific-medical societies, bDMARDs or tsDMARDs should always be used in combination with MTX, as this improves efficacy and reduces the formation of neutralising "anti-drug antibodies" in the case of bDMARDs. Only for patients who are intolerant to MTX or who have an MTX contraindication, monotherapy with a bDMARD or tsDMARD can be considered.
In summary, for patients who have inadequately responded to, or have been intolerant to a previous therapy with one or more bDMARDs and/or tsDMARDs, depending on the previous therapy, a change of 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 upadacitinib in patients with severe rheumatoid arthritis rituximab, in each case in combination with MTX or, where appropriate as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability. Depending on the previous therapy, a change of the mode of action should be considered. A further differentiation of the patient population c (e.g., also with regard to failure on two vs more than two bDMARDs/tsDMARDs) is not made at this time due to the lack of uniform therapy recommendations.

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

2.1.3 Extent and probability of the additional benefit

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

a) Adults with moderate to severe active rheumatoid arthritis who do not have poor prognostic factors and who have responded inadequately to, or have been intolerant to

a prior disease-modifying antirheumatic drug therapy [classical DMARDs, including methotrexate (MTX)] and are eligible for a treatment with Tofacitinib

For adults with moderate to severe active rheumatoid arthritis who do not have poor prognostic factors and who have responded inadequately to, or have been intolerant to a prior disease-modifying antirheumatic drug therapy [classical DMARDs, including methotrexate (MTX)] and are eligible for a treatment with tofacitinib, the additional benefit of tofacitinib (as monotherapy in cases of MTX intolerance or MTX unsuitability, or in combination with MTX) compared with the appropriate comparator therapy is not proven.

Justification for patient population a1:

No data were submitted with the dossier for the assessment of the additional benefit of a therapy with tofacitinib as monotherapy in cases of MTX intolerance or MTX unsuitability compared with the appropriate comparator therapy.

Justification for patient population a2:

No data were submitted with the dossier for the assessment of the additional benefit of a therapy with tofacitinib in combination with MTX compared with the appropriate comparator therapy.

b) Adults with moderate to severe active rheumatoid arthritis for whom first-time therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated and who are eligible for a treatment with Tofacitinib

For adults with moderate to severe active rheumatoid arthritis for whom a first-time treatment with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated and who are candidate for a treatment with tofacitinib, the additional benefit of tofacitinib (as monotherapy in cases of MTX intolerance or MTX unsuitability or in combination with MTX) compared with the appropriate comparator therapy is not proven.

Justification for patient population b1:

In the dossier, no data were presented in the relevant patient population b1 for the assessment of the additional benefit of a therapy with tofacitinib as monotherapy in cases of MTX intolerance or MTX unsuitability compared with the appropriate comparator therapy.

Justification for patient population b2:

The dossier did not provide any assessable data, which are suitable for the question of the new benefit assessment, in the relevant patient population b2 for the assessment of the additional benefit of a therapy with tofacitinib in combination with MTX compared with the appropriate comparator therapy.

The ORAL STRATEGY and ORAL STANDARD studies were the subject of the previous benefit assessment and are unsuitable for the assessment of the additional benefit in the context of the reassessment due to new scientific knowledge according to Section 13 VerfO without redefinition of the patient populations compared to the previous benefit assessment against the background of the now existing limitations in the use of tofacitinib. Within the framework of the written statement procedure, evaluations of the ORAL STRATEGY and ORAL STANDARD studies were submitted subsequently for those sub-populations that, from the pharmaceutical company's point of view, are unconditionally eligible for treatment with tofacitinib, taking into account the new requirements in the product information as of September 2021. However, these are not suitable in their revised version presented for answering the question of the reassessment, as the specifications of the module templates for the subsequently submitted analyses were not met.

The G-BA initiated the new benefit assessment of tofacitinib in March 2021 due to new scientific knowledge in rheumatoid arthritis including the ORAL SURVEILLANCE study. The ORAL SURVEILLANCE study is a randomised, open-label, multicentre study comparing tofacitinib at two different doses (5 mg or 10 mg 2-times daily) in combination with MTX vs the TNFα inhibitors adalimumab or etanercept, each in combination with MTX. The study was prompted by requirements of the Food and Drug Administration (FDA) to investigate the post-authorisation safety profile of tofacitinib. Adult patients aged ≥ 50 years with moderate to severe active rheumatoid arthritis who have inadequately responded to prior treatment with MTX were enrolled in the study. In addition, the patients had to have at least one of the following cardiovascular risk factors:

- Active smoking
- Hypertension
- High-density lipoprotein (HDL) < 40 mg/dl
- Diabetes mellitus
- Family history of coronary heart disease (CHD) (documented clinical CHD or sudden death of a 1st degree male relative < 55 years or 1st degree female relative < 65 years)
- Rheumatoid arthritis-associated extra-articular diseases (e.g., nodules, Sjögren's syndrome, anaemia in chronic disease, pulmonary manifestations)
- History of CHD (including history of revascularisation procedures, coronary artery bypass grafting, myocardial infarction, cardiac arrest, unstable angina pectoris and acute coronary syndrome)

For this patient population, a treatment with tofacitinib, taking into consideration the updated warnings and precautions for the use of tofacitinib in the product information, would only be considered for this patient population, if no suitable treatment alternatives are available. Overall, however, the majority of patients enrolled in the ORAL SURVEILLANCE study were those, for whom first-time therapy with bDMARDs or tsDMARDs was indicated (with the exception of approximately 10% who were pretreated with bDMARDs or tsDMARDs). Irrespective of a pretreatment, all or a majority of the active ingredients that the G-BA has defined as appropriate comparator therapy for population b are suitable alternative treatments for all enrolled patients. This also includes the active ingredients adalimumab and etanercept (which were administered in the comparator arm of the ORAL SURVEILLANCE

study), for which there are no comparable warnings and precautions for use analogous to those for tofacitinib, and which therefore represent suitable treatment alternatives. For the patients in the ORAL SURVEILLANCE study, tofacitinib is therefore no longer an adequate treatment, taking into consideration the warnings and precautions for use, after the update of the product information in autumn 2021. In the overall assessment, the ORAL SURVEILLANCE study is therefore not used to assess the additional benefit of tofacitinib because of the aspects mentioned.

c) Adults with moderate to severe active rheumatoid arthritis who have responded inadequately to, or have been intolerant to prior treatment with one or more bDMARDs and/or tsDMARDs and are eligible for a treatment with Tofacitinib

For adults with moderate to severe active rheumatoid arthritis who have inadequately responded to, or have been intolerant to a previous treatment with one or more bDMARDs and/or tsDMARDs and are eligible for treatment with tofacitinib, the additional benefit of tofacitinib (as monotherapy in cases of MTX intolerance or MTX unsuitability or in combination with MTX) compared with the appropriate comparator therapy is not proven.

Justification for patient population c1:

No data were submitted with the dossier for the assessment of the additional benefit of a therapy with tofacitinib as monotherapy in cases of MTX intolerance or MTX unsuitability compared with the appropriate comparator therapy.

Justification for patient population c2:

No data were submitted with the dossier for the assessment of the additional benefit of a therapy with tofacitinib in combination with MTX compared with the appropriate comparator therapy.

2.1.4 Summary of the assessment

The present assessment is a new benefit assessment of the active ingredient tofacitinib based on an application following new scientific knowledge according to Section 13 (Chapter 5, Section 13, Paragraph 1, Sentence 1 VerfO).

The present assessment relates exclusively to the following therapeutic indication for "Treatment of moderate to severe active rheumatoid arthritis (RA) in adults who have responded inadequately to, or who are intolerant to one or more disease-modifying antirheumatic drugs and are eligible for a treatment with tofacitinib."

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

Patient group a1)

For adults with moderate to severe active rheumatoid arthritis who do not have any poor prognostic factors and who have responded inadequately to, or have been intolerant to a prior disease-modifying anti-rheumatic drug therapy [classical DMARDs, including methotrexate (MTX)] and are eligible for a treatment with tofacitinib, the G-BA determined alternative classical DMARDs, if suitable (leflunomide, sulfasalazine) as monotherapy or combination therapy, to be the appropriate comparator therapy, in the case of MTX intolerance or MTX unsuitability. For this patient group, the pharmaceutical company does not submit any data with the dossier for the assessment of the additional benefit. For this patient group, the additional benefit of tofacitinib as monotherapy compared to the appropriate comparator therapy is not proven.

Patient group a2)

For adults with moderate to severe active rheumatoid arthritis who do not have any poor prognostic factors and who have responded inadequately to, or have been intolerant to a prior disease-modifying anti-rheumatic drug therapy [classical DMARDs, including methotrexate (MTX)] and are eligible for a treatment with tofacitinib, the G-BA determined alternative classical DMARDs, if suitable (MTX, leflunomide, sulfasalazine) as monotherapy or combination therapy, to be the appropriate comparator therapy. For this patient group, the pharmaceutical company does not submit any data with the dossier for the assessment of the additional benefit. For this patient group, the additional benefit of tofacitinib in combination with MTX compared to the appropriate comparator therapy is not proven.

Patient group b1)

For adults with moderate to severe active rheumatoid arthritis for whom a first-time therapy with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated and who are eligible for treatment with tofacitinib, the G-BA has determined bDMARDs or tsDMARDs (adalimumab or baricitinib or certolizumab pegol or etanercept or sarilumab or tocilizumab or upadacitinib) as monotherapy as the appropriate comparator therapy in the case of MTX intolerance or MTX unsuitability. For this patient group, the pharmaceutical company does not submit any data with the dossier for the assessment of the additional benefit. For this patient group, the additional benefit of tofacitinib as monotherapy compared to the appropriate comparator therapy is not proven.

Patient group b2)

For adults with moderate to severe active rheumatoid arthritis for whom a first-time treatment with biologic DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs) is indicated and who are eligible for treatment with tofacitinib, the G-BA determined bDMARDs or tsDMARDs (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or upadacitinib) in combination with MTX as the appropriate comparator therapy. The dossier did not provide any assessable data, which are suitable for the question of the new benefit assessment, in the relevant patient population for the assessment of the additional benefit of a therapy with tofacitinib in combination with MTX compared with the appropriate comparator therapy. For this patient group, the additional benefit of tofacitinib in combination with MTX compared to the appropriate comparator therapy is not proven.

Patient group c1)
For adults with moderate to severe active rheumatoid arthritis who have inadequately responded to, or have been intolerant to a previous treatment with one or more bDMARDs and/or tsDMARDs and who are eligible for treatment with tofacitinib, the G-BA determined a change in bDMARD or tsDMARD therapy (adalimumab or baricitinib or certolizumab pegol or etanercept or sarilumab or tocilizumab or upadacitinib as monotherapy), depending on prior therapy, as the appropriate comparator therapy in the case of MTX intolerance or MTX unsuitability. For this patient group, the pharmaceutical company does not submit any data with the dossier for the assessment of the additional benefit. For this patient group, the additional benefit of tofacitinib as monotherapy compared to the appropriate comparator therapy is not proven.

Patient group c2)
For adults with moderate to severe active rheumatoid arthritis who have inadequately responded to, or have been intolerant to a previous treatment with one or more bDMARDs and/or tsDMARDs and who are eligible for treatment with tofacitinib, the G-BA determined the change in bDMARD or tsDMARD therapy (abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or sarilumab or tocilizumab or upadacitinib in combination with MTX; or, in patients with severe rheumatoid arthritis, rituximab, taking into account the marketing authorisation), depending on prior therapy, as the appropriate comparator therapy. For this patient group, the additional benefit of tofacitinib in combination with MTX compared to the appropriate comparator therapy 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 statutory health insurance (SHI).

The information is based on patient numbers from the information provided by the pharmaceutical company in the dossier, taking into account the current sources for prevalence. In the underlying data, patients treated with tsDMARDs are included for the first time compared to previous dossiers in the therapeutic indication. Overall, this leads to a more complete estimate of the number of patients. The number of patients in the SHI target population is in a plausible order of magnitude for the population covered by the therapeutic indication of rheumatoid arthritis as a whole. However, new proportion values were submitted with the statement for the calculation of patient numbers, taking into account the updated warnings and precautions for the use of tofacitinib from the product information. These were carried out on the basis of the marketing authorisation studies of tofacitinib and were reassessed as part of an addendum to the benefit assessment (number of patients)[6] . Overall, the calculation of the proportion values on the basis of the clinical studies is not necessarily representative and, moreover, not completely comprehensible, so that the overall assessment assumes uncertain data, which are, however, used as an approximation.

[6] IQWiG addendum on patient numbers for tofacitinib (G22-03).

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 Xeljanz (active ingredient: tofacitinib) at the following publicly accessible link (last access: 10 January 2022):

https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. The training material includes instructions on how to manage the potential side effects associated with tofacitinib, particularly severe and opportunistic infections including tuberculosis and herpes zoster. It also points out the need for an effective contraceptive method.

Therapy should be started by a doctor experienced in the diagnosis and treatment of rheumatoid arthritis.
With the start of the reassessment due to new scientific knowledge, warnings and precautions for the use of tofacitinib were added to the product information under 4.4 or updated in consultation with the EMA. These must be taken into account when using tofacitinib.

Use in patients over 65 years of age
Considering the increased risk of serious infections, myocardial infarction, and malignancies with tofacitinib in patients over 65 years of age, tofacitinib should only be used in these patients if no suitable treatment alternatives are available.

Venous thromboembolism (VTE)
Serious VTE events including pulmonary embolism (PE), some of which were fatal, and deep vein thrombosis (DVT), have been observed in patients taking tofacitinib. In a randomised post-authorisation safety study in patients with rheumatoid arthritis who were 50 years of age or older with at least one additional cardiovascular risk factor, a dose dependent increased risk for VTE was observed in a clinical study with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1 of the product information). In a post hoc exploratory analysis within this study, in patients with known VTE risk factors, occurrences of subsequent VTEs were observed more frequently in tofacitinib-treated patients that, at 12 months treatment, had D-dimer level ≥2× ULN versus those with D-dimer level <2× ULN; this was not evident in TNF inhibitor-treated patients. Interpretation is limited by the low number of VTE events and restricted D-dimer test availability (only assessed at Baseline, Month 12, and at the end of the study). In patients who did not have a VTE during the study, mean D-dimer levels were significantly reduced at Month 12 relative to Baseline across all treatment arms. However, D-dimer levels ≥2× ULN at Month 12 were observed in approximately 30% of patients without subsequent VTE events, indicating limited specificity of D-Dimer testing in this study. Tofacitinib should be used with caution in patients with known risk factors for VTE, regardless of indication and dosage. Tofacitinib 10 mg twice daily for maintenance treatment is not recommended in patients with UC who have known VTE risk factors, unless there is no suitable

alternative treatment available (see section 4.2 of the product information). VTE risk factors include previous VTE, patients undergoing major surgery, immobilisation, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, malignancy. Additional VTE risk factors such as age, obesity (BMI ≥30), diabetes, hypertension, smoking status should also be considered. Patients should be re-evaluated periodically during tofacitinib treatment to assess for changes in VTE risk. For patients with RA with known risk factors for VTE, consider testing D-dimer levels after approximately 12 months of treatment. If D-dimer test result is ≥ 2× ULN, confirm that clinical benefits outweigh risks prior to a decision on treatment continuation with tofacitinib. Promptly evaluate patients with signs and symptoms of VTE. Tofacitinib should be discontinued in patients with suspected VTE, regardless of dose or indication.

Major adverse cardiovascular events (including myocardial infarction)
Major adverse cardiovascular events (MACE) have been observed in patients taking tofacitinib.
In a randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of myocardial infarctions was observed with tofacitinib compared to TNF inhibitors. In patients over 65 years of age, patients who are current or past smokers, and patients with other cardiovascular risk factors, tofacitinib should only be used if no suitable treatment alternatives are available.

Malignancy and lymphoproliferative disorder
Tofacitinib may affect host defences against malignancies.
In a randomised post-authorisation safety study in patients with RA who were 50 years of age or older with at least one additional cardiovascular risk factor, an increased incidence of malignancies excluding NMSC, particularly lung cancer and lymphoma, was observed with tofacitinib compared to TNF inhibitors (see sections 4.8 and 5.1 of the product information). Lung cancers and lymphoma in patients treated with tofacitinib have also been observed in other clinical studies and in the post marketing setting. Other malignancies in patients treated with tofacitinib were observed in clinical studies and the post-marketing setting, including, but not limited to, breast cancer, melanoma, prostate cancer, and pancreatic cancer. In patients over 65 years of age, patients who are current or past smokers, and patients with other malignancy risk factors (e.g., current malignancy or history of malignancy other than a successfully treated non-melanoma skin cancer) tofacitinib should only be used if no suitable treatment alternatives are available.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2022).

For cost representation, one year is assumed for all medicinal products. This does not take into account the fact that treatment may be discontinued earlier due to non-response or

intolerance. The discontinuation criteria according to the product information of the individual active ingredients must be taken into account when using the medicinal products.

Treatment period:

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				
Tofacitinib	continuously, 1 - 2 x daily	365	1	365
Methotrexate, if necessary	continuously, 1 x every 7 days	52.1	1	52.1
Appropriate comparator therapy for patient population a				
Methotrexate	continuously, 1 x every 7 days	52.1	1	52.1
Leflunomide	continuously, 1 x daily	365	1	365
Sulfasalazine	continuously, 2 x daily	365	1	365
Appropriate comparator therapy for patient population b				
Methotrexate	continuously, 1 x every 7 days	52.1	1	52.1
Adalimumab	continuously, every 14 days	26.1	1	26.1
Etanercept	continuously, 2 x within 7 days or 1 x every 7 days	52.1 - 104.2	1 - 2	52.1 – 104.2
Certolizumab pegol	continuously, every 14 days	26.1	1	26.1
Golimumab	continuously, 1 x month	12.0	1	12.0

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 x every 7 days	52.1	1	52.1
Tocilizumab	continuously, 1 x every 7 days	52.1	1	52.1
Baricitinib	continuously, 1 x daily	365	1	365
Sarilumab	continuously, 1 x every 14 days	26.1	1	26.1
Infliximab[7]	continuously, every 56 days	6.5	1	6.5
Upadacitinib	continuously, 1 x daily	365	1	365
Appropriate comparator therapy for patient population c				
Methotrexate	continuously, 1 x every 7 days	52.1	1	52.1
Adalimumab	continuously, every 14 days	26.1	1	26.1
Etanercept	continuously, 2 x within 7 days or 1 x every 7 days	52.1 - 104.2	1 - 2	52.1 – 104.2
Certolizumab pegol	continuously, every 14 days	26.1	1	26.1
Golimumab	continuously, 1 x month	12.0	1	12.0
Abatacept	continuously, 1 x every 7 days	52.1	1	52.1

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

Designation of the therapy	Treatment mode	Number of treatments per patient per year	Treatment duration per treatment (days)	Treatment days per patient per year
Tocilizumab	continuously, 1 x every 7 days	52.1	1	52.1
Rituximab	1 x on day 1 and 15 of a minimum 182-day cycle[8]	2	1 - 2	2 - 4
Baricitinib	continuously, 1 x daily	365	1	365
Sarilumab	continuously, 1 x every 14 days	26.1	1	26.1
Infliximab[7]	continuously, every 56 days	6.5	1	6.5
Upadacitinib	continuously, 1 x daily	365	1	365

Consumption:

For the cost representation only the dosages of the general case are considered. Patient-individual dose adjustments (e.g., because of side effects or comorbidities,) are not taken into account when calculating the annual treatment costs.

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

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg).[9]

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

[9] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tofacitinib	5 mg	10 mg	2 x 5 mg	365	730 x 5 mg
	or				
	11 mg	11 mg	1 x 11 mg	365	365 x 11 mg
Methotrexate, if necessary	7.5 mg -	7.5 mg	1 x 7.5 mg	52.1	52.1 x 7.5 mg
	20 mg	20 mg	2 x 10 mg	52.1	104.2 x 10 mg
Appropriate comparator therapy for patient population a					
Methotrexate	7.5 mg -	7.5 mg	1 x 7.5 mg	52.1	52.1 x 7.5 mg
	20 mg	20 mg	2 x 10 mg	52.1	104.2 x 10 mg
Leflunomide	10 mg -	10 mg -	1 x 10 mg -	365	365 x 10 mg -
	20 mg	20 mg	1 x 20 mg	365	365 x 20 mg
Sulfasalazine	1,000 mg -	2,000 mg -	4 x 500 mg -	365	1,460 x 500 mg -
	1,500 mg	3,000 mg	6 x 500 mg	365	2,190 x 500 mg
Appropriate comparator therapy for patient population b					
Monotherapies					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Etanercept	25 mg	25 mg	1 x 25 mg	104.2	104.2 x 25 mg
	or				
	50 mg	50 mg	50 mg	52.1	52.1 x 50 mg
Certolizumab pegol	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Tocilizumab	162 mg	162 mg	1 x 162 mg	52.1	52.1 x 162 mg
Baricitinib	4 mg	4 mg	1 x 4 mg	365	365 x 4 mg
Sarilumab	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Upadacitinib	15 mg	15 mg	1 x 15 mg	365	365 x 15 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Combination therapies with methotrexate					
Methotrexate	7.5 mg -	7.5 mg	1 x 7.5 mg	52.1	52.1 x 7.5 mg
	20 mg	20 mg	2 x 10 mg	52.1	104.2 x 10 mg
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Etanercept	25 mg	25 mg	1 x 25 mg	104.2	104.2 x 25 mg
	or				
	50 mg	50 mg	50 mg	52.1	52.1 x 50 mg
Certolizumab pegol	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Golimumab	50 mg	50 mg	1 x 50 mg	12.0	12.0 x 50 mg
Abatacept	125 mg	125 mg	1 x 125 mg	52.1	52.1 x 125 mg
Tocilizumab	162 mg	162 mg	1 x 162 mg	52.1	52.1 x 162 mg
Baricitinib	4 mg	4 mg	1 x 4 mg	365	365 x 4 mg
Sarilumab	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Infliximab	3 mg/kg bw (231 mg) - 7.5mg/kg bw (577.5 mg)	231 mg - 577.5 mg	3 x 100 mg - 6 x 100 mg	6.5	19.5 x 100 mg – 39 x 100 mg
Upadacitinib	15 mg	15 mg	1 x 15 mg	365	365 x 15 mg
Appropriate comparator therapy for patient population c					
Monotherapies					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Etanercept	25 mg	25 mg	1 x 25 mg	104.2	104.2 x 25 mg
	or				
	50 mg	50 mg	50 mg	52.1	52.1 x 50 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Certolizumab pegol	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Tocilizumab	162 mg	162 mg	1 x 162 mg	52.1	52.1 x 162 mg
Baricitinib	4 mg	4 mg	1 x 4 mg	365	365 x 4 mg
Sarilumab	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Upadacitinib	15 mg	15 mg	1 x 15 mg	365	365 x 15 mg
Combination therapies with methotrexate					
Methotrexate	7.5 mg -	7.5 mg	1 x 7.5 mg	52.1	52.1 x 7.5 mg
	20 mg	20 mg	2 x 10 mg	52.1	104.2 x 10 mg
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Etanercept	25 mg	25 mg	1 x 25 mg	104.2	104.2 x 25 mg
	or				
	50 mg	50 mg	50 mg	52.1	52.1 x 50 mg
Certolizumab pegol	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Golimumab	50 mg	50 mg	1 x 50 mg	12	12 x 50 mg
Abatacept	125 mg	125 mg	1 x 125 mg	52.1	52.1 x 125 mg
Tocilizumab	162 mg	162 mg	1 x 162 mg	52.1	52.1 x 162 mg
Baricitinib	4 mg	4 mg	1 x 4 mg	365	365 x 4 mg
Sarilumab	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Infliximab	3 mg/kg bw (231 mg) - 7.5mg/kg bw (577.5 mg)	231 mg - 577.5 mg	3 x 100 mg - 6 x 100 mg	6.5	19.5 x 100 mg - 39 x 100 mg
Upadacitinib	15 mg	15 mg	1 x 15 mg	365	365 x 15 mg

Designation of the therapy	Dosage/ application	Dosage/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Rituximab	1,000 mg	1,000 mg	1 x 1,400 mg	2 - 4	2 x 1,400 mg - 4 x 1,400 mg

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Tofacitinib 5 mg	182 FCT	€ 3,134.85	€ 1.77	€ 0.00	€ 3,133.08
Tofacitinib 11 mg	91 RET	€ 3,134.85	€ 1.77	€ 0.00	€ 3,133.08
Methotrexate 7.5 mg[10]	30 TAB	€ 33.71	€ 1.77	€ 1.77	€ 30.17
Methotrexate 10 mg[10]	30 TAB	€ 41.59	€ 1.77	€ 2.40	€ 37.42
Appropriate comparator therapy					
Abatacept 125 mg	12 PEN	€ 4,645.64	€ 1.77	€ 262.02	€ 4,381.85
Adalimumab 40 mg[10]	6 SFI	€ 2,859.17	€ 1.77	€ 228.57	€ 2,628.83
Baricitinib 4 mg	98 FCT	€ 4,078.70	€ 1.77	€ 229.65	€ 3,847.28
Certolizumab pegol 200 mg[10]	6 SFI	€ 2,859.17	€ 1.77	€ 228.57	€ 2,628.83
Etanercept 25 mg[10]	24 SFI	€ 2,859.17	€ 1.77	€ 228.57	€ 2,628.83
Etanercept 50 mg[10]	12 SFI	€ 2,859.17	€ 1.77	€ 228.57	€ 2,628.83
Golimumab 50 mg[10]	3 IFE	€ 2,605.92	€ 1.77	€ 0.00	€ 2,604.15
Infliximab 100 mg[10]	5 PIC	€ 3,490.53	€ 1.77	€ 280.08	€ 3,208,68
Leflunomide 10 mg[10]	100 FCT	€ 180.14	€ 1.77	€ 13.36	€ 165.01
Leflunomide 20 mg[10]	100 FCT	€ 280.59	€ 1.77	€ 21.30	€ 257.52
Methotrexate 7.5 mg[10]	30 TAB	€ 33.71	€ 1.77	€ 1.77	€ 30.17
Methotrexate 10 mg[10]	30 TAB	€ 41.59	€ 1.77	€ 2.40	€ 37.42
Rituximab 1,400 mg	1 SFI	€ 2,992.27	€ 1.77	€ 167.60	€ 2,822.90
Sarilumab 200 mg	6 SFI	€ 4,216.37	€ 1.77	€ 237.51	€ 3,977.09

[10] Fixed reimbursement rate

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Sulfasalazine 500 mg[10]	300 EFCT	€ 78.19	€ 1.77	€ 5.29	€ 71.13
Tocilizumab 162 mg	12 SFI	€ 5,505.74	€ 1.77	€ 311.14	€ 5,192.83
Upadacitinib 15 mg	90 RET	€ 3,714.49	€ 1.77	€ 0.00	€ 3,712.72
Abbreviations: EFCT = enteric film-coated tablets; FCT = film-coated tablets; IFE = solution for injection in a pre-filled syringe; SFI = solution for injection; PEN = solution for injection in a pre-filled pen, PIC = powder for the preparation of an infusion solution concentrate, Ret = sustained-release tablets; TAB = tablets					

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Costs for additionally required SHI services:

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

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

Diagnosis of tuberculosis

For the active ingredients of the appropriate comparator therapy of patient populations b or c (abatacept, adalimumab, baricitinib, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, sarilumab, tocilizumab, upadacitinib), costs are regularly incurred for testing for both active and inactive ("latent") tuberculosis infections. The costs presented are a blood test (quantitative determination of an in vitro interferon-gamma release after ex vivo stimulation with antigens specific for Mycobacterium tuberculosis-complex (except BCG)) and a chest radiograph. The tuberculin skin test is not presented due to lack of sensitivity and specificity as well as the possibility of "sensitisation". These examinations are also required when using tofacitinib.

Since there is no regular difference between the medicinal product to be assessed and the appropriate comparator therapy with regard to the tuberculosis test for patient populations b and c, the costs for additionally required SHI services for examinations for tuberculosis infections are not presented in the resolution for patient groups b and c. On the contrary, for the patient population a, there is a regular difference between the diagnostic costs incurred for the medicinal product to be assessed and those for the active ingredients of the appropriate comparator therapy, so that these are consequently taken into account as additionally required SHI services in the resolution.

Diagnosis of chronic hepatitis B

Patients must be tested for the presence of an HBV infection before initiating treatment with

abatacept or adalimumab or baricitinib or certolizumab pegol or etanercept or golimumab or infliximab or rituximab or upadacitinib. These examinations are not required for the use of sarilumab and tocilizumab as the appropriate comparator therapy, but are regularly required for the use of tocilizumab as the medicinal product to be assessed.

For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required[11]. A step-by-step serological diagnosis initially consists of the examination of HBs antigen and anti-HBc antibodies. If both are negative, a past HBV infection can be excluded. If HBs antigen is positive, an active HBV infection is detected.

In deviation from this, additional required SHI services are required for the diagnosis of suspected chronic hepatitis B, which usually differ between the medicinal product to be evaluated and the appropriate comparator therapy and are consequently considered as additionally required SHI services in the resolution.

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Medicinal product to be assessed: Tofacitinib Appropriate comparator therapy for patient population b and c				
Tofacitinib Abatacept Adalimumab Baricitinib Certolizumab pegol Etanercept Golimumab Infliximab Rituximab Sarilumab Tocilizumab Upadacitinib	Quantitative determination of an in vitro interferon-gamma release after ex vivo stimulation with antigens (at least ESAT-6 and CFP-10) specific for Mycobacterium tuberculosis-complex (except BCG) (GOP 32670)	1	€ 58.00	€ 58.00
Tofacitinib Abatacept Adalimumab Baricitinib Certolizumab pegol Etanercept Golimumab Infliximab Rituximab Sarilumab	Chest radiograph (GOP 34241)	1	€ 16.45	€ 16.45

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

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
Tocilizumab Upadacitinib				
Tofacitinib Abatacept Adalimumab Baricitinib Certolizumab pegol Etanercept Golimumab Infliximab Rituximab Upadacitinib	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)[12]	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90
	HBV-DNA (GOP 32823)[13]	1	€ 89.50	€ 89.50

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating in the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

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

4. Process sequence

At its session on 25 May 2021, the Subcommittee on Medicinal Products recently determined the appropriate comparator therapy.

On 31 August 2021 the pharmaceutical company submitted a dossier for the benefit assessment of tofacitinib to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 6 VerfO.

By letter dated 31 August 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient tofacitinib.

The dossier assessment by the IQWiG was submitted to the G-BA on 29 November 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 1 December 2021. The deadline for submitting written statements was 22 December 2021.

The oral hearing was held on 10 January 2022.

By letter dated 11 January 2022, the IQWiG was commissioned with a supplementary assessment of data (patient numbers) submitted in the written statement procedure. The addendum (patient numbers) prepared by IQWiG was submitted to the G-BA on 28 January 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 8 February 2022, and the proposed resolution was approved.

At its session on 17 February 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	25 May 2021	Determination of the appropriate comparator therapy
Working group Section 35a	4 January 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	10 January 2022	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents (patient numbers)

Working group Section 35a	18 January 2022 1 February 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	8 February 2022	Concluding discussion of the draft resolution
Plenum	17 February 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 17 February 2022

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

Prof. Hecken