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 therapeutic indication: ankylosing spondylitis)

of 16 June 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 listed for the first time on 1 May 2017 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 15 November 2021, tofacitinib received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 10 December 2021, i.e. at the latest within four weeks after being notified of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8,

paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient tofacitinib with the new therapeutic indication ankylosing spondylitis.

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 15 March 2022, 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 to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of 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 is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy.

Therapeutic indication of the resolution (resolution of 16.06.2022):

Tofacitinib is indicated for the treatment of adult patients with active AS who have responded inadequately to conventional therapy and who 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, this results in an assessment-relevant patient population that deviates from the therapeutic indication of the marketing authorisation and differs from the formally approved population of adults with active AS who have responded inadequately to conventional therapy, particularly with regard

[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 and 11 mg sustained-release tablets, both as of 03/2022.

to their age, smoking status, the presence of cardiovascular risk factors and risk factors for malignancies.

Specifically, the product information for tofacitinib 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 therapeutic indication and dosage. [...] VTE risk factors include previous VTE, patients undergoing major surgical intervention, immobilisation, myocardial infarction (within previous 3 months), heart failure, use of combined hormonal contraceptives or hormone replacement therapy, inherited coagulation disorder, cancer. Additional VTE risk factors such as old 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. Discontinue tofacitinib in patients with suspected VTE, regardless of dose or therapeutic 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 assessment of tofacitinib in active AS to also specify the patient population of the resolution in this regard and, furthermore, to restrict the assessment within adults with active AS who have responded inadequately to conventional therapy to patients who are eligible for treatment with tofacitinib.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a1) Adults with active ankylosing spondylitis who have inadequately responded to conventional therapy and who are eligible for treatment with tofacitinib

Appropriate comparator therapy for tofacitinib:

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

a2) Adults with active ankylosing spondylitis who have had an inadequate response to, or intolerance to prior therapy with biologic antirheumatic drugs (bDMARDs) and who are eligible for treatment with tofacitinib

Appropriate comparator therapy for tofacitinib:

- switching to a different bDMARD: TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL17 inhibitor (secukinumab)

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the G-BA shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

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

on 1. In addition to non-steroidal anti-inflammatory drugs (NSAIDs) for the symptomatic treatment of pain and inflammation, glucocorticoids and biologics are approved for this therapeutic indication. The marketing authorisation covers biologics in the therapeutic indication following a failure to respond to conventional therapies (or in the case of a contraindication to NSAIDs). In the present therapeutic indication, these are the TNF-α inhibitors infliximab, adalimumab, golimumab, certolizumab pegol,

etanercept, the IL-17 inhibitors secukinumab and ixekizumab as well as the JAK inhibitors upadacitinib and tofacitinib.

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

on 3. There are three resolutions of the G-BA in the therapeutic indication of radiographic axial spondyloarthritis (ankylosing spondylitis): for secukinumab dated 2 June 2016, for ixekizumab dated 21 January 2021 and for upadacitinib dated 15 July 2021.

on 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V". The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a, paragraph 7 SGB V.

The active ankylosing spondylitis (AS) is the radiographic form of active axial spondyloarthritis (radiographic axSpA); both terms are used synonymously and the term axSpA is used hereafter. Both the German S3 guideline[3] from 2019, as well as the current European ASAS-EULAR-Guideline[4] of 2016/2017 provide for the evidence-based use of NSAIDs in conventional (first-line-) therapy of axSpA for all sub-forms (symptomatic or continuous use). After the failure of therapy with NSAIDs or conventional therapy, the use of biologics (bDMARDs) is recommended on the basis of the available evidence. Conventional, classical DMARDs (e.g., MTX, sulfasalazine, leflunomide) are neither approved for the therapeutic indication axSpA nor is their use supported by the available evidence. The guidelines distinguish between the older TNF-α inhibitors and the newer biologics. Within the product classes of TNF-α inhibitors, however, no distinction is made in the therapy recommendation; within the TNF-α inhibitors approved in Germany, there is therefore no prioritisation. Furthermore, no head-to-head comparisons of the active ingredients would allow prioritisation; the evidence is mainly based on RCTs with placebo comparisons.

Overall, the treatment recommendations for axial spondyloarthritis after the failure of conventional therapy focus on the use of biologics. For the therapeutic indication, it is assumed that for patients after failure of a conventional therapy or NSAIDs, a continuation of the sole conventional therapy with NSAIDs or glucocorticoids is not (any longer) indicated according to medical assessment. Treatment recommendations rarely explicitly distinguish between the radiographic and non-radiographic forms of axSpA. Nor is a distinction by the severity grade of axSpA apparent in the underlying evidence: Neither the German S3 guideline[3]nor the EULAR-LL[4] or the EMA guideline[5] distinguish between severity grade in their recommendations for axSpA. Rather, a therapy decision is made in everyday care depending

[3] German Society for Rheumatology (DGRh). Axial spondyloarthritis including ankylosing spondylitis and early forms; S3 guideline [online]. AWMF register number 060-003. 2019 Version. Berlin (GER): Association of the Scientific Medical Societies (AWMF); 2019. [Accessed: 07.04.2020).

[4] ASAS-EULAR Recommendations: Van der Heide D et al, Ann Rheum Dis 2017;0:1-14.

[5] EMA Guideline on the clinical investigation of medicinal products for the treatment of Axial Spondyloarthritis - Adopted guideline (CPMP/EWP/4891/03 Rev.1) 12 October 2017; EMA Draft Guideline on the clinical investigation of medicinal products for the treatment of Axial Spondyloarthritis - Draft (CPMP/EWP/4891/03 Rev.1) 2016.

on the disease manifestation (e.g., axial, peripheral), the failure to respond to previous therapies and the disease activity.

No additional benefit was derived for either the IL-17 inhibitor ixekizumab or the JAK inhibitor upadacitinib in the early benefit assessment. Also, there are currently no guideline recommendations for the use of ixekizumab or upadacitinib, so these active ingredients are not yet considered established in care for this indication. Furthermore, also against the background of the ongoing EMA PRAC procedure, the significance of the JAK inhibitors cannot be conclusively assessed at present.

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

On a1)

For the therapy of r-axSpA after the failure of NSAIDs, all approved TNF-α inhibitors as well as the IL-17 inhibitor secukinumab, which has been approved since 2015, can be considered. The recommendations from the latest guidelines available in the indication unanimously see - especially for patients with certain comorbidities - the use of the IL-17 inhibitor secukinumab as an equal alternative to the established TNF-α inhibitors. Thus, for the "second-line therapy" of r-axSpA, the approved TNF-α inhibitors ((etanercept or adalimumab or infliximab or golimumab or certolizumab pegol)) or secukinumab are determined as appropriate comparator therapy; the named active ingredients are equally appropriate treatment options.

On a2)

For the "third-line therapy" of r-axSpA after the failure of a first TNF-α inhibitor or IL-17 inhibitor, the evidence is overall weaker compared to "second-line therapy". Regardless, even after a biologic failure, the available evidence does not allow prioritisation within the agents of TNF-α inhibitors or the IL-17 inhibitor secukinumab considered for "third-line therapy". Instead, it depends on comorbidities and patient-individual criteria as well as on the previous therapy to which further bDMARD is switched after the failure of a first therapy with a bDMARD. Against this background, in this line of therapy of active, radiographic axSpA, a switch to another approved bDMARD that is established in use is currently considered appropriate. Further differentiation of the patient population (e.g., also with regard to failure on 1 vs >1 bDMARD) is not made at this time due to the lack of uniform therapy recommendations.

Taking into account the respective authorisation status of the medicinal product in conjunction with the clinical course and against the background of the available body of evidence, TNF-α inhibitors (etanercept or adalimumab or infliximab or golimumab or

certolizumab pegol) or an IL-17 inhibitor (secukinumab) are determined as the appropriate comparator therapy for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to a conventional therapy (patient group a1). For adults with active ankylosing spondylitis who have had an inadequate response to, or intolerance to previous therapy with biologic antirheumatic drugs (bDMARDs) (patient group a2), a switch to another biological disease-modifying antirheumatic drug is determined to be an appropriate comparator therapy: switching to a TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL-17 inhibitor (secukinumab); the above active ingredients are considered equally appropriate treatment options.

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:

a1) Adults with active ankylosing spondylitis who have responded inadequately to conventional therapy and who are eligible for treatment with tofacitinib

An additional benefit is not proven.

a2) Adults with active ankylosing spondylitis who have had an inadequate response to, or intolerance to prior therapy with biologic antirheumatic drugs (bDMARDs) and who are eligible for treatment with tofacitinib

An additional benefit is not proven.

Justification for a1 and a2:

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

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient tofacitinib. The therapeutic indication assessed here is as follows: "Tofacitinib is indicated for the treatment of adult patients with active ankylosing spondylitis (AS) who have responded inadequately to conventional therapy".

Two patient groups were distinguished for the benefit assessment:

Patient group a1

For adults with active ankylosing spondylitis who have inadequately responded to conventional therapy and who are eligible for treatment with tofacitinib, the G-BA determined a TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (secukinumab) as an appropriate comparator therapy. For this patient group, the pharmaceutical company does not submit any suitable direct comparator data regarding the appropriate comparator therapy in the dossier for the assessment of the additional benefit. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment. Thus, no adequate data are available to assess the additional benefit of tofacitinib. In the overall assessment, the additional benefit of tofacitinib compared to the appropriate comparator therapy is not proven for this patient group.

Patient group a2

For adults with active ankylosing spondylitis who have had an inadequate response to, or intolerance to previous therapy with biologic antirheumatic drugs (bDMARD) and who are eligible for treatment with tofacitinib, the G-BA determined that switching to another bDMARD - a TNF-α inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL-17 inhibitor (secukinumab) was an appropriate comparator therapy. For this patient group, the pharmaceutical company does not submit any suitable direct comparator data regarding the appropriate comparator therapy in the dossier for the assessment of the additional benefit. Furthermore, no indirect comparisons were presented to address the question of the benefit assessment. Thus, no adequate data are available to assess the additional benefit of tofacitinib. In the overall assessment, the additional benefit of tofacitinib compared to the appropriate comparator therapy is not proven for this patient group.

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

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

The information is based on the data provided by the pharmaceutical company in the dossier. The figures are based on prevalence and incidence data from diagnosed patients.
Overall, the calculation of the number of patients tends to be underestimated and subject to uncertainties. This results in the same number of patients that also formed the basis in the

early benefit assessment of upadacitinib and ixekizumab[6] respectively. Due to the non-consideration of the updated warnings and precautions for use of tofacitinib from the product information for the calculation of patient numbers, uncertain data are assumed in the overall assessment, but are used as an approximation.

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: 14 April 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.

Treatment with tofacitinib should only be initiated and monitored by doctors experienced in treating ankylosing spondylitis.

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.

Against the background of the ongoing EMA PRAC procedure, the safety profile of the JAK inhibitors cannot be conclusively assessed at present.

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 May 2022).

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

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

[6] Resolution of the G-BA on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V for ixekizumab dated 21 January 2021 as well as for upadacitinib dated 15 July 2021.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Tofacitinib	continuously, 2 x daily	365	1	365
Appropriate comparator therapy				
Patient populations a1) + a2)				
Adalimumab	continuously, 1 x every 14 days	26.1	1	26.1
Certolizumab pegol	continuously, 1 x every 14 days	26.1	1	26.1
Etanercept	continuously, 1 x every 7 days	52.1	1	52.1
Golimumab	continuously, 1 x monthly	12	1	12
Infliximab	continuously, 1 x every 56 – 42 days	6.5 – 8.7	1	6.5 – 8.7
Secukinumab	continuously, 1 x monthly	12	1	12

Consumption:

For dosages depending on body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were applied (average body weight: 77.0 kg).[7]

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.

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

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Tofacitinib	5 mg	10 mg	2 x 5 mg	365	730 x 5 mg
Appropriate comparator therapy					
Patient populations a1) + a2)					
Adalimumab	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Certolizumab pegol	200 mg	200 mg	1 x 200 mg	26.1	26.1 x 200 mg
Etanercept	50 mg	50 mg	1 x 50 mg	52.1	52.1 x 50 mg
Golimumab	50 mg	50 mg	1 x 50 mg	12	12 x 50 mg
Infliximab	5mg/kg = 385 mg	385 mg	4 x 100 mg	6.5 – 8.7	26 x 400 mg – 34.8 x 400 mg
Secukinumab	150 mg – 300 mg	150 mg – 300 mg	1 x 150 mg – 2 x 150 mg	12	12 x 150 mg – 24 x 150 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal 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
Appropriate comparator therapy					

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
Adalimumab 40 mg[8]	6 SFI	€ 2,859.17	€ 1.77	€ 228.57	€ 2,628.83
Certolizumab pegol 200 mg[8]	6 SFI	€ 2,859.17	€ 1.77	€ 0.00	€ 2,857.40
Etanercept 50 mg[8]	12 SFI	€ 2,859.17	€ 1.77	€ 228.57	€ 2,628.83
Golimumab 50 mg[8]	3 IFE	€ 2,605.92	€ 1.77	€ 0.00	€ 2,604.15
Infliximab 100 mg[8]	5 PIC	€ 3,490.53	€ 1.77	€ 280.08	€ 3,208,68
Secukinumab 150 mg	6 PEN	€ 4,653.99	€ 1.77	€ 0.00	€ 4,652.22
Abbreviations: IFE = solution for injection in a pre-filled syringe; SFI = solution for injection; PEN = solution for injection in a pre-filled pen, PIC = powder for the preparation of an infusion solution concentrate, RET = retard tablets					

LAUER-TAXE® last revised: 15 May 2022

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

Diagnosis of chronic hepatitis B

Patients must be tested for the presence of HBV infection before initiating treatment with adalimumab or certolizumab pegol or etanercept or golimumab or infliximab. These investigations are not required for the use of secukinumab as appropriate comparator therapy but are regularly required for the use of tofacitinib as the medicinal product to be assessed.

For the diagnosis of suspected chronic hepatitis B, sensibly coordinated steps are required[9]. A

[8] Fixed reimbursement rate

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

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 total, additionally required SHI services are required for the diagnosis of suspected chronic hepatitis B and examinations for tuberculosis infections which usually differ between the medicinal product to be assessed 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 populations a1) and a2)				
Tofacitinib adalimumab Certolizumab pegol Etanercept Golimumab Infliximab	Quantitative determination of an in vitro interferon-gamma release after ex vivo stimulation with antigens (at least ESAT-6 and CFP-10) specific for Mycobacterium tuberculosis-complex (except BCG) (GOP 32670)	1	€ 58.00	€ 58.00
Tofacitinib adalimumab Certolizumab pegol Etanercept Golimumab Infliximab	Chest radiograph (GOP 34241)	1	€ 16.45	€ 16.45
Tofacitinib adalimumab Certolizumab pegol Etanercept Golimumab Infliximab	HBs antigen (GOP 32781)	1	€ 5.50	€ 5.50
	Anti-HBs antibody (GOP 32617)[10]	1	€ 5.50	€ 5.50
	Anti-HBc antibody (GOP 32614)	1	€ 5.90	€ 5.90

[10] Only if HBs antigen negative and anti-HBc antibody positive

Designation of the therapy	Designation of the service	Number	Unit cost	Costs per patient per year
	HBV-DNA (GOP 32823)[11]	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.

4. Process sequence

At its session on 11 February 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 10 December 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 1, sentence 2 VerfO.

By letter dated 13 December 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.

[11] Invoicing for GOP 32823 possible before or during antiviral therapy with interferon and/or nucleic acid analogues.

The dossier assessment by the IQWiG was submitted to the G-BA on 11 March 2022, and the written statement procedure was initiated with publication on the website of the G-BA on 15 March 2022. The deadline for submitting written statements was 5 April 2022.

The oral hearing was held on 25 April 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 June 2022, and the proposed resolution was approved.

At its session on 16 June 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	11 February 2020	Determination of the appropriate comparator therapy
Working group Section 35a	20 April 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	25 April 2022	Conduct of the oral hearing
Working group Section 35a	3 May 2022 17 May 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal products	24 May 2022	Concluding discussion of the draft resolution
Plenum	16 June 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 16 June 2022

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

Prof. Hecken