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: Polyarticular juvenile idiopathic arthritis, RF+ or RF- polyarthritis and extended oligoarthritis, and juvenile psoriatic arthritis, ≥ 2 years)

of 3 March 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 18 August 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 15 September 2021, i.e. at the latest within four weeks after the notification of the pharmaceutical company 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 (polyarticular juvenile idiopathic arthritis, RF+ or RF- polyarthritis and extended oligoarthritis, and juvenile psoriatic arthritis, ≥ 2 years).

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 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 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 active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs.

Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate.

Therapeutic indication of the resolution (resolution of 3 March 2022):

see approved new therapeutic indication

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), who have responded inadequately to previous therapy with conventional DMARDs (including MTX)

Appropriate comparator therapy for tofacitinib:

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

a bDMARD (adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX; if necessary, as monotherapy, taking into account the respective authorisation status in the case of MTX intolerance or unsuitability

b) Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), who have responded inadequately to previous therapy with one or more bDMARDs

Appropriate comparator therapy for tofacitinib:

a change of bDMARD therapy (abatacept or adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX; if necessary, as monotherapy, taking into account the respective authorisation status in case of MTX intolerance or unsuitability, depending on prior therapy

c) Patients 2 years of age and older with juvenile psoriatic arthritis who have responded inadequately to previous DMARD therapy

Appropriate comparator therapy for tofacitinib:

Therapy according to doctor's instructions

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 Federal Joint Committee has already determined the patient-relevant benefit 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. Glucocorticoids, non-steroidal anti-inflammatory drugs (NSAIDs), conventional disease-modifying antirheumatic drugs (cDMARDs; including MTX, sulfasalazine and hydroxychloroquine) and biologic DMARDs (bDMARDs; here etanercept, adalimumab,

golimumab, tocilizumab, abatacept) are approved for the treatment of polyarticular juvenile idiopathic arthritis (pJIA). For the approved therapeutic indications of cDMARDs and bDMARDs, some specifications on the approved age and, if applicable, on the approved JIA subtypes have to be additionally considered. Also, the active ingredients abatacept and golimumab are only approved in combination with MTX.

Specifically, the TNFα inhibitor etanercept is approved for the treatment of juvenile psoriatic arthritis (jPsA) in adolescents 12 years of age and older who have inadequately responded to NSAIDs and DMARDs.

On 2. Non-medicinal measures at the expense of the SHI are not considered as sole appropriate comparator therapy in the present therapeutic indication.

On 3. In the therapeutic indication under consideration here, no resolutions of the G-BA are available:

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present therapeutic indication, with a focus on the polyarticular form of JIA as well as on jPsA.

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.

For the treatment of patients 2 years of age and older with pJIA, it can first be stated that different diseases can be distinguished within the therapeutic indication of JIA, whereby several subtypes can be characterised by a polyarticular course - including the polyarticular forms of rheumatoid factor positive [RF+] or rheumatoid factor negative [RF-] polyarthritis specified in the approved therapeutic indication of tofacitinib, and also the extended oligoarthritis. The G-BA considers it appropriate to differentiate the patient population according to pJIA (a+b) and jPsA (c) for the determination of the appropriate comparator therapy since juvenile PsA, which is also specified in the approved therapeutic indication of tofacitinib, is another subtype of JIA that is not counted as pJIA. This is also supported by the existing differences in the therapeutic indications of the approved medicinal products for different JIA subtypes as well as by the recommendations of the guidelines.

In view of the fact that JIA is usually diagnosed at an age ≤ 16 years and that JIA (e.g. in demarcation from rheumatoid arthritis diagnosed in advanced adulthood) is an independent clinical picture, the therapeutic indication to be assessed here includes patients 2 years of age and older - including children, adolescents and also adults with a corresponding diagnosis of JIA in childhood or adolescence.

<u>On a) and (b) patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis)</u>

The German guideline (S2k guideline of the DGKJ and GKJR from 2019) recommends the use of conventional DMARDs (cDMARDs) in the first-line therapy of pJIA after failure of (symptomatic) NSAIDs, including in particular a treatment with methotrexate.

In the further course of the disease, it can be deduced from the recommendations that therapy of pJIA should be carried out with a (first) bDMARD after failure of cDMARDs. In addition, if a first bDMARD fails, therapy should be switched to another bDMARD. In this context, the aggregated evidence for bDMARDs gives evidence-based preference to combination with MTX over monotherapy with bDMARDs, if possible and if the authorisation status of the bDMARD does not conflict with this. If necessary, both the first and the other bDMARD can be given as monotherapy in the case of MTX intolerance or unsuitability, taking into account the respective authorisation status. Within the class of bDMARDs, the German guideline only differentiates in its recommendation on abatacept, while for the other approved bDMARDs, the specific recommendations of the guideline do not derive any priority or subordination among each other, neither within the TNFα inhibitors, nor between TNFα inhibitors and the IL inhibitor tocilizumab. The recommendation level for the active ingredient abatacept is lowered compared to that of the other approved bDMARDs in the German S2k guideline, so that abatacept is regarded as subordinate to adalimumab, etanercept, golimumab and tocilizumab and, against this background, the use of abatacept is currently only considered appropriate for those patients who have failed or not tolerated a first bDMARD.

The G-BA assumed for the patient population covered by the marketing authorisation with insufficient response to previous treatment with conventional DMARDs (including MTX) that these patients are not (or no longer) eligible for sole (symptomatic) therapy with NSAIDs and/or glucocorticoids. Irrespective of this, the use of glucocorticoids (systemic and/or intra-articular) should always be possible in the context of flare therapy. Even though it is a heterogeneous clinical picture with different subtypes of JIA, the G-BA currently sees no need to further subdivide the three patient groups with regard to the underlying JIA subtypes. Also, at present, neither the authorisation status of the cDMARDs or bDMARDs with regard to age and/or JIA subtype nor the recommendations derived from the aggregated evidence result in the need for a further subdivision.

Taking into account the aggregated evidence and the respective authorisation status, the G-BA considers the use of a (first) bDMARD (including adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX, if necessary as monotherapy, as appropriate for patients 2 years of age and older with active pJIA who have responded inadequately to previous treatment with conventional DMARDs (including MTX) (population a1+a2), taking into account the respective authorisation status in the case of MTX intolerance or unsuitability. The above-mentioned options are equally appropriate options. For patients 2 years of age and older with active pJIA who responded inadequately to previous treatment with one or more bDMARDs (population b1+b2), the G-BA considers change of bDMARD therapy (abatacept or adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX; if necessary, as monotherapy, as appropriate comparator therapy taking into account the respective authorisation status in case of MTX intolerance or unsuitability, depending on prior therapy. The options mentioned are each considered to be equally appropriate comparator therapies.

<u>On c) Patients 2 years of age and older with juvenile psoriatic arthritis who have inadequately responded to previous DMARD therapy</u>

No guidelines could be identified for the treatment of jPsA. The German guideline on juvenile idiopathic arthritis (S2k guideline of the DGKJ and GKJR from 2019) also takes jPsA into account in parts, but references are mainly made to evidence from pJIA. Overall, the guideline recommends the use of methotrexate for the treatment of jPsA after failure of (symptomatic) NSAIDs and, if necessary, short-term use of glucocorticoids. If there is an inadequate response or intolerance to cDMARDs, the guideline advocates the use of TNFα inhibitors. Only the TNFα inhibitor etanercept is currently approved for the treatment of active juvenile psoriatic arthritis in adolescents aged 12 years and older who have inadequately responded to DMARDs. Currently, in cases of inadequate response or intolerance to cDMARDs, the therapeutic significance of MTX in combination with a TNFα inhibitor (here etanercept) cannot be assessed.

Against this background, in the absence of medicinal products approved for the treatment of jPsA in patients 2 years of age and older, the G-BA considers treatment according to the doctor's instructions to be appropriate. In the context of a therapy according to the doctor's instructions, the active ingredient etanercept is considered to be a suitable comparator for patients 2 years of age and older in the present therapeutic indication for patients 2 years of age and older with juvenile psoriatic arthritis who have responded inadequately to previous DMARD therapy.

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

2.1.3 Extent and probability of the additional benefit

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

a) Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), who have responded inadequately to previous therapy with conventional DMARDs (including MTX)

For patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), who have responded inadequately to previous treatment with conventional DMARDs (including MTX), the additional benefit of tofacitinib (as monotherapy in case of MTX intolerance or MTX unsuitability or in combination with MTX) compared to the appropriate comparator therapy is not proven.

Justification for a1 and a2:

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

b) Patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), who have responded inadequately to previous therapy with one or more bDMARDs

For patients 2 years of age and older with active pJIA (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), who have responded inadequately to previous treatment with one or more bDMARDs, the additional benefit of tofacitinib (as monotherapy in case of MTX intolerance or MTX unsuitability or in combination with MTX) compared to the appropriate comparator therapy is not proven.

Justification for b1 and b2:

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

c) Patients 2 years of age and older with juvenile psoriatic arthritis who have inadequately responded to previous DMARD therapy

For patients 2 years of age and older with juvenile psoriatic arthritis who have responded inadequately to previous DMARD therapy, the additional benefit of tofacitinib compared to the appropriate comparator therapy is not proven.

Justification for c:

In his 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 active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), and juvenile psoriatic arthritis (PsA) in patients 2 years of age and older, who have responded inadequately to previous therapy with DMARDs. Tofacitinib can be given in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate".

Five patient groups were distinguished for the benefit assessment:

Patient group a1

For patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), who have responded inadequately to previous treatment with conventional DMARDs (including MTX), the G-BA determined a bDMARD (adalimumab or etanercept or tocilizumab) as monotherapy as an appropriate comparator therapy in case of MTX intolerance or MTX unsuitability. 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. Overall, the additional benefit of tofacitinib as monotherapy compared to the appropriate comparator therapy is not proven for this patient group.

Patient group a2

For patients 2 years of age and older with active polyarticular juvenile idiopathic arthritis (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), who have responded inadequately to previous treatment with conventional DMARDs (including MTX), the G-BA determined a bDMARD (adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX 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 in combination with MTX compared to the appropriate comparator therapy is not proven for this patient group.

Patient group b1

For patients 2 years of age and older with active pJIA (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), who have responded inadequately to previous treatment with one or more bDMARDs, the G-BA determined a change in bDMARD therapy (adalimumab or etanercept or tocilizumab) as monotherapy, depending on prior therapy, as an appropriate comparator therapy in case of MTX intolerance or MTX unsuitability. 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 as monotherapy compared to the appropriate comparator therapy is not proven for this patient group.

Patient group b2

For patients 2 years of age and older with active pJIA (rheumatoid factor positive [RF+] or negative [RF-] polyarthritis and extended oligoarthritis), who have responded inadequately to previous treatment with one or more bDMARDs, the G-BA determined a change in bDMARD therapy (abatacept or adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX, depending on prior therapy, 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 picture for this patient group the additional benefit of tofacitinib in combination with MTX compared with the appropriate comparator therapy is not proven.

Patient group c)

For patients 2 years of age and older with juvenile psoriatic arthritis who have responded inadequately to previous DMARD therapy, the G-BA determined a therapy according to doctor's instructions as the 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 these patients.

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

The information on the number of patients is based on the target population in statutory health insurance (SHI).
The information is based on the data provided by the pharmaceutical company in the dossier. The calculation of the size of the target population was based on routine data analyses and is subject to uncertainties in the overall picture. These result, among other things, from the methodology used for the proportion values to distinguish between treatment with cDMARDs and bDMARDs.

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: 1 February 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 patients with JIA (juvenile idiopathic arthritis) and jPsA (juvenile psoriatic arthritis).

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: 01 March 2022).

Treatment period:

The recommended treatment modes for tocilizumab in children ≥ 2 years and adults differ according to the product information[2]. The frequency of use is every 7 days and every 21 days.

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
Methotrexate, if necessary	Continuously, 1 x every 7 days	52.1	1	52.1
Appropriate comparator therapy for patient population a				
Methotrexate, if necessary	Continuously, 1 x every 7 days	52.1	1	52.1
Adalimumab	1x every 14 days	26.1	1	26.1
Etanercept	1 x every 7 days or 2 x within 7 days	52.1	1 - 2	52.1 – 104.2

[2] https://www.ema.europa.eu/en/documents/product-information/roactemra-epar-product-information_en.pdf (last accessed: 19 January 2022)

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Golimumab	1 x monthly (always on the same day)	12.0	1	12.0
Tocilizumab	Children ≥ 2 years			
	Continuously, 1 x every 21 days	17.4	1	17.4
	Adults			
	Continuously, 1 x every 7 days	52.1	1	52.1
Appropriate comparator therapy for patient population b				
Methotrexate, if necessary	Continuously, 1 x every 7 days	52.1	1	52.1
Abatercept	Continuously, 1 x every 7 days	52.1	1	52.1
Adalimumab	1x every 14 days	26.1	1	26.1
Etanercept	1 x every 7 days or 2 x within 7 days	52.1	1 - 2	52.1 – 104.2
Golimumab	1 x monthly (always on the same day)	12.0	1	12.0
Tocilizumab	Children ≥ 2 years			
	Continuously, 1 x every 21 days	17.4	1	17.4
	Adults			
	Continuously, 1 x every 7 days	52.1	1	52.1
Appropriate comparator therapy for patient population c				
Therapy according to doctor's instructions	Different from patient to patient			

Consumption

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

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or 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. The average body weight of a 2-year-old child is 14.1 kg with an average height of 0.93 m while the average weight of an adult is 77.0 kg. From this, a body surface area of 0.59 m^2 is calculated for children 2 years of age and 1.90 m^2 for adults (calculation according to Du Bois 1916).

For patients < 40 kg body weight (BW), the administration of an oral solution is intended according to table 2 of the product information of tofacitinib[3]. From a body weight of ≥ 40 kg BW, administration of an oral solution or a film-coated tablet is optional. These specifications are taken into account for the calculation of the annual treatment costs.

Methotrexate is available on the market in both oral and parenteral dosage forms. For the cost representation, it is assumed that patients with a body weight of 35 kg or more (corresponding to an age of approx. 9 to 10 years) can usually take the more economical option (tablets). Conversely, the parenteral dosage form is used to calculate the annual treatment costs for the lower range (children ≥ 2 years).

Golimumab is administered for children < 40 kg BW using an injector[4], which is not the most economical dosage form available, according to Simponi's product information. The dosage for children 2 years of age and older is given as 30 mg/m^2 body surface area (BSA), which, taking into account the above framework criteria, corresponds to a single dose of 17.7 mg.

According to the product information, the use of abatacept is only approved with the dosage form of the injection solution for children 2 years and older. Intravenous administration is not

[3] https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf (last access: 17 January 2022)
[4] https://www.ema.europa.eu/en/documents/product-information/simponi-epar-product-information_en.pdf (last accessed: 22 December 2021).

indicated for this age group and is therefore not included in the calculation of annual treatment costs for children 2 years of age and older.[5]

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	Children ≥ 2 years				
	3.2 mg - 5 mg	6.4 mg - 10 mg	2 x 3.2 mg - 2 x 5 mg	365	730 x 3.2 mg - 730 x 5 mg
	Adults				
	5.0 mg	10.0 mg	2 x 5.0 mg	365	730 x 5.0 mg
Methotrexate, if necessary[6]	Children ≥ 2 years				
	10 - 30 mg/ m^2 BSA = 6.7 mg - 20.1 mg	6.7mg - 20.1mg	1 x 7.5 mg + 1 x 20 mg	52.1	52.1 x 7.5 mg + 52.1 x 20 mg
	Adults				
	7.5 mg - 20 mg	7.5 mg - 20 mg	1 x 7.5 mg - 2 x 10 mg	52.1	52.1 x 7.5 mg - 104.2 x 10 mg
Appropriate comparator therapy for patient population a					
Monotherapy					
Methotrexate[6]	Children ≥ 2 years				
	10 - 30 mg/ m^2 BSA = 6.7 mg - 20.1 mg	6.7mg - 20.1mg	1 x 7.5 mg + 1 x 20 mg	52.1	52.1 x 7.5 mg + 52.1 x 20 mg
	Adults				
	7.5 mg - 20 mg	7.5 mg - 20 mg	1 x 7.5 mg - 2 x 10 mg	52.1	52.1 x 7.5 mg - 104.2 x 10 mg
Adalimumab	Children ≥ 2 years				

[5] https://www.ema.europa.eu/en/documents/product-information/orencia-epar-product-information_en.pdf (last accessed: 22 December 2021).

[6] For the presentation of the consumption and the calculation of the annual treatment costs, only the parenteral dosage form was used for the population of children illustrated due to their age.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	20 mg	20 mg	1 x 20 mg	26.1	26.1 x 20 mg
	Adults				
	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Etanercept	Children ≥ 2 years				
	0.4 mg/kg BW = 5.64 mg	5.64 mg	1 x 10 mg	104.2	104.2 x 10 mg
	or				
	0.8 mg/ kg BW = 11.28 mg	11.28 mg	2 x 10 mg	52.1	104.2 x 10 mg
	Adults				
	25 mg	25 mg	1 x 25 mg	104.2	104.2 x 25 mg
	or				
	50 mg	50 mg	1 x 50 mg	52.1	52.1 x 50 mg
Tocilizumab[7]	Children ≥ 2 years				
	162 mg	162 mg	1 x 162 mg	17.4	17.4 x 162 mg
	Adults				
	162 mg	162 mg	1 x 162 mg	52.1	52.1 x 162 mg
Combination therapy					
Methotrexate[6]	Children ≥ 2 years				
	10 - 30 mg/ m^2 BSA = 6.7 mg - 20.1 mg	6.7mg - 20.1mg	1 x 7.5 mg - 1 x 20 mg	52.1	52.1 x 7.5 mg + 52.1 x 20 mg
	Adults				
	7.5 mg - 20 mg	7.5 mg - 20 mg	1 x 7.5 mg - 2 x 10 mg	52.1	52.1 x 7.5 mg - 104.2 x 10 mg

[7] Only the most economical dosage form (solution for injection) was used for the presentation of the consumption and the calculation of the annual treatment costs.

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Adalimumab	Children > 2 years				
	20 mg	20 mg	1 x 20 mg	26.1	26.1 x 20 mg
	Adults				
	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Etanercept	Children ≥ 2 years				
	0.4 mg/kg BW = 5.64 mg	5.64 mg	1 x 10 mg	104.2	104.2 x 10 mg
	or				
	0.8 mg/ kg BW = 11.28 mg	11.28 mg	2 x 10 mg	52.1	104.2 x 10 mg
	Adults				
	25 mg	25 mg	1 x 25 mg	104.2	104.2 x 25 mg
	or				
	50 mg	50 mg	1 x 50 mg	52.1	52.1 x 50 mg
Golimumab	Children ≥ 2 years				
	30 mg/ m^2 = 17.7 mg	17.7 mg	1 x 45 mg	12.0	12.0 x 45 mg
	Adults				
	50 mg	50 mg	1 x 50 mg	12.0	12.0 x 50 mg
Tocilizumab[7]	Children ≥ 2 years				
	162 mg	162 mg	1 x 162 mg	17.4	17.4 x 162 mg
	Adults				
	162 mg	162 mg	1 x 162 mg	52.1	52.1 x 162 mg
Appropriate comparator therapy for patient population b					
Monotherapy					
Methotrexate[6]	Children ≥ 2 years				
	10 - 30 mg/ m^2 BSA = 6.7 mg - 20.1 mg	6.7 mg – 20.1 mg	1 x 7.5 mg – 1 x 20 mg	52.1	52.1 x 7.5 mg – 52.1 x 20 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	Adults				
	7.5 mg - 20 mg	7.5 mg - 20 mg	1 x 7.5 mg - 2 x 10 mg	52.1	52.1 x 7.5 mg - 104.2 x 10 mg
Adalimumab	Children ≥ 2 years				
	20 mg	20 mg	1 x 20 mg	26.1	26.1 x 20 mg
	Adults				
	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Etanercept	Children ≥ 2 years				
	0.4 mg/kg BW = 5.64 mg	5.64 mg	1 x 10 mg	104.2	104.2 x 10 mg
	or				
	0.8 mg/kg BW = 11.28 mg	11.28 mg	2 x 10 mg	52.1	104.2 x 10 mg
	Adults				
	25 mg	25 mg	1 x 25 mg	104.2	104.2 x 25 mg
	or				
	50 mg	50 mg	1 x 50 mg	52.1	52.1 x 50 mg
Tocilizumab[7]	Children ≥ 2 years				
	162 mg	162 mg	162 mg	17.4	17.4 x 162 mg
	Adults				
	162 mg	162 mg	162 mg	52.1	52.1 x 162 mg
Combination therapy					
Methotrexate[6]	Children ≥ 2 years				
	10 – 30 mg/m^2 BSA = 6.7 mg – 20.1 mg	6.7 mg – 20.1 mg	1 x 7.5 mg – 1 x 20 mg	52.1	52.1 x 7.5 mg – 52.1 x 20 mg
	Adults				

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	7.5 mg - 20 mg	7.5 mg - 20 mg	1 x 7.5 mg - 2 x 10 mg	52.1	52.1 x 7.5 mg - 104.2 x 10 mg
Abatacept	Children ≥ 2 years				
	50 mg	50 mg	1 x 50 mg	52.1	52.1 x 50 mg
	Adults				
	125 mg	125 mg	1 x 125 mg	52.1	52.1 x 125 mg
Adalimumab	Children ≥ 2 years				
	20 mg	20 mg	1 x 20 mg	26.1	26.1 x 20 mg
	Adults				
	40 mg	40 mg	1 x 40 mg	26.1	26.1 x 40 mg
Etanercept	Children ≥ 2 years				
	0.4 mg/kg BW = 5.64 mg	5.64 mg	1 x 10 mg	104.2	104.2 x 10 mg
	or				
	0.8 mg/kg BW = 11.28 mg	11.28 mg	2 x 10 mg	52.1	104.2 x 10 mg
	Adults				
	25 mg	25 mg	1 x 25 mg	104.2	104.2 x 25 mg
	or				
	50 mg	50 mg	1 x 50 mg	52.1	52.1 x 50 mg
Golimumab	Children ≥ 2 years				
	30 mg/m^2 = 17.7 mg	17.7 mg	1 x 45 mg	12.0	12.0 x 45 mg

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
	Adults				
	50 mg	50 mg	1 x 50 mg	12.0	12.0 x 50 mg
Tocilizumab[7]	Children ≥ 2 years				
	162 mg	162 mg	162 mg	17.4	17.4 x 162 mg
	Adults				
	162 mg	162 mg	162 mg	52.1	52.1 x 162 mg
Appropriate comparator therapy for patient population c					
Therapy according to doctor's instructions	Different from patient to patient				

Costs:

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

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 240 mg	1 OS	€ 848.43	€ 1.77	€ 0.00	€ 846.66
Tofacitinib 5 mg	182 FCT	€ 3,134.85	€ 1.77	€ 0.00	€ 3,133.08

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
Methotrexate 7.5 mg[8]	12 IFE	€ 153.95	€ 1.77	€ 11.28	€ 140.90
Methotrexate 7.5 mg[8]	30 TAB	€ 33.71	€ 1.77	€ 1.77	€ 30.17
Methotrexate 10 mg[8]	30 TAB	€ 41.59	€ 1.77	€ 2.40	€ 37.42
Methotrexate 20 mg[8]	12 IFE	€ 270.94	€ 1.77	€ 20.54	€ 248.63
Appropriate comparator therapy					
Abatacept 50 mg	4 SFI	€ 642.29	€ 1.77	€ 34.94	€ 605.58
Abatacept 125 mg	12 PEN	€ 4,645.64	€ 1.77	€ 262.02	€ 4,381.85
Adalimumab 20 mg	1 SFI	€ 256.18	€ 1.77	€ 13.56	€ 240.85
Adalimumab 40 mg[8]	6 SFI	€ 2,859.17	€ 1.77	€ 228.57	€ 2,628.83
Etanercept 10 mg	4 DSS	€ 207.04	€ 1.77	€ 10.84	€ 194.43
Etanercept 25 mg[8]	24 SFI	€ 2,859.17	€ 1.77	€ 228.57	€ 2,628.83
Etanercept 50 mg[88]	12 SFI	€ 2,859.17	€ 1.77	€ 228.57	€ 2,628.83
Golimumab 45 mg	1 SFI	€ 1,845.88	€ 1.77	€ 102.13	€ 1,741.98
Golimumab 50 mg[8]	3 IFE	€ 2,605.92	€ 1.77	€ 0.00	€ 2,604.15
Methotrexate 7.5 mg[8]	12 IFE	€ 153.95	€ 1.77	€ 11.28	€ 140.90
Methotrexate 7.5 mg[8]	30 TAB	€ 33.71	€ 1.77	€ 1.77	€ 30.17
Methotrexate 10 mg[8]	30 TAB	€ 41.59	€ 1.77	€ 2.40	€ 37.42
Methotrexate 20 mg[8]	12 IFE	€ 270.94	€ 1.77	€ 20.54	€ 248.63
Tocilizumab 162 mg	12 SFI	€ 5,505.74	€ 1.77	€ 311.14	€ 5,192.83
Abbreviations: FCT = film-coated tablets, IFE = solution for injection in a pre-filled syringe, SFI = solution for injection, OS = oral solution, PEN = solution for injection in a pre-filled pen, TAB = tablets, DSS = dry substance with solvent.					

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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

[8] Fixed reimbursement rate

For active ingredients of the appropriate comparator therapy of the patient populations a and b (abatacept, adalimumab, etanercept, golimumab, tocilizumab), costs are regularly incurred for examination of 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 a and b, the costs for additionally required SHI services for tests for tuberculosis infections are not presented in the resolution for patient groups a and b.

Diagnosis of chronic hepatitis B

Patients must be tested for the presence of HBV infection prior to initiating treatment with abatacept or adalimumab or etanercept or golimumab. These examinations are not required for the use of tocilizumab as the 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 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.

Additionally required SHI services are required for the diagnosis of suspected chronic hepatitis B, which usually differ between the medicinal product to be assessed and tocilizumab as 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 a and b				
Tofacitinib Abatacept Adalimumab	Quantitative determination of an in vitro interferon-gamma release after ex vivo stimulation with	1	€ 58.00	€ 58.00

[9] "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
Etanercept Golimumab Tocilizumab	antigens (at least ESAT-6 and CFP-10) specific for Mycobacterium tuberculosis-complex (except BCG) (GOP 32670)			
Tofacitinib Abatacept Adalimumab Etanercept Golimumab Tocilizumab	Chest radiograph (GOP 34241)	1	€ 16.45	€ 16.45
Tofacitinib Abatacept Adalimumab Etanercept Golimumab	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
	HBV-DNA (GOP 32823)[11]	1	€ 89.50	€ 89.50

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 25 August 2020, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

The appropriate comparator therapy determined by the G-BA was reviewed. The Subcommittee on Medicinal Products determined parts of the appropriate comparator therapy again at its session on 24 August 2021.

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

On 15 September 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 16 September 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 13 December 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 15 December 2021. The deadline for submitting written statements was 5 January 2022.

The oral hearing was held on 24 January 2022.

On 3 February 2022, the IQWiG submitted a new version of IQWiG's dossier assessment to the G-BA. This version 1.1 dated 2 February 2022 replaces version 1.0 of the dossier assessment dated 13 December 2021. The assessment result was not affected by the changes in version 1.1 compared to version 1.0.

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

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 22 February 2022, and the proposed resolution was approved.

At its session on 3 March 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	25 August 2020 24 August 2021	Determination of the appropriate comparator therapy
Working group Section 35a	18 January 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	24 January 2022	Conduct of the oral hearing
Working group Section 35a	1 February 2022 15 February 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	22 February 2022	Concluding discussion of the draft resolution

Plenum	3 March 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 3 March 2022

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

Prof. Hecken