IQWiG Reports – Commission No. A21-121

Tofacitinib (polyarticular juvenile idiopathic arthritis and juvenile psoriatic arthritis) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Tofacitinib (polyartikuläre juvenile idiopathische Arthritis und juvenile Psoriasis-Arthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 December 2021). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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IQWiG thanks the medical and scientific advisor for her contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by one person.

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment as well as their treatment goals. The respondents were not involved in the actual preparation of the dossier assessment.

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Table of contents

List of tables[2]

Page

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
DMARD	disease modifying antirheumatic drug
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
jPsA	juvenile psoriatic arthritis
pJIA	polyarticular juvenile idiopathic arthritis
MTX	methotrexate
RCT	randomized controlled trial
RF	rheumatoid factor
SGB	Sozialgesetzbuch (Social Code Book)

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug tofacitinib. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 16 September 2021.

Research question

The aim of this report is to assess the added benefit of tofacitinib in comparison with the appropriate comparator therapy (ACT) in patients with active polyarticular juvenile idiopathic arthritis (pJIA) and juvenile psoriatic arthritis (jPsA) from the age of 2 years who have had an inadequate response to prior therapy with disease modifying antirheumatic drugs (DMARDs). For this report, pJIA includes rheumatoid factor positive (RF+) or negative (RF-) polyarthritis as well as extended oligoarthritis. Tofacitinib can be used in combination with methotrexate (MTX) or as monotherapy in case of intolerance to MTX or unsuitability of continued MTX therapy.

The G-BA's specification of the ACT results in the research questions presented in Table 2.

Table 2: Research questions of the benefit assessment of tofacitinib

Research question	Therapeutic indication	ACT[a]
1	Patients from the age of 2 years with active pJIA who have had an inadequate response to prior therapy with classic DMARDs (including MTX)[b]	bDMARD (adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX; in case of MTX intolerance or unsuitability, as monotherapy in consideration of the respective approval status
2	Patients from the age of 2 years with active pJIA who have had an inadequate response to prior therapy with one or more bDMARDs[b]	Switch of bDMARD therapy (abatacept or adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX; in case of MTX intolerance or unsuitability, in the form of monotherapy in consideration of the respective approval status, depending on prior therapy
3	Patients from the age of 2 years with (active) jPsA who have had an inadequate response to prior therapy with DMARDs[b]	Therapy upon the physician's discretion[c]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, patients included in the therapeutic indication are assumed to be (or have become) ineligible for (symptomatic) monotherapy with NSAIDs and/or glucocorticoids. For flare treatment, the use of (systemic and/or intraarticular) glucocorticoids should be possible.
c. The TNFα antagonist etanercept is approved for the treatment of juvenile psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, MTX therapy. In the present therapeutic indication, the active substance etanercept is deemed a suitable comparator for patients from the age of 2 years.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; jPsA: juvenile psoriatic arthritis; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; pJIA: polyarticular juvenile idiopathic arthritis; TNF: tumour necrosis factor

In departure from the G-BA's specification, the company's dossier discusses only 2 research questions. For patients with pJIA, the allocation of research questions 1 and 2 as well as the respective specification of the ACT is in line with the G-BA's. However, in addition to patients with pJIA, the company includes in these research questions patients with jPsA, rather than analysing this patient group through a separate research question. With this approach, the company complies with the ACT specified by the G-BA for patients with pJIA, but for those with jPsA, it departs from the G-BA's specification by using the same ACT as for patients with pJIA. Departing from the company's approach, this benefit assessment uses the ACT specified by the G-BA even for patients with jPsA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of added benefit.

Results

In line with the company's assessment, the check of completeness of the study pool did not identify any relevant RCT for assessing added benefit of tofacitinib in comparison with the ACT. The company also did not present any other data for assessing added benefit.

Therefore, no suitable data are available for assessing the added benefit of tofacitinib in comparison with the ACT in patients with active pJIA and jPsA from the age of 2 years who have had an inadequate response to a prior therapy with DMARDs. Consequently, there is no hint of added benefit of tofacitinib in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of tofacitinib.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e. no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Tofacitinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Patients from the age of 2 years with active pJIA who have had an inadequate response to prior therapy with classic DMARDs (including MTX)[b]	One bDMARD (adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX; in case of MTX intolerance or unsuitability, possibly as monotherapy in consideration of the respective approval status	Added benefit not proven
2	Patients from the age of 2 years with active pJIA who have had an inadequate response to prior therapy with one or more bDMARDs[b]	A switch in bDMARD therapy (abatacept or adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX; in case of MTX intolerance or unsuitability, possibly in the form of monotherapy in consideration of the respective approval status, depending on prior therapy	Added benefit not proven
3	Patients from the age of 2 years with (active) jPsA who have had an inadequate response to prior therapy with DMARDs[b]	Therapy upon the physician's discretion[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, patients included in the therapeutic indication are assumed to not (or no longer) be eligible for (symptomatic) monotherapy with NSAIDs and/or glucocorticoids. For flare treatment, the use of (systemic and/or intraarticular) glucocorticoids should be possible.
c. The TNFα antagonist etanercept is approved for the treatment of juvenile psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, MTX therapy. In the present therapeutic indication, the active substance etanercept is deemed a suitable comparator for patients from the age of 2 years.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; jPsA: juvenile psoriatic arthritis; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; pJIA: polyarticular juvenile idiopathic arthritis; TNF: tumour necrosis factor

The G-BA decides on the added benefit.

2.2 Research question

The aim of this report is to assess the added benefit of tofacitinib in comparison with the ACT in patients from the age of 2 years with active pJIA or jPsA who have had an inadequate response to prior DMARD therapy. pJIA includes RF-positive or RF-negative polyarthritis as well as extended oligoarthritis. Tofacitinib can be used in combination with MTX or as monotherapy in case of intolerance to MTX or unsuitability of continued MTX therapy.

The G-BA's specification of the ACT results in the research questions presented in Table 4.

Table 4: Research questions of the benefit assessment of tofacitinib

Research question	Therapeutic indication	ACT[a]
1	Patients from the age of 2 years with active pJIA who have had an inadequate response to prior therapy with classic DMARDs (including MTX)[b]	bDMARD (adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX; in case of MTX intolerance or unsuitability, as monotherapy in consideration of the respective approval status
2	Patients from the age of 2 years with active pJIA who have had an inadequate response to prior therapy with one or more bDMARDs[b]	Switch of bDMARD therapy (abatacept or adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX; in case of MTX intolerance or unsuitability, in the form of monotherapy in consideration of the respective approval status, depending on prior therapy
3	Patients from the age of 2 years with (active) jPsA who have had an inadequate response to prior therapy with DMARDs[b]	Therapy upon the physician's discretion[c]

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, patients included in the therapeutic indication are assumed to be (or have become) ineligible for (symptomatic) monotherapy with NSAIDs and/or glucocorticoids. For flare treatment, the use of (systemic and/or intraarticular) glucocorticoids should be possible.
c. The TNFα antagonist etanercept is approved for the treatment of juvenile psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, MTX therapy. In the present therapeutic indication, the active substance etanercept is deemed a suitable comparator for patients from the age of 2 years.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; jPsA: juvenile psoriatic arthritis; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; pJIA: polyarticular juvenile idiopathic arthritis; TNF: tumour necrosis factor

In departure from the G-BA's specification, the company's dossier discusses only 2 research questions. For patients with pJIA, the definition of research questions 1 and 2 as well as the respective specification of the ACT is in line with the G-BA's. However, the company subjects both the pJIA patients and the jPsA patients to these research questions, rather than investigating the latter under a separate research question. With this approach, the company complies with the ACT specified by the G-BA for patients with pJIA, but for those with jPsA, it departs from the G-BA's specification by using the same ACT as for patients with pJIA.

Unlike the company, this benefit assessment uses the ACT specified by the G-BA even for patients with jPsA. Since the company did not submit any suitable data (see Section 2.3 for an explanation), the company's approach remains inconsequential for this benefit assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

Sources cited by the company in the dossier:

- Study list on tofacitinib (as of 25 July 2021)
- Bibliographic literature search on tofacitinib (most recent search on 2 August 2021)
- Search in trial registries / study results databases on tofacitinib (most recent search on 2 August 2021)
- Search on the G-BA website on tofacitinib (most recent search on 2 August 2021)
- Bibliographic literature search on the ACT (most recent search on 2 August 2021)
- Search in trial registries or results databases on the ACT (most recent search on 2 August 2021)
- Search on the G-BA website on the ACT (most recent search on 2 August 2021)

To check the completeness of the study pool:

- Search in trial registries for tofacitinib (most recent search on 30 September 2021); see Appendix A of the full dossier assessment for search strategies.

The check of completeness of the study pool did not identify any relevant RCTs for assessing the added benefit of tofacitinib in comparison with the ACT for any of the 3 research questions of this benefit assessment. This is in line with the company's assessment in that it likewise did not identify any relevant RCT. However, the company did not analyse patients with jPsA in a separate research question and hence defined an ACT not specified by the G-BA for this patient group (see Section 2.2). This is of no consequence for this benefit assessment since the check of completeness of the study pool did not identify any relevant RCTs for assessing the added benefit of tofacitinib in comparison with the ACT in patients with jPsA.

The company further reports that it searched for RCTs to perform an indirect comparison between tofacitinib and the ACT. However, the company states that it found no suitable studies from this search, and the company's dossier therefore does not present an indirect comparison. Module 4 A, Section 4.4.2 of the company's dossier refers to results from the placebo-

controlled approval study A3921104 [3]. The company correctly decided not to use these results to derive any added benefit, however. Overall, the company sees no proof of added benefit of tofacitinib in comparison with the ACT.

The company's approach is plausible. The A3921104 study is a randomized, double-blind study comparing tofacitinib with placebo after response to 18-week tofacitinib therapy. The study included patients 2 to 17 years of age with active RF-positive polyarthritis, RF-negative polyarthritis, extended oligoarthritis, systemic juvenile idiopathic arthritis without active systemic disease, jPsA, or enthesitis-associated arthritis. The study did not implement the ACT for any of the 3 research questions of this benefit assessment. Concurring with the company, the study is therefore deemed unsuitable for assessing added benefit of tofacitinib in comparison with the ACT.

2.4 Results on added benefit

No suitable data are available for assessing the added benefit of tofacitinib in comparison with the ACT in patients with active pJIA and jPsA from the age of 2 years who have had an inadequate response to prior therapy with DMARDs. Consequently, there is no hint of added benefit of tofacitinib in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 presents a summary of the results of the benefit assessment of tofacitinib in comparison with the ACT.

Table 5: Tofacitinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Patients from the age of 2 years with active pJIA who have had an inadequate response to prior therapy with classic DMARDs (including MTX)[b]	bDMARD (adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX; in case of MTX intolerance or unsuitability, as monotherapy in consideration of the respective approval status	Added benefit not proven
2	Patients from the age of 2 years with active pJIA who have had an inadequate response to prior therapy with one or more bDMARDs[b]	Switch of bDMARD therapy (abatacept or adalimumab or etanercept or golimumab or tocilizumab) in combination with MTX; in case of MTX intolerance or unsuitability, in the form of monotherapy in consideration of the respective approval status, depending on prior therapy	Added benefit not proven
3	Patients from the age of 2 years with (active) jPsA who have had an inadequate response to prior therapy with DMARDs[b]	Therapy upon the physician's discretion[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, patients included in the therapeutic indication are assumed to be (or have become) ineligible for (symptomatic) monotherapy with NSAIDs and/or glucocorticoids. For flare treatment, the use of (systemic and/or intraarticular) glucocorticoids should be possible.
c. The TNFα antagonist etanercept is approved for the treatment of juvenile psoriatic arthritis in adolescents from the age of 12 years who have had an inadequate response to, or who have proved intolerant of, MTX therapy. In the present therapeutic indication, the active substance etanercept is deemed a suitable comparator for patients from the age of 2 years.

ACT: appropriate comparator therapy; bDMARD: biologic DMARD; DMARD: disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; jPsA: juvenile psoriatic arthritis; MTX: methotrexate; NSAID: nonsteroidal anti-inflammatory drug; pJIA: polyarticular juvenile idiopathic arthritis; TNF: tumour necrosis factor

The above assessment concurs with that of the company.

The G-BA decides on the added benefit.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

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