IQWiG Reports – Commission No. A20-66

Ixekizumab (axial spondyloarthritis) –

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

Extract

[1] Translation of Sections 2.1 to 2.7 of the dossier assessment *Ixekizumab (axiale Spondyloarthritis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 October 2020). Please note: This translation 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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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
bDMARD	biologic disease-modifying antirheumatic drug
CRP	C-reactive protein
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
MRI	magnetic resonance imaging
NSAID	non-steroidal antirheumatic drug
Q2W	administration every 2 weeks
Q4W	administration every 4 weeks
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TNFα	tumour necrosis factor alpha

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 ixekizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 27 July 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of ixekizumab in comparison with the appropriate comparator therapy (ACT) in adult patients with axial spondyloarthritis in the following subindications:

- adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to conventional therapy,
- adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to prior therapy with biologic disease-modifying antirheumatic drugs (bDMARDs), and
- adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately to, or who are intolerant to conventional therapy.

In accordance with the G-BA's specification of the ACT, 3 research questions resulted for the benefit assessment. These are presented in Table 2.

Table 2: Research questions of the benefit assessment of ixekizumab

Research question	Subindication	ACT[a]
A1	Adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to conventional therapy	a TNFα inhibitor (etanercept or adalimumab or infliximab or golimumab or certolizumab pegol) or an IL-17 inhibitor (secukinumab)
A2	Adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to prior therapy with bDMARDs	Switch to another biologic disease-modifying antirheumatic drug: TNFα inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL-17 inhibitor (secukinumab)
B	Adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but with objective signs of inflammation as indicated by elevated CRP and/or MRI who have responded inadequately to, or who are intolerant to conventional therapy	TNFα inhibitor (etanercept or adalimumab or golimumab or certolizumab pegol)[b]

a. Presentation of the respective ACT specified by the G-BA.
b. According to the specifications of the G-BA, a change within the drug class is indicated after a failure of a TNFα inhibitor.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; G-BA: Federal Joint Committee; IL-17: interleukin-17; MRI: magnetic resonance imaging; TNFα: tumour necrosis factor alpha

Overall, the company followed the specification of the ACT without choosing one of the ACT options specified by the G-BA in each case. For research question A1, the company did not consider secukinumab as an ACT, which remains without consequence for the present assessment, as there is no relevant study.

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

Results

Research question A1 (adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to conventional therapy)

For research question A1 (see table above), no relevant RCT was identified for the direct comparison of ixekizumab with the ACT. This resulted in no hint of an added benefit of ixekizumab in comparison with the ACT for adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to conventional therapy; an added benefit is therefore not proven.

Research question A2 (adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to prior therapy with bDMARDs)

For research question A2 (see table above), no relevant RCT was identified for the direct comparison of ixekizumab with the ACT. This resulted in no hint of an added benefit of

ixekizumab in comparison with the ACT for adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to prior therapy with bDMARDs; an added benefit is therefore not proven.

Research question B (adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but with objective signs of inflammation as indicated by elevated CRP and/or MRI who have responded inadequately to, or who are intolerant to conventional therapy)

For research question B (see table above), no relevant RCT was identified by the check of the study pool for the direct comparison of ixekizumab with the ACT. This resulted in no hint of an added benefit of ixekizumab in comparison with the ACT for adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but with objective signs of inflammation as indicated by elevated CRP and/or MRI who have responded inadequately to, or who are intolerant to conventional therapy; an added benefit is therefore not proven.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug ixekizumab compared with the ACT is assessed as follows:

For the assessment of the added benefit of ixekizumab, no suitable data are available for any of the 3 research questions. An added benefit of ixekizumab in comparison with the ACT is therefore not proven in any of the 3 research questions.

Table 3 shows a summary of probability and extent of the added benefit of ixekizumab.

[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: Ixekizumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
A1	Adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to conventional therapy	a TNFα inhibitor (etanercept or adalimumab or infliximab or golimumab or certolizumab pegol) or an IL-17 inhibitor (secukinumab)	Added benefit not proven
A2	Adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to prior therapy with bDMARDs	Switch to another biologic disease-modifying antirheumatic drug: TNFα inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL-17 inhibitor (secukinumab)	Added benefit not proven
B	Adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but with objective signs of inflammation as indicated by elevated CRP and/or MRI who have responded inadequately to, or who are intolerant to conventional therapy	TNFα inhibitor (etanercept or adalimumab or golimumab or certolizumab pegol)[b]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. According to the specifications of the G-BA, a change within the drug class is indicated after a failure of a TNFα inhibitor.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; G-BA: Federal Joint Committee; IL-17: interleukin-17; MRI: magnetic resonance imaging ; TNFα: tumour necrosis factor alpha

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report is the assessment of the added benefit of ixekizumab in comparison with the ACT in adult patients with axial spondyloarthritis in the following subindications:

- adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to conventional therapy,
- adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to prior therapy with bDMARDs, and
- adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but with objective signs of inflammation as indicated by elevated CRP and/or MRI who have responded inadequately to, or who are intolerant to conventional therapy.

In accordance with the G-BA's specification of the ACT, 3 research questions resulted for the benefit assessment. These are presented in Table 4.

Table 4: Research questions of the benefit assessment of ixekizumab

Research question	Subindication	ACT[a]
A1	Adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to conventional therapy	a TNFα inhibitor (etanercept or adalimumab or infliximab or golimumab or certolizumab pegol) or an IL-17 inhibitor (secukinumab)
A2	Adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to prior therapy with bDMARDs	Switch to another biologic disease-modifying antirheumatic drug: TNFα inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL-17 inhibitor (secukinumab)
B	Adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but with objective signs of inflammation as indicated by elevated CRP and/or MRI who have responded inadequately to, or who are intolerant to conventional therapy	TNFα inhibitor (etanercept or adalimumab or golimumab or certolizumab pegol)[b]

a. Presentation of the respective ACT specified by the G-BA.
b. According to the specifications of the G-BA, a change within the drug class is indicated after a failure of a TNFα inhibitor.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; G-BA: Federal Joint Committee; IL-17: interleukin-17; MRI: magnetic resonance imaging; TNFα: tumour necrosis factor alpha

Overall, the company followed the specification of the ACT without choosing one of the ACT options specified by the G-BA in each case. After consulting the company, the G-BA added secukinumab as a further option to the ACT for research question A1. In the dossier for research question A1, however, the company referred to the earlier specification of the G-BA without secukinumab and followed this earlier specification. The company's approach for research question A1 remains without consequence for the present assessment, as overall no relevant study in comparison with the ACT options specified by the company was identified for this research question (see Section 2.4).

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the 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 of the company in the dossier:

- study list on ixekizumab (status: 25 May 2020)

- bibliographical literature search on ixekizumab (last search on 25 May 2020)
- search in trial registries/trial results databases for studies on ixekizumab (last search on 25 May 2020)
- search on the G-BA website for ixekizumab (last search on 25 May 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ixekizumab (last search on 30 July 2020)

Concurring with the company, the check of the completeness of the study pool did not produce any RCTs of direct comparison of ixekizumab versus the ACT for any of the 3 research questions. The company did not intend to conduct an indirect comparison for any of the 3 research questions.

2.4 Research question A1 (adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to conventional therapy)

In the therapeutic indication of research question A1 (see Table 4), no relevant study is available for the assessment of the added benefit of ixekizumab. The company presented the data from the approval study COAST-V [3], but did not use this study for its benefit assessment. This is appropriate.

The COAST-V study is a double-blind, randomized, controlled multicentre study. A total of 341 adult patients with active ankylosing spondylitis were included. These patients had not previously received treatment with a bDMARD and had responded inadequately to, or were intolerant to conventional therapy with at least 2 non-steroidal antirheumatic drugs (NSAIDs). Patients were randomly assigned to 2 different treatment regimens (every 2 weeks or every 4 weeks [Q2W or Q4W]) with ixekizumab, treatment with adalimumab, or administration of placebo. Only the Q4W treatment with an initial dose of 160 mg ixekizumab is in compliance with the Summary of Product Characteristics (SPC) [4].

After 16 weeks, patients from the adalimumab and placebo arms switched to treatment with ixekizumab. All patients continued treatment with ixekizumab until week 52.

An active-controlled study duration of only 16 weeks is too short to be able to show an added benefit of ixekizumab in the present therapeutic indication. Regardless of the study duration, which was too short, only 39 of the 81 (< 50%) patients included in the Q4W ixekizumab arm received an approval-compliant initial dose of 160 mg [3,4].

For the reasons mentioned, the COAST-V study is not suitable for the derivation of an added benefit of ixekizumab in comparison with the ACT for the treatment of adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to conventional therapy; an added benefit is therefore not proven. Following the assessment of the company, the study was therefore not used for the present benefit assessment.

2.4.1 Results on added benefit

The company did not provide any data for the assessment of the added benefit of ixekizumab in comparison with the ACT in the treatment of adult patients with active radiographic axial spondyloarthritis who have responded inadequately to, or who are intolerant to conventional therapy. This resulted in no hint of an added benefit of ixekizumab in comparison with the ACT; an added benefit is therefore not proven.

2.4.2 Probability and extent of added benefit

Since no suitable data are available for the assessment of the added benefit of ixekizumab in comparison with the ACT for adult patients with active radiographic axial spondyloarthritis who have responded inadequately to, or who are intolerant to conventional therapy, an added benefit of ixekizumab in this research question is not proven.

This concurs with the company's assessment.

2.5 Research question A2 (adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to prior therapy with bDMARDs)

In the therapeutic indication of research question A2 (see Table 4), there is no relevant study that investigated ixekizumab in comparison with the ACT. The company presented data from the approval study COAST-W [5], but did not use this study for its benefit assessment. This is appropriate.

The COAST-W study is a double-blind, randomized, controlled multicentre study. A total of 316 adult patients with active ankylosing spondylitis were included. These patients had previously responded inadequately to, or were intolerant both to therapy with ≥ 2 NSAIDs and to 1 or 2 tumour necrosis factor alpha (TNFα) inhibitors. Patients were randomly assigned to ixekizumab with the treatment regimens Q2W or Q4W, or to administration of placebo.

Since the COAST-W study did not compare ixekizumab with the ACT, the study is not suitable for the derivation of an added benefit of ixekizumab. Following the assessment of the company, the study was therefore not used for the present benefit assessment.

2.5.1 Results on added benefit

The company did not provide any suitable data for the assessment of the added benefit of ixekizumab in comparison with the ACT in the treatment of adult patients with active radiographic axial spondyloarthritis who have responded inadequately to, or who are intolerant to prior therapy with bDMARDs. This resulted in no hint of an added benefit of ixekizumab in comparison with the ACT; an added benefit is therefore not proven.

2.5.2 Probability and extent of added benefit

Since no suitable data are available for the assessment of the added benefit of ixekizumab in comparison with the ACT for adult patients with active radiographic axial spondyloarthritis who have responded inadequately to, or who are intolerant to prior therapy with bDMARDs, an added benefit of ixekizumab in this research question is not proven.

This concurs with the company's assessment.

2.6 Research question B (adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but with objective signs of inflammation as indicated by elevated CRP and/or MRI who have responded inadequately to, or who are intolerant to conventional therapy)

In the therapeutic indication of research question B (see Table 4), there is no study that investigated ixekizumab in comparison with the ACT. The company presented data from the approval study COAST-X [6], but did not use this study for its benefit assessment. This is appropriate.

The COAST-X study is a double-blind, randomized, controlled multicentre study. A total of 303 adult patients with active non-radiographic axial spondyloarthritis who had not received prior treatment with bDMARDs were included. Further inclusion criteria included an inadequate response to therapy with ≥ 2 NSAIDs or an intolerance to these drugs, as well as the presence of objective signs of inflammation by presence of sacroiliitis on MRI or elevated CRP. Patients were randomly assigned to ixekizumab with the treatment regimens Q2W or Q4W, or to administration of placebo.

Since the COAST-X study did not compare ixekizumab with the ACT, the study is not suitable for the derivation of an added benefit of ixekizumab. Following the assessment of the company, the study was therefore not used for the present benefit assessment.

2.6.1 Results on added benefit

The company did not provide any data for the assessment of the added benefit of ixekizumab in comparison with the ACT in the treatment of adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but with objective signs of inflammation as indicated by elevated CRP and/or MRI who have responded inadequately to, or who are intolerant to conventional therapy. This resulted in no hint of an added benefit of ixekizumab in comparison with the ACT; an added benefit is therefore not proven.

2.6.2 Probability and extent of added benefit

Since no data are available for the assessment of the added benefit of ixekizumab in comparison with the ACT for adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but with objective signs of inflammation as indicated by

elevated CRP and/or MRI who have responded inadequately to, or who are intolerant to conventional therapy, an added benefit of ixekizumab in this research question is not proven.

This concurs with the company's assessment.

2.7 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of ixekizumab in comparison with the ACT is summarized in Table 5.

Table 5: Ixekizumab – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
A1	Adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to conventional therapy	a TNFα inhibitor (etanercept or adalimumab or infliximab or golimumab or certolizumab pegol) or an IL-17 inhibitor (secukinumab)	Added benefit not proven
A2	Adult patients with active ankylosing spondylitis who have responded inadequately to, or who are intolerant to prior therapy with bDMARDs	Switch to another biologic disease-modifying antirheumatic drug: TNFα inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or IL-17 inhibitor (secukinumab)	Added benefit not proven
B	Adult patients with active axial spondyloarthritis without radiographic evidence of ankylosing spondylitis, but with objective signs of inflammation as indicated by elevated CRP and/or MRI who have responded inadequately to, or who are intolerant to conventional therapy	TNFα inhibitor (etanercept or adalimumab or golimumab or certolizumab pegol[b])	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. According to the specifications of the G-BA, a change within the drug class is indicated after a failure of a TNFα inhibitor.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; CRP: C-reactive protein; G-BA: Federal Joint Committee; IL-17: interleukin-17; MRI: magnetic resonance imaging; TNFα: tumour necrosis factor alpha

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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The full report (German version) is published under https://www.iqwig.de/en/projects/a20-66.html.