IQWiG Reports – Commission No. A21-16

Upadacitinib (ankylosing spondylitis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Upadacitinib (ankylosierende Spondylitis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 April 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.

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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
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
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 upadacitinib. 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 1 February 2021.

Research question

The aim of this report is to assess the added benefit of upadacitinib in comparison with the appropriate comparator therapy (ACT) in adult patients with active ankylosing spondylitis who had an inadequate response to conventional therapy.

The ACT specified by the G-BA depends on the patient's prior treatment. The resulting research questions are presented in Table 2.

Table 2: Research questions of the benefit assessment of upadacitinib

Research question	Indication	ACT[a]
1	Adult patients with active ankylosing spondylitis who inadequately responded to conventional therapy	A TNF-alpha inhibitor (etanercept or adalimumab or infliximab or golimumab or certolizumab pegol) or an IL17 inhibitor (secukinumab)
2	Adult patients with active ankylosing spondylitis who inadequately responded to prior therapy with biologic disease-modifying antirheumatic drugs (bDMARDs) or who do not tolerate bDMARDs	Switch to another biologic disease-modifying antirheumatic drug: TNF-alpha inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL17 inhibitor (secukinumab)

a. Presented is the ACT specified by the G-BA.

ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL: interleukin; TNF: tumour necrosis factor

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

No relevant study was identified for assessing the added benefit of upadacitinib in comparison with the ACT.

For research question 1, the company has presented results of the RCT SELECT-AXIS-1. This is an exclusively placebo-controlled RCT. It is unsuitable for deriving an added benefit. The company has not presented any studies for research question 2.

Hence, the company has not presented any studies comparing upadacitinib with the ACT. Consequently, there is no hint of any added benefit of upadacitinib 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]

On the basis of the presented results, the probability and extent of added benefit of the drug upadacitinib in comparison with the ACT have been assessed as follows:

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

Table 3: Upadacitinib – probability and extent of added benefit

Indication	ACT[a]	Probability and extent of added benefit
Adult patients with active ankylosing spondylitis who inadequately responded to conventional therapy	A TNF-alpha inhibitor (etanercept or adalimumab or infliximab or golimumab or certolizumab pegol) or an IL17 inhibitor (secukinumab)	Added benefit not proven
Adult patients with active ankylosing spondylitis who inadequately responded to prior therapy with biologic disease-modifying antirheumatic drugs (bDMARDs) or who do not tolerate bDMARDs	Switch to another biologic disease-modifying antirheumatic drug: TNF-alpha inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL17 inhibitor (secukinumab)	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL: interleukin; TNF: tumour necrosis factor		

The G-BA decides on the added benefit.

[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].

2.2 Research question

The aim of this report is to assess the added benefit of upadacitinib in comparison with the ACT in adult patients with active ankylosing spondylitis who had an inadequate response to conventional therapy.

The ACT specified by the G-BA depends on the patient's prior treatment. The resulting research questions are presented in Table 4.

Table 4: Research questions of the benefit assessment of upadacitinib

Research question	Indication	ACT[a]
1	Adult patients with active ankylosing spondylitis who inadequately responded to conventional therapy	A TNF-alpha inhibitor (etanercept or adalimumab or infliximab or golimumab or certolizumab pegol) or an IL17 inhibitor (secukinumab)
2	Adult patients with active ankylosing spondylitis who inadequately responded to prior therapy with biologic disease-modifying antirheumatic drugs (bDMARDs) or who do not tolerate bDMARDs	Switch to another biologic disease-modifying antirheumatic drug: TNF-alpha inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL17 inhibitor (secukinumab)
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL: interleukin; TNF: tumour necrosis factor		

The company followed the specification of the ACT for both research questions. However, it did not explicitly select one of the possible drugs for its 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 Research question 1: Patients with active ankylosing spondylitis who inadequately responded to conventional therapy

2.3.1 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 upadacitinib (as of 1 December 2020)
- Bibliographic literature search on upadacitinib (most recent search on 1 December 2020)
- Search in trial registries / study results databases on upadacitinib (most recent search on 1 December 2020)
- Search on the G-BA website on upadacitinib (most recent search on 1 December 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on upadacitinib (most recent search on 3 February 2021)

The check did not reveal any relevant studies for assessing the added benefit of upadacitinib in comparison with the ACT.

Likewise, the company reported not having identified any relevant studies for the present research question. For research question 1, it has nevertheless presented the results of a study (SELECT-AXIS-1). However, it presented the results only as supplementary information and did not use this study to derive any added benefit. The company's approach is appropriate.

The SELECT-AXIS-1 study is a placebo-controlled RCT. The study included adult patients with active ankylosing spondylitis who inadequately responded to therapy with nonsteroidal antiinflammatory drugs (NSAIDs) or did not tolerate them [3]. They were randomized in a 1:1 ratio to treatment with upadacitinib 15 mg once daily or placebo. After 14 weeks, patients of the placebo arm started to receive upadacitinib treatment. Since the study therefore offers no comparison with the ACT and the controlled study phase had a treatment duration of only 14 weeks, the study is irrelevant for assessing added benefit.

2.3.1.1 Results

The company has not presented any studies comparing upadacitinib with the ACT. Consequently, there is no hint of any added benefit of upadacitinib in comparison with the ACT. An added benefit is therefore not proven.

This rating concurs with the company's assessment.

2.3.2 Probability and extent of added benefit

The company has not presented any data suitable for deriving any added benefit in adult patients with active ankylosing spondylitis who inadequately responded to conventional therapy. Consequently, there is no proof of added benefit of upadacitinib in comparison with the ACT.

This rating concurs with the company's assessment.

2.4 Research question 2: Patients with active ankylosing spondylitis who inadequately responded to prior therapy with biologic disease-modifying antirheumatic drugs or who do not tolerate these drugs

2.4.1 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 upadacitinib (as of 1 December 2020)
- Bibliographic literature search on upadacitinib (most recent search on 1 December 2020)
- Search in trial registries / study results databases on upadacitinib (most recent search on 1 December 2020)
- Search on the G-BA website on upadacitinib (most recent search on 1 December 2020)

To check the completeness of the study pool:

- Search in trial registries for studies on upadacitinib (most recent search on 3 February 2021)

No relevant study was identified from the check. Likewise, the company has not presented any data for this research question.

2.4.2 Results on added benefit

The company has not presented any studies comparing upadacitinib with the ACT. Consequently, there is no hint of any added benefit of upadacitinib in comparison with the ACT. An added benefit is therefore not proven.

This rating concurs with the company's assessment.

2.4.3 Probability and extent of added benefit

The company has not presented any data suitable for deriving any added benefit in adult patients with active ankylosing spondylitis who inadequately responded to prior therapy with biological disease-modifying antirheumatic drugs (bDMARDs) or who do not tolerate them. Consequently, there is no proof of added benefit of upadacitinib in comparison with the ACT.

This rating concurs with the company's assessment.

2.5 Probability and extent of added benefit – summary

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

Table 5: Upadacitinib – probability and extent of added benefit

Indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with active ankylosing spondylitis who inadequately responded to conventional therapy	A TNF-alpha inhibitor (etanercept or adalimumab or infliximab or golimumab or certolizumab pegol) or an IL17 inhibitor (secukinumab)	Added benefit not proven
Adult patients with active ankylosing spondylitis who inadequately responded to prior therapy with biologic disease-modifying antirheumatic drugs (bDMARDs) or who do not tolerate bDMARDs	Switch to another biologic disease-modifying antirheumatic drug: TNF-alpha inhibitor (adalimumab or certolizumab pegol or etanercept or golimumab or infliximab) or an IL17 inhibitor (secukinumab)	Added benefit not proven
a. Presented is the ACT specified by the G-BA. ACT: appropriate comparator therapy; bDMARD: biologic disease-modifying antirheumatic drug; G-BA: Federal Joint Committee; IL: interleukin; 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.

1. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a21-116.html.