Upadacitinib (Crohn's disease)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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[1] Translation of Sections I 1 to I 4 of the dossier assessment *Upadacitinib (Morbus Crohn) – Nutzenbewertung gemäß § 35a SGB V*. 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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IQWiG thanks the medical and scientific advisor for his 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 Birgit Kaltz.

IQWiG thanks the respondent for participating in the written exchange about how she experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I 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)

I 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 28 April 2023.

Research question

The aim of this report is to assess the added benefit of upadacitinib in comparison with the appropriate comparator therapy (ACT) in patients with moderate to severe active Crohn's disease who have had an inadequate response, lost response or were intolerant to conventional therapy or a biologic agent.

The research questions shown in Table 2 are derived from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of upadacitinib

Research question	Therapeutic indication	ACT[a]
1	Adults with moderate to severe active Crohn's disease[b] who have had an inadequate response, lost response or were intolerant to conventional therapy	A TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)
2	Adults with moderate to severe active Crohn's disease[b] who have had an inadequate response, lost response or were intolerant to treatment with a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)	A TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)[c, d]

a. Presented is the respective ACT specified by the G-BA.
b. For patients who continue to be candidates for drug therapy, a decision in favour of surgical resection is assumed to represent an individualized choice for that particular patient if necessary and is not the rule; surgical resection is therefore to be disregarded when determining the ACT.
c. In addition to a change of drug class, a change within the drug class can also be considered. Any potential dose adjustment options are assumed to have already been exhausted.
d. Continuation of an inadequate therapy does not concur with the specified ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

The company followed the G-BA's specification of the ACT for both research questions.

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

Results

No suitable data are available for assessing the added benefit of upadacitinib in comparison with the ACT in adult patients with moderate to severe active Crohn's disease who had an inadequate response, lost response or are intolerant to conventional therapy or a biologic agent. There is no hint of an added benefit of upadacitinib in comparison with the ACT for either of the two research questions; an added benefit is therefore not proven.

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

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

Table 3: Upadacitinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with moderate to severe active Crohn's disease[b] who have had an inadequate response, lost response or were intolerant to conventional therapy	A TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)	Added benefit not proven
2	Adults with moderate to severe active Crohn's disease[b] who have had an inadequate response, lost response or were intolerant to treatment with a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)	A TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)[c, d]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. For patients who continue to be candidates for drug therapy, a decision in favour of surgical resection is assumed to represent an individualized choice for that particular patient if necessary and is not the rule; surgical resection is therefore to be disregarded when determining the ACT.
c. In addition to a change of drug class, a change within the drug class can also be considered. Any potential dose adjustment options are assumed to have already been exhausted.
d. Continuation of an inadequate therapy does not concur with the specified ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; 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].

I 2 Research question

The aim of this report is to assess the added benefit of upadacitinib in comparison with the ACT in patients with moderate to severe active Crohn's disease who have had an inadequate response, lost response or were intolerant to conventional therapy or a biologic agent.

The research questions shown in Table 4 are derived from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of upadacitinib

Research question	Therapeutic indication	ACT[a]
1	Adults with moderate to severe active Crohn's disease[b] who have had an inadequate response, lost response or were intolerant to conventional therapy	A TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)
2	Adults with moderate to severe active Crohn's disease[b] who have had an inadequate response with, lost response to, or are intolerant to treatment with a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)	A TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)[c, d]

a. Presented is the respective ACT specified by the G-BA.
b. For patients who continue to be candidates for drug therapy, a decision in favour of surgical resection is assumed to represent an individualized choice for that particular patient if necessary and is not the rule; surgical resection is therefore to be disregarded when determining the ACT.
c. In addition to a change of drug class, a change within the drug class can also be considered. Any potential dose adjustment options are assumed to have already been exhausted.
d. Continuation of an inadequate therapy does not concur with the specified ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

The company followed the G-BA's specification of the ACT for both research questions.

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

I 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 upadacitinib (status: 19 April 2023)
- bibliographical literature search on upadacitinib (last search on 3 April 2023)
- search in trial registries/trial results databases for studies on upadacitinib (last search on 3 April 2023)
- search on the G-BA website for upadacitinib (last search on 3 April 2023)

To check the completeness of the study pool:

- search in trial registries for studies on upadacitinib (last search on 15 May 2023); for search strategies, see I Appendix A of the full dossier assessment

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of upadacitinib in comparison with the ACT for either of the 2 research questions. This concurs with the company’s assessment.

However, in Module 4 A, the company presents results of the studies U-EXCEED and U-EXCEL as well as U-ENDURE [3-5], which compare upadacitinib with placebo, for all research questions. The studies U-EXCEED and U-EXCEL included adults (18-75 years) with moderate to severe active Crohn's disease who had an inadequate response or were intolerant to conventional therapy and/or a biologic. The U-ENDURE study included adults from the studies U-EXCEED and U-EXCEL who had shown a clinical response to upadacitinib. Instead of using the 3 studies to derive the added benefit, the company consequently presented its results only as supplementary information.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of upadacitinib in comparison with the ACT in adult patients with moderate to severe active Crohn's disease who have had an inadequate response, lost response or are intolerant to conventional therapy or a biologic agent. There is no hint of an added benefit of upadacitinib in comparison with the ACT for either of the two research questions; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

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

Table 5: Upadacitinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
1	Adults with moderate to severe active Crohn's disease[b] who have had an inadequate response, lost response or were intolerant to conventional therapy	A TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)	Added benefit not proven
2	Adults with moderate to severe active Crohn's disease[b] who have had an inadequate response, lost response or were intolerant to treatment with a biologic agent (TNF-α antagonist or integrin inhibitor or interleukin inhibitor)	A TNF-α antagonist (adalimumab or infliximab) or integrin inhibitor (vedolizumab) or interleukin inhibitor (ustekinumab)[c, d]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. For patients who continue to be candidates for drug therapy, a decision in favour of surgical resection is assumed to represent an individualized choice for that particular patient if necessary and is not the rule; surgical resection is therefore to be disregarded when determining the ACT.
c. In addition to a change of drug class, a change within the drug class can also be considered. Any potential dose adjustment options are assumed to have already been exhausted.
d. Continuation of an inadequate therapy does not concur with the specified ACT.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; TNF: tumour necrosis factor

The assessment described above concurs with that of the company in each case.

The G-BA decides on the added benefit.

I 6 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. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 6.1 [online]. 2022 [Zugriff: 27.01.2022]. URL: https://www.iqwig.de/methoden/allgemeine-methoden-v6-1.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://dx.doi.org/10.1002/bimj.201300274.

3. A Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Participants With Moderately to Severely Active Crohn's Disease Who Have Inadequately Responded to or Are Intolerant to Biologic Therapy [online]. 2022. URL: https://clinicaltrials.gov/ct2/show/NCT03345836.

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5. A Maintenance and Long-Term Extension Study of the Efficacy and Safety of Upadacitinib (ABT-494) in Participants With Crohn's Disease Who Completed the Studies M14-431 or M14-433 [online]. 2022. URL: https://clinicaltrials.gov/ct2/show/NCT03345823.

The full report (German version) is published under https://www.iqwig.de/en/projects/a23-38.html.