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Upadacitinib (ulcerative colitis) –

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

Extract

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Upadacitinib (Colitis ulcerosa) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 November 2022). 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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Patient and family involvement

No feedback was received in the framework of the present 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)
SPC	Summary of Product Characteristics

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 25 August 2022.

Research question

The aim of this report is to assess the added benefit of upadacitinib in comparison with the appropriate comparator therapy (ACT) in adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or are intolerant to either conventional therapy or a biologic agent.

The research questions shown in Table 2 were 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]
Adults with moderately to severely active ulcerative colitis[b]		
1	Patients who have had an inadequate response, lost response, or were intolerant to conventional therapy	A TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or **ustekinumab**[c]
2	Patients who have had an inadequate response, lost response, or were intolerant to a biologic agent[d]	Switching treatment to vedolizumab or tofacitinib or **ustekinumab** or a TNF-α antagonist (adalimumab or infliximab or golimumab), each taking into account approval and prior treatment(s)[c,e]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. For patients who continue to be candidates for drug therapy, a decision in favour of surgical resection is presumed to represent an individualized choice for that particular patient if necessary and as not being the rule; surgical resection is therefore to be disregarded when determining the ACT.
c. If infliximab is used, it should be combined with a thiopurine, if necessary.
Corticosteroids are generally deemed appropriate for flare treatment.
Continuation of an inadequate therapy does not constitute an implementation of the ACT.
d. As biologic agents, the G-BA has listed the following: TNF-α antagonist or integrin inhibitor or interleukin inhibitor.
e. Switching within or between drug classes is permitted. Any possible dose adjustments are presumed to have already been exhausted. In case of primary failure of TNF-α antagonist treatment, switching to another drug class is indicated. In secondary failure of TNF-α antagonist treatment, a switch within the drug class may be considered.

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

The company followed the G-BA's specification of the ACT. However, the company departed from the G-BA's research questions by deriving added benefit for the entire approval

population, without drawing separate conclusions for the respective research questions 1 and 2. In line with the G-BA's specification, the present assessment attempts to answer the 2 research questions separately, each in comparison with the ACT specified by the G-BA.

The assessment is 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 12 months were used for the derivation of the added benefit.

Results

Concurring with the company, no relevant RCTs which would allow a direct comparison of upadacitinib with the ACT were found for either of the 2 research questions.

The company submitted an adjusted indirect comparison on the basis of RCTs using the common comparator of placebo. On the side of the intervention to be assessed, upadacitinib, the company included the studies M14-234 (hereinafter referred to as U-ACHIEVE) and M14-675 (hereinafter referred to as U-ACCOMPLISH). On the side of the comparator therapy, ustekinumab, the company presented the UNIFI study.

The U-ACHIEVE and U-ACCOMPLISH studies are randomized, double-blind studies comparing upadacitinib (in various dosages) versus placebo in patients with moderately to severely active ulcerative colitis who have had inadequate response, loss of response, or intolerance to conventional or biologic therapy. The U-ACHIEVE study comprises an induction phase of a maximum of 16 weeks as well as a 52-week maintenance phase for patients who had exhibited clinical response after 8 weeks. After the 8-week induction phase, U-ACCOMPLISH participants who exhibited a clinical response likewise switched to the U-ACHIEVE maintenance phase.

The UNIFI study is a randomized, double-blind study comparing ustekinumab with placebo in patients with moderately to severely active ulcerative colitis who have had inadequate or no response or failed to tolerate conventional or biologic therapy. The study likewise consists of an 8-week induction phase (patients exhibiting no response after 8 weeks were allowed to receive continued treatment for an additional 8 weeks) and a 44-week maintenance phase.

Indirect comparison unsuitable for answering the benefit assessment's research questions

The therapeutic indication to be assessed can be divided into 2 research questions based on patients' prior treatment. Research question 1 comprises patients with conventional prior treatment, while research question 2 comprises patients previously treated with biologic agents. However, the analyses submitted by the company combine patients with ulcerative colitis who inadequately responded to conventional therapy (research question 1) and patients who inadequately responded to a biologic agent (research question 2) or who did not tolerate these prior therapies. The company has not presented separate analyses broken down by prior treatment. In Module 4A, the company argues that due to the unavailability of data broken down by prior treatment, answering these research questions separately is impossible, particularly for

tolerability. Overall, the company did not present sufficient information on the extent to which the total populations of the U-ACHIEVE, U-ACCOMPLISH, and UNIFI studies are suitable for answering the individual research questions.

Irrespective of the company's failure to analyse the 2 research questions separately, the studies included by the company for the indirect comparison did not exhibit sufficient similarity to allow an adjusted indirect comparison. On the basis of the presented information, it is conceivable for the U-ACHIEVE study to have enrolled more patients with more severe disease. Comparable disease severity among the included study populations, however, is a prerequisite for performing an adjusted indirect comparison. Furthermore, the U-ACHIEVE and U-ACCOMPLISH studies placed greater limitations in the prior and concomitant therapy of ulcerative colitis with immunosuppressants than did the UNIFI study.

Overall, the presented adjusted indirect comparison is unsuitable for the benefit assessment of upadacitinib in comparison with the ACT.

Results on added benefit

Since no usable data are available for the benefit assessment, there is no hint of an 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]

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

[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: Upadacitinib – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults with moderately to severely active ulcerative colitis[b]			
1	Patients who have had an inadequate response, lost response, or were intolerant to conventional therapy	A TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or **ustekinumab**[c]	Added benefit not proven
2	Patients who have had an inadequate response, lost response, or were intolerant to a biologic agent[d]	Switching treatment to vedolizumab or tofacitinib or **ustekinumab** or a TNF-α antagonist (adalimumab or infliximab or golimumab), each taking into account approval and prior treatment(s)[c,e]	Added benefit not proven

a. Presented is the respective ACT specified by the GBA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. For patients who continue to be candidates for drug therapy, a decision in favour of surgical resection is presumed to represent an individualized choice for that particular patient if necessary and as not being the rule; surgical resection is therefore to be disregarded when determining the ACT.
c. If infliximab is used, it should be combined with a thiopurine, if necessary.
Corticosteroids are generally deemed appropriate for flare treatment.
Continuation of an inadequate therapy does not constitute an implementation of the ACT.
d. As biologic agents, the G-BA has listed the following: TNF-α antagonist or integrin inhibitor or interleukin inhibitor.
e. Switching within or between drug classes is permitted. Any possible dose adjustments are presumed to have already been exhausted. In case of primary failure of TNF-α antagonist treatment, switching to another drug class is indicated. In secondary failure of TNF-α antagonist treatment, a switch within the drug class may be contemplated.

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

The GBA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of upadacitinib in comparison with the ACT in adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or are intolerant to either conventional therapy or a biologic agent.

The research questions shown in Table 4 were 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]
Adults with moderately to severely active ulcerative colitis[b]		
1	Patients who have had an inadequate response, lost response, or were intolerant to conventional therapy	A TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or **ustekinumab**[c]
2	Patients who have had an inadequate response, lost response, or were intolerant to a biologic agent[d]	Switching treatment to vedolizumab or tofacitinib or **ustekinumab** or a TNF-α antagonist (adalimumab or infliximab or golimumab), each taking into account approval and prior treatment(s)[c,e]

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. For patients who continue to be candidates for drug therapy, a decision in favour of surgical resection is presumed to represent an individualized choice for that particular patient if necessary and as not being the rule; surgical resection is therefore to be disregarded when determining the ACT.
c. If infliximab is used, it should be combined with a thiopurine, if necessary.
Corticosteroids are generally deemed appropriate for flare treatment.
Continuation of an inadequate therapy does not constitute an implementation of the ACT.
d. As biologic agents, the G-BA has listed the following: TNF-α antagonist or integrin inhibitor or interleukin inhibitor.
e. Switching within or between drug classes is permitted. Any possible dose adjustments are presumed to have already been exhausted. In case of primary failure of TNF-α antagonist treatment, switching to another drug class is indicated. In secondary failure of TNF-α antagonist treatment, a switch within the drug class may be contemplated.

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

The company followed the G-BA's specification of the ACT. However, the company departed from the G-BA’s research questions by deriving added benefit for the entire approval population, without drawing separate conclusions for the respective research questions 1 and 2. In line with the G-BA’s specification, the present assessment attempts to answer the 2 research questions separately, each in comparison with the ACT specified by the G-BA. Since no usable data were available for either of the 2 research questions designated by the G-BA, the assessment below is performed in a joint section of the report.

The assessment is conducted by means of patient-relevant outcomes based on the data provided by the company in the dossier. RCTs with a minimum duration of 12 months were used for the derivation of 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: 8 July 2022)
- bibliographical literature search on upadacitinib (last search on 2 June 2022)
- search in trial registries / trial results databases for studies on upadacitinib (last search on 2 June 2022)
- search on the G-BA website for upadacitinib (last search on 2 June 2022)
- bibliographical literature search on the ACT (last search on 2 June 2022)
- search in trial registries / trial results databases for studies on the ACT (last search on 2 June 2022)
- search on the G-BA website for the ACT (last search on 2 June 2022)

To check the completeness of the study pool:

- search in trial registries for studies on upadacitinib (last search on 13 September 2022); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check identified no study for the direct comparison of upadacitinib with the ACT in the present therapeutic indication.

Since there are no studies of direct comparison, the company presented an adjusted indirect comparison based on RCTs via the common comparator of placebo. For the indirect comparison, the company found the studies M14-234 [3] (hereinafter referred to as U-ACHIEVE) and M14-675 [3] (hereinbelow referred to as U-ACCOMPLISH) on the intervention side and the UNIFI study [4] on the comparator side.

The presented adjusted indirect comparison is unsuitable for assessing the benefit of upadacitinib versus the ACT. This is explained below.

Evidence provided by the company

Studies on the intervention side

U-ACHIEVE study

The U-ACHIEVE study is a randomized, double-blind study comparing upadacitinib versus placebo; the study consists of an induction phase (Substudies 1 and 2) and a maintenance phase (Substudy 3). The study included patients with moderately to severely active ulcerative colitis who responded inadequately or not at all to conventional or biologic therapy or were intolerant to these therapies. In Substudy 1 (induction phase), patients were randomly allocated to treatment in 5 treatment arms – 4 dosages of upadacitinib (7.5 mg, 15 mg, 30 mg, and 45 mg)

and placebo, each being administered for 8 weeks. In Substudy 2 (induction phase), the 45 mg dose of upadacitinib or placebo was administered for 8 weeks. Patients who exhibited no clinical response within 8 weeks on upadacitinib or placebo were allowed to receive a further 8 weeks of treatment or switch from placebo to 8 weeks of upadacitinib treatment.

Substudy 3 (maintenance phase) consists of 4 cohorts. Cohort 1 is relevant for the analyses presented by the company. It included patients with a clinical response to 8-week induction treatment with 15 mg, 30 mg, and 45 mg dosages of upadacitinib in Substudy 1 or in the 45 mg dosage in Substudy 2. Patients who exhibited clinical response in Substudy 2 (induction phase) after an initial 8 weeks of placebo and subsequent 8 weeks of 45 mg upadacitinib were likewise included in Cohort 1 of Substudy 3. Said patients were randomized to treatment with various upadacitinib dosages (15 mg, 30 mg) or placebo, receiving this maintenance therapy for 52 weeks. Patients exhibiting clinical response following an induction phase of 16 weeks of upadacitinib were not included in Cohort 1 (maintenance phase).

U-ACCOMPLISH study

The U-ACCOMPLISH induction study compares upadacitinib at the 45 mg dose versus placebo and is designed like the U-ACHIEVE Substudy 2 (induction phase). In this study as well, patients who exhibited no clinical response after 8 weeks on upadacitinib or placebo were allowed to be treated for another 8 weeks or to switch from placebo to 8 weeks of upadacitinib treatment. U-ACCOMPLISH participants exhibiting a clinical response after 8 weeks on 45 mg upadacitinib were likewise included in Cohort 1 of The U-ACHIEVE Substudy 3 (maintenance phase).

According to the Summary of Product Characteristics (SPC) [5], the approved upadacitinib dosage in the induction phase is 45 mg once daily. In the maintenance phase, dosages of 15 mg and 30 mg once daily are approved, depending on patient-specific factors such as disease burden, response in the induction phase, and age. In the indirect comparison, the company used the treatment arms with 45 mg upadacitinib for the induction phase and those with 15 mg and 30 mg upadacitinib for the maintenance phase.

Study on the comparator therapy side

UNIFI study

The UNIFI study is a randomized double-blind study comparing ustekinumab with placebo. The study included patients with moderately to severely active ulcerative colitis who responded inadequately or not at all to conventional or biologic therapy or were intolerant to these therapies. The study consists of an 8-week induction phase (patients not responding after 8 weeks were allowed to receive continued treatment for an additional 8 weeks) and a 44-week maintenance phase. In the induction phase, patients were randomly allocated to 3 treatment arms – 2 ustekinumab dosages (one dose of 130 mg intravenously [i.v.] or one weight-adjusted dose of ~ 6 mg/kg body weight i.v.) and placebo. For analyses of the induction phase, the

company's Module 4A presents only results on the weight-adjusted dose of ~ 6 mg/kg bodyweight.

In the maintenance phase, patients with clinical response on ustekinumab were randomly allocated to treatment with 2 different ustekinumab dosages (90 mg subcutaneously [s.c.] every 12 weeks, 90 mg s.c. every 8 weeks) or placebo.

According to the SPC [6,7], ustekinumab treatment is induced with a body-weight-based single intravenous dose of ~ 6 mg/kg body weight. Eight weeks after the intravenous dose, 90 mg ustekinumab is to be administered every 12 weeks. Patients who lose response on an administration every 12 weeks may benefit from increasing the dosage frequency to 8 weeks. Based on the clinical assessment, these patients may then receive the next dose either every 8 weeks or every 12 weeks.

In both the U-ACHIEVE and the UNIFI studies, only patients with clinical response in the induction phase were included in the maintenance phase and followed up. Hence, these studies fail to provide data on the study's entire duration for all patients in the given therapeutic indication.

Indirect comparison unsuitable for answering the benefit assessment's research questions

The therapeutic indication to be assessed can be divided into 2 research questions based on patients' prior treatment. Research question 1 comprises patients with conventional prior treatment, while research question 2 comprises patients previously treated with biologic agents (see Table 4). The analyses submitted by the company, however, combine patients with ulcerative colitis who inadequately responded to conventional therapy (research question 1) and those who inadequately responded to a biologic agent (research question 2). The company has not presented separate analyses broken down by prior treatment. In Module 4A, the company argues that due to the unavailability of data broken down by prior treatment, answering these research questions separately is impossible, particularly for tolerability. In all, the company did not present sufficient information on the extent to which the total populations of the U-ACHIEVE, U-ACCOMPLISH, and UNIFI studies are suitable for answering the individual research questions.

Irrespective of the company's failure to analyse the 2 research questions separately, the studies included by the company for the indirect comparison did not exhibit sufficient similarity.

Lack of similarity of the U-ACCOMPLISH/U-ACHIEVE and UNIFI studies

A central prerequisite for the inclusion of studies in an adjusted indirect comparison is a similarity check [1,8,9]. According to the similarity assumption, the studies considered are comparable with regard to possible effect modifiers across all interventions. Potential effect modifiers (e.g. patient characteristics, study characteristics, intervention characteristics) as well as methodological factors (e.g. outcome characteristics) must be taken into account [10].

Irrespective of a detailed check of the similarity of the studies, it is impossible to derive sufficient similarity on the basis of the available data, for instance when comparing disease severity in the study populations. The available studies represent disease severity by the Mayo score, which rates disease severity on a scale of 0 to 12. The company used different Mayo score thresholds for characterizing the population of the U-ACHIEVE study than were used for characterizing the UNIFI study. For instance, in the U-ACHIEVE Substudy 3 (maintenance phase), about 49% of participants had a Mayo score ≤ 9 and about 51% a Mayo score of > 9. At the baseline of the UNIFI study's maintenance phase, about 87% had a Mayo score of ≤ 10 and about 13% had a Mayo score > 10. On the basis of these distributions, the U-ACHIEVE study might conceivably have included more patients with greater disease severity. Comparable disease severity among the included study populations, however, is a prerequisite for performing an adjusted indirect comparison.

Furthermore, the U-ACHIEVE and U-ACCOMPLISH studies, which included more patients with particularly severe disease, placed greater limitations in the prior and concomitant therapy of ulcerative colitis with immunosuppressants than did the UNIFI study. For instance, the U-ACHIEVE study excluded patients who received azathioprine or 6-mercaptopurine within 10 days before screening. It also disallowed initiating such treatment during the study. In the UNIFI study, in contrast, patients who had received immunosuppressants such as azathioprine or 6-mercaptopurine already ≥ 12 weeks prior to screening and had been at a stable dose for at least 4 weeks were allowed to continue treatment. At baseline of the UNIFI study's maintenance phase, about 27% of patients were treated with immunosuppressants, while only 0.4% of patients in the U-ACHIEVE Substudy 3 (maintenance phase) received such therapy.

Different event rates in the common comparator arms of the studies included by the company

Relevant differences between study populations are likewise found in the presented results for the common comparator arms. In several outcomes, consistently higher response rates are found in the UNIFI placebo arm than in the U-ACHIEVE placebo arm. For instance, in the U-ACHIEVE Substudy 3 (maintenance phase), 11% of patients in the common comparator arm achieved remission versus 24% in the UNIFI placebo arm.

I 4 Results on added benefit

No suitable data are available to assess the added benefit of upadacitinib in comparison with the ACT in adults with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional treatment or a biologic agent. There is consequently no hint of added benefit of upadacitinib in comparison with the ACT for either research question of the present benefit assessment; an added benefit is therefore not proven for either of them.

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
Adults with moderately to severely active ulcerative colitis[b]			
1	Patients who have had an inadequate response, lost response, or were intolerant to conventional therapy	A TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or **ustekinumab**[c]	Added benefit not proven
2	Patients who have had an inadequate response, lost response, or were intolerant to a biologic agent[d]	Switching treatment to vedolizumab or tofacitinib or **ustekinumab** or a TNF-α antagonist (adalimumab or infliximab or golimumab), each taking into account approval and prior treatment(s)[c,e]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. For patients who continue to be candidates for drug therapy, a decision in favour of surgical resection is presumed to represent an individualized choice for that particular patient if necessary and as not being the rule; surgical resection is therefore to be disregarded when determining the ACT.
c. If infliximab is used, it should be combined with a thiopurine, if necessary.
Corticosteroids are generally deemed appropriate for flare treatment.
Continuation of an inadequate therapy does not constitute an implementation of the ACT.
d. As biologic agents, the G-BA has listed the following: TNF-α antagonist or integrin inhibitor or interleukin inhibitor.
e. Switching within or between drug classes is permitted. Any possible dose adjustments are presumed to have already been exhausted. In case of primary failure of TNF-α antagonist treatment, switching to another drug class is indicated. In secondary failure of TNF-α antagonist treatment, a switch within the drug class may be contemplated.

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

The assessment described above deviates from that by the company, which derived a hint of major added benefit for both research questions.

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.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a22-91.html.