IQWiG Reports – Commission No. A21-166

Ozanimod (ulcerative colitis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ozanimod (Colitis ulcerosa) – Nutzenbewertung gemäß § 35a SGB V* (Version 2.0; Status: 9 May 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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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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[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 ozanimod. 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 14 December 2021.

Research question

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

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

Table 2: Research questions of the benefit assessment of ozanimod

Research question	Therapeutic indication	ACT[a]
Adults with moderately to severely active ulcerative colitis[b]		
1	Patients who have had an inadequate response with, lost response to, are have intolerance or contraindications to conventional treatment	A TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or tofacitinib or ustekinumab
2	Patients who have had an inadequate response with, lost response to, or are intolerant to treatment with a biologic drug (TNFα antagonist or integrin inhibitor or interleukin inhibitor)	Vedolizumab or tofacitinib or a TNF-α antagonist (adalimumab or infliximab or golimumab) or ustekinumab, each in consideration of approval and prior treatment(s)[c]

a. Presented is the respective ACT specified by the G-BA. Ozanimod is assumed to be administered as long-term therapy (induction and maintenance). Hence, drugs which are options only for the initial reduction of disease activity according to the guideline are disregarded below. Corticosteroids are generally deemed appropriate for flare treatment. Continuation of an inadequate therapy does not constitute an implementation of the ACT.
b. Patients who continue to be eligible for drug therapy (e.g. biologic drugs and JAK inhibitors) are not yet deemed candidates for proctocolectomy.
c. Switching within or between drug classes is permitted. Any possible dose adjustments are presumed to have already been exhausted. In case of primary treatment failure with a TNFα antagonist, switching to another drug class is indicated; in case of secondary treatment failure with a TNFα antagonist, switching within the drug class may be contemplated.

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

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 12 months were used for the derivation of the added benefit.

Results

Concurring with the company's assessment, the check for completeness of the study pool did not identify any relevant RCTs which allow a direct comparison of ozanimod with the ACT for either of the 2 research questions. Nevertheless, the company included the placebo-controlled study TRUE NORTH as the best available evidence in its benefit assessment. From this study, the company derived a hint of non-quantifiable added benefit for ozanimod for each of the research questions. However, the TRUE NORTH study is unsuitable for assessing the added benefit of ozanimod in comparison with the ACT specified by the G-BA because the study's placebo arm did not implement active therapy as in the ACT.

Hence, no suitable data are available to assess the added benefit of ozanimod in comparison with the ACT in adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to either conventional treatment or a biologic drug. Consequently, there is no hint of added benefit of ozanimod in comparison with the ACT for either research question; an added benefit is therefore not proven for either of them.

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 ozanimod.

[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: Ozanimod – 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 with, lost response to, or have intolerance or contraindications to conventional treatment	A TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or tofacitinib or ustekinumab	Added benefit not proven
2	Patients who have had an inadequate response with, lost response to, or are intolerant to treatment with a biologic drug (TNFα antagonist or integrin inhibitor or interleukin inhibitor)	Vedolizumab or tofacitinib or a TNF-α antagonist (adalimumab or infliximab or golimumab) or ustekinumab, each in consideration of approval and prior treatment(s)[c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. Ozanimod is assumed to be administered as long-term therapy (induction and maintenance). Hence, drugs which are options only for the initial reduction of disease activity according to the guideline are disregarded below. Corticosteroids are generally deemed appropriate for flare treatment. Continuation of an inadequate therapy does not constitute an implementation of the ACT.
b. Patients who continue to be eligible for drug therapy (e.g. biologic drugs and JAK inhibitors) are not yet deemed candidates for proctocolectomy.
c. Switching within or between drug classes is permitted. Any possible dose adjustments are presumed to have already been exhausted. In case of primary treatment failure with a TNFα antagonist, switching to another drug class is indicated; in case of secondary treatment failure with a TNFα antagonist, switching within the drug class may be contemplated.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; JAK: Janus kinase inhibitors; 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 ozanimod in comparison with the ACT in adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to either conventional treatment or a biologic drug.

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

Table 4: Research questions of the benefit assessment of ozanimod

Research question	Therapeutic indication	ACT[a]
Adults with moderately to severely active ulcerative colitis[b]		
1	Patients who have had an inadequate response with, lost response to, or have intolerance or contraindications to conventional treatment	A TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or tofacitinib or ustekinumab
2	Patients who have had an inadequate response with, lost response to, or are intolerant to treatment with a biologic drug (TNFα antagonist or integrin inhibitor or interleukin inhibitor)	Vedolizumab or tofacitinib or a TNF-α antagonist (adalimumab or infliximab or golimumab) or ustekinumab, each in consideration of approval and prior treatment(s)[c]

a. Presented is the respective ACT specified by the G-BA. Ozanimod is assumed to be administered as long-term therapy (induction and maintenance). Hence, drugs which are options only for the initial reduction of disease activity according to the guideline are disregarded below. Corticosteroids are generally deemed appropriate for flare treatment. Continuation of an inadequate therapy does not constitute an implementation of the ACT.
b. Patients who continue to be eligible for drug therapy (e.g. biologic drugs and JAK inhibitors) are not yet deemed candidates for proctocolectomy.
c. Switching within or between drug classes is permitted. Any possible dose adjustments are presumed to have already been exhausted. In case of primary treatment failure with a TNFα antagonist, switching to another drug class is indicated; in case of secondary treatment failure with a TNFα antagonist, switching within the drug class may be contemplated.

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

On receipt of the dossier, the G-BA adjusted the ACT on 14 December 2021 in accordance with the presentation in Table 4 [3]. This does not result in any changes for research question 1. Regarding research question 2, the adjustment now excludes patients who have had an inadequate response, lost response, or were intolerant to a Janus kinase (JAK) inhibitor. The adjustment does not affect the drugs or drug classes identified as ACTs. The present benefit assessment was conducted based on the adjusted ACT.

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 12 months were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Due to the adjustment of the ACT after receipt of the dossier, the data provided in the company's dossier refer to the ACT of which the company was informed by the G-BA in June

2021 [4]. The company reports following the ACT specified by the G-BA for both research questions.

The company's approach is of no consequence for the benefit assessment part of this dossier assessment, because the data submitted in the company's dossier do not allow a comparison of ozanimod with the ACT (see Section 2.3). For research question 2, this applies both to the original and the adjusted patient population of the ACT specified by the G-BA.

2.3 Information retrieval and study pool

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

- study list on ozanimod (status: 23 September 2021)
- bibliographical literature search on ozanimod (last search on 23 September 2021)
- search in trial registries / trial results databases for studies on ozanimod (last search on 23 September 2021)
- search on the G-BA website for ozanimod (last search on 24 September 2021)

To check the completeness of the study pool:

- search in trial registries for studies on ozanimod (last search on 27 December 2021); for search strategies, see Appendix A of the full dossier assessment

The check for completeness of the study pool identified no relevant RCT allowing a direct comparison of ozanimod versus the ACT. This applies to both research questions and corresponds to the company's assessment.

Evidence provided by the company

To assess the added benefit of ozanimod versus the ACT, the company did not find any directly comparative RCTs. As best available evidence, however, it used the placebo-controlled approval study of ozanimod (TRUE NORTH [5]) to derive added benefit. For each of the research questions, the company derived a hint of non-quantifiable added benefit of ozanimod, arguing that the results of the TRUE NORTH study demonstrate a previously unachieved improvement of treatment-related benefit, while no quantifiable conclusion on added benefit versus the ACT can be drawn on the basis of the placebo-controlled study.

The company's approach was not appropriate. The TRUE NORTH study is a randomized double-blind, 2-phase study (induction and maintenance phase) comparing ozanimod with placebo. It included adult patients (18–75 years of age) with moderately to severely active ulcerative colitis. The study enrolled both patients pretreated only with conventional treatments and patients who had already received biologic drugs for the treatment of ulcerative colitis. Throughout the entire study phase, the study protocol disallowed the use of all drugs and drug classes listed as ACTs by the G-BA. Consequently, TRUE NORTH participants on placebo did

not receive active therapy as specified in the ACT (see Table 4). Hence, the study is unsuitable for assessing any added benefit of ozanimod in comparison with the ACT specified by the G-BA.

Evidence for an adjusted indirect comparison

Against the background of the TRUE NORTH study, the company reportedly performed a systematic search for studies which used the intervention of ozanimod and are suitable for an adjusted indirect comparison via the common comparator of placebo. In this search, the company did not find any other relevant RCTs for the intervention side of the indirect comparison. The company argues that the TRUE NORTH study, which is composed of an induction and a maintenance phase, is unsuitable for carrying out an adjusted indirect comparison for methodological reasons (including the selection and re-randomization of induction-phase ozanimod responders for the maintenance phase). Therefore, the company decided to perform neither a systematic search for RCTs with ACT drugs nor an indirect comparison.

In all, the company therefore submitted neither direct nor indirect comparative evidence suitable for the present benefit assessment.

2.4 Results on added benefit

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

2.5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of the added benefit of ozanimod in comparison with the ACT.

Table 5: Ozanimod – 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 with, lost response to, or have intolerance or contraindications to conventional treatment	A TNF-α antagonist (adalimumab or infliximab or golimumab) or vedolizumab or tofacitinib or ustekinumab	Added benefit not proven
2	Patients who have had an inadequate response with, lost response to, or are intolerant to treatment with a biologic drug (TNFα antagonist or integrin inhibitor or interleukin inhibitor)	Vedolizumab or tofacitinib or a TNF-α antagonist (adalimumab or infliximab or golimumab) or ustekinumab, each in consideration of approval and prior treatment(s)[c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. Ozanimod is assumed to be administered as long-term therapy (induction and maintenance). Hence, drugs which are options only for the initial reduction of disease activity according to the guideline are disregarded below. Corticosteroids are generally deemed appropriate for flare treatment. Continuation of an inadequate therapy does not constitute an implementation of the ACT.
b. Patients who continue to be eligible for drug therapy (e.g. biologic drugs and JAK inhibitors) are not yet deemed candidates for proctocolectomy.
c. Switching within or between drug classes is permitted. Any possible dose adjustments are presumed to have already been exhausted. In case of primary treatment failure with a TNFα antagonist, switching to another drug class is indicated; in case of secondary treatment failure with a TNFα antagonist, switching within the drug class may be contemplated.

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

The assessment described above deviates from that by the company, which derived a hint of a non-quantifiable added benefit for ozanimod regarding each of the research questions.

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/a21-166.html.