Mirikizumab (ulcerative colitis)

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

EXTRACT

Project: A23-73 Version: 1.0 Status: 9 October 2023

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Mirikizumab (Colitis Ulcerosa) – Nutzenbewertung gemäß § 35a SGB V*. 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.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Mirikizumab (ulcerative colitis) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

14 July 2023

Internal Project No.

A23-73

Address of publisher

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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 and the German Crohn's disease / Ulcerative Colitis Association (Deutsche Morbus Crohn / Colitis ulcerosa Vereinigung) for participating in the written exchange and for their support. The respondent and the German Crohn's disease / Ulcerative Colitis Association were not involved in the actual preparation of the dossier assessment.

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Keywords

Mirikizumab, Colitis – Ulcerative, Benefit Assessment

Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

[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 mirikizumab. 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 July 2023.

Research question

The aim of this report is to assess the added benefit of mirikizumab 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 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of mirikizumab

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 to conventional treatment	A TNF-α antagonist (adalimumab or infliximab[c] or golimumab) or vedolizumab or ustekinumab
2	Patients who have had an inadequate response with, lost response to, or are intolerant to biologic treatment[d]	Switching treatment to vedolizumab or tofacitinib or ustekinumab or a TNF-α antagonist (adalimumab or infliximab[c] or golimumab), each taking into account regulatory approval and prior treatment(s)[e]

a. Presented is the respective ACT specified by the G-BA. Mirikizumab 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. 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 to not be 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.
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 potential dose adjustment options are assumed 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 stated that it followed the ACT specified by the G-BA and also named filgotinib and ozanimod as additional ACTs for both research questions. The company's deviation from the ACT specified by the G-BA will not be further commented below, as the company did not present any suitable data for the benefit assessment – neither compared with a comparator therapy designated by the company nor compared with the ACT specified by the G-BA. In addition, the company generally follows the research questions specified by the G-BA. However, it derives the 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 is conducted separately for the 2 research questions, 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 52 weeks are used for the derivation of 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 mirikizumab versus the ACT for either of the 2 research questions. Nevertheless, the company has included in its benefit assessment the randomized placebo-controlled studies LUCENT 1 and LUCENT 2 as the best available evidence. From these studies, the company derived a hint of nonquantifiable added benefit for mirikizumab. However, the LUCENT 1 and LUCENT 2 studies are unsuitable for assessing the added benefit of mirikizumab in comparison with the ACT specified by the G-BA because the studies' placebo arms did not implement active therapy as in the ACT. Hence, the studies are unsuitable for assessing any added benefit of mirikizumab in comparison with the ACT specified by the G-BA.

Results on added benefit

Since no suitable data are available for the benefit assessment, there is no hint of an added benefit of mirikizumab 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 mirikizumab.

Table 3: Mirikizumab – 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 to conventional treatment	A TNF-α antagonist (adalimumab or infliximab[c] or golimumab) or vedolizumab or ustekinumab	Added benefit not proven
2	Patients who have had an inadequate response with, lost response to, or are intolerant to biologic treatment[d]	Switching treatment to vedolizumab or tofacitinib or ustekinumab or a TNF-α antagonist (adalimumab or infliximab[c] or golimumab), each taking into account regulatory approval and prior treatment(s)[e]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. Mirikizumab 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 concur with implementation of the ACT.
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 to not be 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.
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 potential dose adjustment options are assumed 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 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 mirikizumab 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 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of mirikizumab

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 to conventional treatment	A TNF-α antagonist (adalimumab or infliximab[c] or golimumab) or vedolizumab or ustekinumab
2	Patients who have had an inadequate response with, lost response to, or are intolerant to biologic treatment[d]	Switching treatment to vedolizumab or tofacitinib or ustekinumab or a TNF-α antagonist (adalimumab or infliximab[c] or golimumab), each taking into account regulatory approval and prior treatment(s)[e]

a. Presented is the respective ACT specified by the G-BA. Mirikizumab 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 concur with implementation of the ACT.
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 to not be 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.
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 potential dose adjustment options are assumed 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

On receipt of the dossier, the G-BA adjusted the ACT on 28 July 2023 as presented in Table 4 [3]. This does not result in any changes for research question 2. As a result of the adjustment, the drug tofacitinib is no longer part of the ACT for research question 1. The present benefit assessment was conducted in accordance with the adjusted ACT.

Due to the adjustment of the ACT after receipt of the dossier, the information in the company's dossier is based on the old ACT. The company stated that it followed the ACT specified by the G-BA and also named filgotinib and ozanimod as additional ACTs for both

research questions. For the extension of the ACT, the company refers to the current S3 guideline for the therapeutic indication of ulcerative colitis [4]. Said guideline recommends both the Janus kinase inhibitors tofacitinib and filgotinib as well as ozanimod as treatment options for adult patients with moderately to severely active ulcerative colitis who have responded inadequately to conventional therapy or biologics treatment, no longer respond to it, or exhibit intolerance.

The company's deviation from the ACT specified by the G-BA will not be further commented on below because the company did not present any suitable data for the benefit assessment – neither compared to a comparator therapy designated by the company nor compared to the ACT specified by the G-BA (see Section I 3).

The company generally followed the G-BA's specification of the 2 research questions. However, it derives the 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 is conducted separately for the 2 research questions, 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 on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 52 weeks are used for the derivation of 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 mirikizumab (status: 24 April 2023)
- bibliographical literature search on mirikizumab (last search on 24 April 2023)
- search in trial registries / trial results databases for studies on mirikizumab (last search on 24 April 2023)
- search on the G-BA website for mirikizumab (last search on 24 April 2023)

To check the completeness of the study pool:

- search in trial registries for studies on mirikizumab (last search on 11 August 2023); for search strategies, see Appendix I A of the full dossier assessment

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

The company deviates from the ACT specified by the G-BA but does not identify any relevant study, even compared to the drugs it took into account as supplementary information (see Chapter I 2).

Evidence provided by the company

LUCENT 1 and LUCENT 2 studies

For the assessment of added benefit of mirikizumab versus the ACT, the company did not find any directly comparative RCTs. As best available evidence, however, the company used the randomized placebo-controlled approval studies of mirikizumab (LUCENT 1 and LUCENT 2 [5]) for its derivation of added benefit. Across all research questions, the company derived an indication of nonquantifiable added benefit of mirikizumab, arguing that the results of the LUCENT 1 and LUCENT 2 studies demonstrate a previously unachieved improvement of benefit relevant to treatment, while no quantifiable conclusion on added benefit versus the ACT can be drawn on the basis of the placebo-controlled study design.

The approach of the company is not appropriate. The LUCENT 1 and LUCENT 2 studies are double-blind, randomized studies comparing mirikizumab versus placebo which build upon each other. For the dossier, the company has presented analyses of patients who had a response to mirikizumab in the LUCENT 1 study and were rerandomized to the LUCENT 2 study. It has included adult patients (aged 18 to 80 years) with moderately to severely active

ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to treatment with at least 1 conventional or biologic agent. Throughout the entire 52-week study phase, the study protocols disallowed the use of all drugs and drug classes listed as ACTs by the G-BA. Consequently, LUCENT 1 and LUCENT 2 participants on placebo did not receive active therapy as in the ACT (see Table 4). Hence, the studies are unsuitable for assessing any added benefit of mirikizumab in comparison with the ACT specified by the G-BA.

Evidence for an adjusted indirect comparison

The company states that the study design generally allows an indirect comparison with placebo as a possible common comparator. However, it argues that for methodological reasons, the consecutive studies LUCENT 1 (induction study) and LUCENT 2 (maintenance study) are unsuitable for conducting an adjusted indirect comparison. The company explains that the patients in the LUCENT 2 study's placebo arm received mirikizumab as part of the induction study and that comparability with patients who received only placebo should therefore be viewed critically. 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.

Discontinued RCT for direct comparison with vedolizumab

In Module 4 A, the company identifies its study LUCENT-ACT [6,7] as an RCT on mirikizumab in the therapeutic indication to be assessed. This study is a double-blind, randomized, parallel-group study comparing mirikizumab with vedolizumab and placebo in adult patients with moderately to severely active ulcerative colitis. The company reports that this directly comparative study was not used for the benefit assessment because the reporting did not provide sufficient information to assess the methodology or results. The study was cancelled before any patients were enrolled.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of mirikizumab in comparison with the ACT in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to conventional therapy or a biologic agent. There is no hint of an added benefit of mirikizumab in comparison with the ACT for either of the 2 research questions; an added benefit is therefore not proven for either of them.

I 5 Probability and extent of added benefit

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

Table 5: Mirikizumab – 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 to conventional treatment	A TNF-α antagonist (adalimumab or infliximab[c] or golimumab) or vedolizumab or ustekinumab	Added benefit not proven
2	Patients who have had an inadequate response with, lost response to, or are intolerant to biologic treatment[d]	Switching treatment to vedolizumab or tofacitinib or ustekinumab or a TNF-α antagonist (adalimumab or infliximab[c] or golimumab), each taking into account regulatory approval and prior treatment(s)[e]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. Mirikizumab 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 concur with implementation of the ACT.
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 to not be 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.
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 potential dose adjustment options are assumed 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 assessment described above deviates from the assessment by the company, which derived an indication of nonquantifiable added benefit across research questions on the basis of the placebo-controlled studies LUCENT 1 and LUCENT 2.

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/a23-73.html.