Etrasimod
(ulcerative colitis)

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

EXTRACT

Project: A24-42 Version: 1.0 Status: 8 Jul 2024 DOI: 10.60584/A24-42_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Etrasimod (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

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

Commissioning agency

Federal Joint Committee

Commission awarded on

15 April 2024

Internal Project No.

A24-42

DOI-URL

https://doi.org/10.60584/A24-42_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice

No advisor on medical and scientific questions was involved in the present dossier assessment.

Patient and family involvement

No patients or families were involved in the present dossier assessment.

IQWiG employees involved in the dossier assessment

- Caroline Wöhl
- Christiane Balg
- Mandy Kromp
- Ulrike Lampert
- Daniela Preukschat
- Veronika Schneck
- Anke Schulz
- Claudia Selbach

Keywords

Etrasimod, 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)
TNF	tumour necrosis factor

I 1 Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) has commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug etrasimod. 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 15 April 2024.

Research question

The aim of this report is to assess the added benefit of etrasimod in comparison with the appropriate comparator therapy (ACT) in adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

The research questions presented in Table 2 result from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of etrasimod

Research question	Therapeutic indication	ACT[a]
Adults and adolescents 16 years of age and older 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[c] (adalimumab or golimumab or infliximab[d]) or vedolizumab or ustekinumab or ozanimod
2	Patients who have had an inadequate response, lost response, or were intolerant to a biological agent[e]	Vedolizumab or tofacitinib or ustekinumab or filgotinib or ozanimod or a TNF-α antagonist[c] (adalimumab or golimumab orinfliximab[d])[f]

a. Presented is the respective ACT specified by the G-BA. Etrasimod 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 is not the rule; surgical resection is therefore to be disregarded when determining the ACT.
c. Only the TNF-α antagonists infliximab (only for severe ulcerative colitis) and adalimumab are approved for 16- and 17-year-olds.
d. If infliximab is used, it should be combined with a thiopurine, if necessary.
e. As biologic agents, the G-BA has listed the following: TNF-α antagonist or integrin inhibitor or interleukin inhibitor.
f. 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 contemplated.

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

In deviation from the G-BA's definition of the ACT, the company divided the patient populations from research questions 1 and 2 into the 2 populations consisting of adults and of adolescents aged 16 years and older. The company stated that it followed the definition of the G-BA's ACT and furthermore named mirikizumab for the population of adults from research question 1 and mirikizumab and upadacitinib for the population of adults from research question 2 as additional treatment options of the ACT. For the population of adolescents aged 16 years and older from research questions 1 and 2, the company named adalimumab or infliximab as options for the ACT, but, according to the G-BA's note, did not take into account that infliximab is only approved for the treatment of severe active ulcerative colitis in the present therapeutic indication.

The company's deviation from the ACT specified by the G-BA will not be further commented on below, as the company did not present any suitable data for the benefit assessment – neither versus a comparator therapy specified by the company nor versus the ACT specified by the G-BA. In line with the G-BA's specification, the present assessment attempted to answer 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 24 weeks were used for deriving any added benefit.

Results

In agreement with the company, the check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of etrasimod in comparison with the ACT.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of etrasimod 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 probability and extent of the added benefit of etrasimod.

[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: Etrasimod – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults and adolescents 16 years of age and older 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[c] (adalimumab or golimumab or infliximab[d]) or vedolizumab or ustekinumab or ozanimod	Added benefit not proven
2	Patients who have had an inadequate response, lost response, or were intolerant to a biological agent[e]	Vedolizumab or tofacitinib or ustekinumab or filgotinib or ozanimod or a TNF-α antagonist[c] (adalimumab or golimumab orinfliximab[d])[f]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. Etrasimod 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 is not the rule; surgical resection is therefore to be disregarded when determining the ACT.
c. Only the TNF-α antagonists infliximab (only for severe ulcerative colitis) and adalimumab are approved for 16- and 17-year-olds.
d. If infliximab is used, it should be combined with a thiopurine, if necessary.
e. As biologic agents, the G-BA has listed the following: TNF-α antagonist or integrin inhibitor or interleukin inhibitor.
f. 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 contemplated.

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

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of etrasimod in comparison with the appropriate comparator therapy (ACT) in adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent.

The research questions presented in Table 4 result from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of etrasimod

Research question	Therapeutic indication	ACT[a]
Adults and adolescents 16 years of age and older 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[c] (adalimumab or golimumab or infliximab[d]) or vedolizumab or ustekinumab or ozanimod
2	Patients who have had an inadequate response, lost response, or were intolerant to a biological agent[e]	Vedolizumab or tofacitinib or ustekinumab or filgotinib or ozanimod or a TNF-α antagonist[c] (adalimumab or golimumab orinfliximab[d])[f]

a. Presented is the respective ACT specified by the G-BA. Etrasimod 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 is not the rule; surgical resection is therefore to be disregarded when determining the ACT.
c. Only the TNF-α antagonists infliximab (only for severe ulcerative colitis) and adalimumab are approved for 16- and 17-year-olds.
d. If infliximab is used, it should be combined with a thiopurine, if necessary.
e. As biologic agents, the G-BA has listed the following: TNF-α antagonist or integrin inhibitor or interleukin inhibitor.
f. 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 contemplated.

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

In deviation from the G-BA's definition of the ACT, the company divided the patient populations from research questions 1 and 2 into the 2 populations consisting of adults and of adolescents aged 16 years and older. The company stated in Module 3 A of the dossier that it followed the definition of the G-BA's ACT and furthermore named mirikizumab for the population of adults from research question 1 and mirikizumab and upadacitinib for the population of adults from research question 2 as additional treatment options of the ACT. The company justified expanding the ACT on the grounds that it intended to reflect the current therapeutic landscape in the therapeutic indication of ulcerative colitis. For the population of

adolescents aged 16 years and older from research questions 1 and 2, the company named adalimumab or infliximab as options for the ACT, but, according to the G-BA's note, did not take into account that infliximab is only approved for the treatment of severe active ulcerative colitis in the present therapeutic indication.

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 Chapter I 3). In line with the G-BA’s specification, the present assessment attempted to answer 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 24 weeks were used for deriving any 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 etrasimod (status: 16 January 2024)
- bibliographical literature search on etrasimod (last search on 16 January 2024)
- search in trial registries/trial results databases for studies on etrasimod (last search on 16 January 2024)
- search on the G-BA website for etrasimod (last search on 16 January 2024)

To check the completeness of the study pool:

- search in trial registries for studies on etrasimod (last search on 24 April 2024); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the check of the completeness of the study pool identified no relevant RCT comparing Etrasimod with the respective ACT defined by the G-BA for any of the 2 research questions.

As described in Chapter I 2, the company deviated from the G-BA's definition of the different research questions and the respective ACT, but also did not identify any relevant study for the drugs it additionally considered.

In Module 4 A of the dossier, the company presented the results of the approval-justifying RCT APD334-301 (ELEVATE UC 52) [3]. The RCT ELEVATE UC 52 is a double-blind study comparing etrasimod with placebo. It included adults and adolescents (aged 16 to a maximum of 80 years) with moderately to severely active ulcerative colitis who had an inadequate response, lost response, or were intolerant to (at least) 1 conventional therapy or (at least) 1 therapy with a biologic agent or a Janus kinase inhibitor. According to the study protocol, the use of all drugs or drug classes listed in the G-BA's ACT was disallowed during the 52-week treatment phase. Consequently, ELEVATE UC 52 participants on placebo did not receive active therapy as specified in the ACT (see Table 4). In agreement with the company’s assessment, the ELEVATE UC 52 study is not suitable for deriving conclusions on the added benefit of etrasimod compared with the ACT for both research questions.

I 4 Results on added benefit

No suitable data are available for assessing the added benefit of etrasimod in comparison with the ACT in adults and adolescents 16 years of age and older with moderately to severely active ulcerative colitis who have had an inadequate response, lost response to, or are intolerant to conventional therapy or a biologic agent. There is no hint of an added benefit of etrasimod 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

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

Table 5: Etrasimod – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Adults and adolescents 16 years of age and older 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[c] (adalimumab or golimumab or infliximab[d]) or vedolizumab or ustekinumab or ozanimod	Added benefit not proven
2	Patients who have had an inadequate response, lost response, or were intolerant to a biological agent[e]	Vedolizumab or tofacitinib or ustekinumab or filgotinib or ozanimod or a TNF-α antagonist[c] (adalimumab or golimumab orinfliximab[d])[f]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. Etrasimod 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 is not the rule; surgical resection is therefore to be disregarded when determining the ACT.
c. Only the TNF-α antagonists infliximab (only for severe ulcerative colitis) and adalimumab are approved for 16- and 17-year-olds.
d. If infliximab is used, it should be combined with a thiopurine, if necessary.
e. As biologic agents, the G-BA has listed the following: TNF-α antagonist or integrin inhibitor or interleukin inhibitor.
f. 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 contemplated.

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

The assessment described above corresponds to that of the company, whereby the company, in contrast to G-BA, differentiated between adults and adolescents aged 16 years and older and divided the target population into 4 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.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 06.10.2023]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.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://doi.org/10.1002/bimj.201300274.

3. Sandborn WJ, Vermeire S, Peyrin-Biroulet L et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. Lancet 2023; 401(10383): 1159-1171. https://doi.org/10.1016/S0140-6736(23)00061-2.

The full report (German version) is published under https://www.iqwig.de/en/projects/a24-42.html.