Acalabrutinib
(mantle cell lymphoma; monotherapy)

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

EXTRACT

Project: A25-90 Version: 1.0 Status: 24 Sep 2025 DOI: 10.60584/A25-90_en

[1] Translation of Sections I 1 to I 4 of the dossier assessment *Acalabrutinib (Mantelzell-Lymphom; Monotherapie) – Nutzenbewertung gemäß § 35a SGB V*. Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher

Institute for Quality and Efficiency in Health Care

Topic

Acalabrutinib (mantle cell lymphoma; monotherapy) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

01 July 2025

Internal Project No.

A25-90

DOI-URL

https://doi.org/10.60584/A25-90_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Acalabrutinib (mantle cell lymphoma; monotherapy); Benefit assessment according to §35a SGB V; Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-90_en.

Keywords

Acalabrutinib, Lymphoma – Mantle-Cell, Benefit Assessment

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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

No feedback was received in the framework of the present dossier assessment.

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Part I: Benefit assessment

I Table of contents

Page

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
BTK	Bruton’s tyrosine kinase
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 acalabrutinib. 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 01 July 2025.

Research question

The aim of this report is to assess the added benefit of acalabrutinib in comparison with the appropriate comparator therapy (ACT) in adult patients with relapsed or refractory mantle cell lymphoma not previously treated with a Bruton tyrosine kinase (BTK) inhibitor.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of acalabrutinib

Therapeutic indication	**ACT[a]**
Adult patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK inhibitor	Individualized treatment[b, c, d] choosing from: ▪ bendamustine + rituximab[e] ▪ lenalidomide ± rituximab ▪ R-CHOP[e] ▪ VRCAP ▪ R-BAC ▪ R-FCM[e] ▪ ibrutinib
a. Presented is the ACT specified by the G-BA. b. The term "individualized treatment" is used instead of previously used terms such as "patient-specific therapy" or "treatment of physician's choice". This ensures consistency with the terms used in European health technology assessments (EU HTAs). c. The treatment decision in particular takes into account the response to and duration of remission under prior therapies, and the patient's general condition. d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study). e. According to the available evidence, repeat immunochemotherapy in the form of R-FCM, R-CHOP or bendamustine + rituximab is only indicated for adults with a late relapse after prior therapy. Due to myelotoxicity, among other things, R-FCM can only be considered as a treatment option for patients in sufficiently good general condition. Bendamustine + rituximab is a treatment option for adults in poor general condition. BTK: Bruton tyrosine kinase; EU: European Union; G-BA: Federal Joint Committee; HTA: health technology assessment; R-BAC: rituximab + bendamustine + cytarabine; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-FCM: fludarabine + cyclophosphamide + mitoxantrone + rituximab; VRCAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone	

The G-BA adjusted the ACT on 08 April 2025. In its dossier, however, the company refers to the consultation with the G-BA on 29 November 2024 and specifies an individualized treatment selected from the treatment options listed above as an ACT, as well as the additional options temsirolimus, venetoclax, high-dose therapy with allogeneic stem cell transplant and high-dose therapy with autologous stem cell transplant. The present assessment is implemented in comparison with the ACT specified by the G-BA.

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) were used to derive the added benefit.

Results

The check of the completeness of the information retrieval did not identify any relevant study for assessing the added benefit of acalabrutinib 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 acalabrutinib in comparison with the ACT for adult patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK; 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 acalabrutinib.

[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: Acalabrutinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK inhibitor	Individualized treatment[b, c, d] choosing from: ▪ bendamustine + rituximab[e] ▪ lenalidomide ± rituximab ▪ R-CHOP[e] ▪ VRCAP ▪ R-BAC ▪ R-FCM[e] ▪ ibrutinib	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The term "individualized treatment" is used instead of previously used terms such as "patient-specific therapy" or "treatment of physician's choice". This ensures consistency with the terms used in European health technology assessments (EU HTAs).
c. The treatment decision in particular takes into account the response to and duration of remission under prior therapies, and the patient's general condition.
d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study).
e. According to the available evidence, repeat immunochemotherapy in the form of R-FCM, R-CHOP or bendamustine + rituximab is only indicated for adults with a late relapse after prior therapy. Due to myelotoxicity, among other things, R-FCM can only be considered as a treatment option for patients in sufficiently good general condition. Bendamustine + rituximab is a treatment option for adults in poor general condition.

BTK: Bruton tyrosine kinase; EU: European Union; G-BA: Federal Joint Committee; HTA: health technology assessment; R-BAC: rituximab + bendamustine + cytarabine; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-FCM: fludarabine + cyclophosphamide + mitoxantrone + rituximab; VRCAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of acalabrutinib in comparison with the ACT in adult patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK inhibitor.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of acalabrutinib

Therapeutic indication	**ACT[a]**
Adult patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK inhibitor	Individualized treatment[b, c, d] choosing from: ▪ bendamustine + rituximab[e] ▪ lenalidomide ± rituximab ▪ R-CHOP[e] ▪ VRCAP ▪ R-BAC ▪ R-FCM[e] ▪ ibrutinib

a. Presented is the ACT specified by the G-BA.
b. The term "individualized treatment" is used instead of previously used terms such as "patient-specific therapy" or "treatment of physician's choice". This ensures consistency with the terms used in European health technology assessments (EU HTAs).
c. The treatment decision in particular takes into account the response to and duration of remission under prior therapies, and the patient's general condition.
d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study).
e. According to the available evidence, repeat immunochemotherapy in the form of R-FCM, R-CHOP or bendamustine + rituximab is only indicated for adults with a late relapse after prior therapy. Due to myelotoxicity, among other things, R-FCM can only be considered as a treatment option for patients in sufficiently good general condition. Bendamustine + rituximab is a treatment option for adults in poor general condition.

BTK: Bruton tyrosine kinase; EU: European Union; G-BA: Federal Joint Committee; HTA: health technology assessment; R-BAC: rituximab + bendamustine + cytarabine; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-FCM: fludarabine + cyclophosphamide + mitoxantrone + rituximab; VRCAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone

The G-BA adjusted the ACT on 08 April 2025. In its dossier, however, the company refers to the consultation with the G-BA on 29 November 2024 and specifies an individualized treatment selected from the treatment options listed above as an ACT, as well as the additional options temsirolimus, venetoclax, high-dose therapy with allogeneic stem cell transplant and high-dose therapy with autologous stem cell transplant.

The present assessment is implemented in comparison with the ACT specified by the G-BA. 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.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs were used to derive the added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

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

Sources used by the company in the dossier:

- Study list on acalabrutinib (status: 19 May 2025)
- Bibliographical literature search on acalabrutinib (last search on 20 May 2025)
- Search in trial registries/trial results databases for studies on acalabrutinib (last search on 19 May 2025)
- Search on the G-BA website for acalabrutinib (last search on 20 May 2025)

To check the completeness of the study pool:

- Search in trial registries for studies on acalabrutinib (last search on 10 July 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, this review did not identify any relevant studies.

For reasons of clinical relevance and to describe the medical benefit, the company presents the single-arm approval study ACE-LY-004 [3]. The ACE-LY-004 study does not include any comparisons with the ACT; therefore, data on the comparison of acalabrutinib with the comparator therapy specified by the G-BA are not available.

I 4 Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of acalabrutinib in comparison with the ACT for adult patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

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

Table 5: Acalabrutinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with relapsed or refractory mantle cell lymphoma not previously treated with a BTK inhibitor	Individualized treatment[b, c, d] choosing from: ▪ bendamustine + rituximab[e] ▪ lenalidomide ± rituximab ▪ R-CHOP[e] ▪ VRCAP ▪ R-BAC ▪ R-FCM[e] ▪ ibrutinib	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. The term "individualized treatment" is used instead of previously used terms such as "patient-specific therapy" or "treatment of physician's choice". This ensures consistency with the terms used in European health technology assessments (EU HTAs).
c. The treatment decision in particular takes into account the response to and duration of remission under prior therapies, and the patient's general condition.
d. For the implementation of individualized treatment in a study of direct comparison, the investigators are assumed to have a choice between several treatment options enabling an individualized treatment decision (multicomparator study).
e. According to the available evidence, repeat immunochemotherapy in the form of R-FCM, R-CHOP or bendamustine + rituximab is only indicated for adults with a late relapse after prior therapy. Due to myelotoxicity, among other things, R-FCM can only be considered as a treatment option for patients in sufficiently good general condition. Bendamustine + rituximab is a treatment option for adults in poor general condition.

BTK: Bruton tyrosine kinase; EU: European Union; G-BA: Federal Joint Committee; HTA: health technology assessment; R-BAC: rituximab + bendamustine + cytarabine; R-CHOP: rituximab, cyclophosphamide, doxorubicin, vincristine, prednisone; R-FCM: fludarabine + cyclophosphamide + mitoxantrone + rituximab; VRCAP: bortezomib, rituximab, cyclophosphamide, doxorubicin, prednisone

The assessment described above concurs with the company's assessment.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a25-90.html.