IQWiG Reports – Commission No. A21-80

Berotralstat (hereditary angioedema) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Berotralstat (hereditäres Angioödem) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 September 2021). 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
Berotralstat (hereditary angioedema) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
8 June 2021

Internal Commission No.
A21-80

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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.

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Keywords: Berotralstat, Angioedemas – Hereditary, Benefit Assessment

Table of contents

List of tables[2]

Page

[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)
HAE	hereditary angioedema
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 berotralstat. 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 8 June 2021.

Research question

This assessment aims to assess the added benefit of berotralstat in comparison with the appropriate comparator therapy (ACT) in adults and adolescents aged 12 years and older for the routine prevention of recurrent attacks of hereditary angioedema (HAE).

The G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2: Research question of the benefit assessment of berotralstat

Therapeutic indication	**ACT**[a]
Routine prevention of recurrent attacks of HAE[b] in adults and adolescents aged 12 years and older[c]	Routine prophylaxis with C1 esterase inhibitor[c]
a. Presented is the respective ACT specified by the G-BA. b. The therapeutic indication of berotralstat is assumed to comprise only patients with HAE type I or type II. c. Both study arms should provide for acute treatment of HAE attacks. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HAE: hereditary angioedema	

The company followed the G-BA's specification by identifying routine prophylaxis with C1 esterase inhibitor as the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used for the derivation of the added benefit.

Results

In line with the company's assessment, the check of completeness of the study pool did not identify any relevant RCT for assessing added benefit of berotralstat in comparison with the ACT. The company also did not present any other data for assessing added benefit.

Hence, no suitable data are available for assessing the added benefit of berotralstat in the routine prevention of recurrent attacks of HAE in adults and adolescents aged 12 years and older in comparison with the ACT. Consequently, there is no hint of added benefit of berotralstat 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 presents a summary of the probability and extent of added benefit of berotralstat.

Table 3: Berotralstat – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Routine prevention of recurrent attacks of HAE[b] in adults and adolescents aged 12 years and older[c]	Routine prophylaxis with C1 esterase inhibitor[c]	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. The therapeutic indication of berotralstat is assumed to comprise only patients with HAE type I or type II. c. Both study arms should provide for acute treatment of HAE attacks. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HAE: hereditary angioedema		

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].

2.2 Research question

This assessment aims to assess the added benefit of berotralstat in comparison with the ACT in adults and adolescents aged 12 years and older for the routine prevention of recurrent attacks of hereditary angioedema (HAE).

The G-BA's specification of the ACT results in the research question presented in Table 4.

Table 4: Research question of the benefit assessment of berotralstat

Therapeutic indication	**ACT**[a]
Routine prevention of recurrent attacks of HAE[b] in adults and adolescents aged 12 years and older[c]	Routine prophylaxis with C1 esterase inhibitor[c]
a. Presented is the respective ACT specified by the G-BA. b. The therapeutic indication of berotralstat is assumed to comprise only patients with HAE type I or type II. c. Both study arms should provide for acute treatment of HAE attacks. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HAE: hereditary angioedema	

The company followed the G-BA's specification by identifying routine prophylaxis with C1 esterase inhibitor as the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

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

Sources cited by the company in the dossier:

- Study list on berotralstat (as of 27 April 2021)
- Bibliographic literature search on berotralstat (most recent search on 27 April 2021)
- Search in trial registries / study results databases on berotralstat (most recent search on 27 April 2021)
- Search on the G-BA website on berotralstat (most recent search on 30 April 2021)
- Bibliographic literature search on the ACT (most recent search on 27 April 2021)
- Search in trial registries or results databases on the ACT (most recent search on 27 April 2021)
- Search on the G-BA website for the ACT (most recent search on 30 April 2021)

To check the completeness of the study pool:

- Search in trial registries for berotralstat (most recent search on 28 June 2021); see Appendix A of the full dossier assessment for the search strategies.

The check of completeness of the study pool did not find any relevant RCT for assessing the added benefit of berotralstat in comparison with the ACT. This concurs with the company's assessment.

Evidence provided by the company

To assess the added benefit of berotralstat versus the ACT, the company did not find any directly comparative RCTs. To present the medical benefit, however, it used the two placebo-controlled approval studies conducted in the therapeutic indication, APeX-2 [3] and APeX-J [4]. Consistent with logic, the company did not derive any added benefit from them, however. The company reported that, in view of the two studies, it conducted a systematic search for an indirect comparison between berotralstat and the ACT using placebo as the common comparator. The company, by its own account, first found 2 RCTs in this search, but after assessing the study design, outcome recording, and comparator therapy, it deemed them unsuitable. The company reports that it did not present an indirect comparison for this reason. Overall, therefore, the company does not see proof of added benefit of berotralstat.

The company's approach is plausible. The APeX-2 and APeX-J studies are randomized, double-blind studies investigating routine prophylaxis with berotralstat in comparison with placebo in patients aged 12 years and older with clinically diagnosed HAE type I or type II. According to the exclusion criteria, neither study allowed the use of C1 esterase inhibitors for the prophylaxis of HAE attacks within 14 days before screening or starting treatment during the study. Hence, the ACT of routine prophylaxis with C1 esterase inhibitor has not been implemented in the placebo arm of either study. Concurring with the company, the studies are therefore deemed unsuitable for assessing added benefit of berotralstat in comparison with the ACT.

2.4 Results on added benefit

No suitable data are available for assessing the added benefit of berotralstat for the routine prevention of recurrent attacks of HAE in adults and adolescents aged 12 years and older in comparison with the ACT. Consequently, there is no hint of added benefit of berotralstat in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 presents a summary of the results of the benefit assessment of berotralstat in comparison with the ACT.

Table 5: Berotralstat – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Routine prevention of recurrent attacks of HAE[b] in adults and adolescents aged 12 years and older[c]	Routine prophylaxis with C1 esterase inhibitor[c]	Added benefit not proven
a. Presented is the respective ACT specified by the G-BA. b. The therapeutic indication of berotralstat is assumed to comprise only patients with HAE type I or type II. c. Both study arms should provide for acute treatment of HAE attacks. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; HAE: hereditary angioedema		

The above assessment concurs with that of the company.

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.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a21-80.html.