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Albutrepenonacog alfa (haemophilia B) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Albutrepenonacog alfa (Hämophilie B) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 11 January 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 Dragana Mitrovic and Christian Schepperle

IQWiG thanks the respondents for participating in the written exchange about how they experienced the disease and its treatment and about the treatment goals. The respondents were 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)
MAIC	matching-adjusted indirect comparison
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

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 albutrepenonacog alfa. 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 October 2021.

Research question

The aim of the present report was to assess the added benefit of albutrepenonacog alfa compared with the appropriate comparator therapy (ACT) in the treatment and prevention of bleeding events in patients with haemophilia B (congenital factor IX deficiency).

The research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of albutrepenonacog alfa

Therapeutic indication	**ACT**[a]
Treatment and prevention of bleeding events in patients with haemophilia B (congenital factor IX deficiency)	**Recombinant** or human plasma-derived **coagulation factor IX products**[b]
a. Presentation of the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. b. Company's choice: eftrenonacog alfa. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification and selected the recombinant coagulation factor eftrenonacog alfa from among the presented options.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. For prophylactic treatment, a minimum study duration of 6 months applies. The assessment of event-based treatment requires a study duration of at least 50 exposure days.

Results

The company identified no randomized controlled trials (RCTs) involving a direct comparison of albutrepenonacog alfa versus the ACT. Due to the lack of directly comparative data, the company presented comparisons of individual arms from different studies in the section "Other investigations".

On the albutrepenonacog alfa side, the company included the open-label, uncontrolled, multicentre studies CSL654_2004, CSL654_3001, CSL654_3002, CSL654_3003, and CSL654_5005, which included treatment-experienced male haemophilia B patients. The studies CSL654_2004 and CSL654_3001 each included adults and adolescents aged 12 to 65 years; the CSL654_3002 study included children < 12 years, and the studies CSL654_3003 and CSL654_5005 included all age groups. The studies each enrolled a total of 17 to 83 patients. Study durations were between 4 months and 3 years. Except for the ongoing CSL654_5005 study, all studies have been completed.

For eftrenonacog alfa, the company uses the studies B-LONG, Kids B-LONG, and B-YOND, which included treatment-experienced male haemophilia B patients. The B-LONG study included adults and adolescents aged 12 years and older, the Kids B-LONG study included children aged < 12 years, and the B-YOND study, an extension study of the 2 B-LONG studies, included all age groups. The studies each enrolled a total of 30 to 123 patients. The study durations were between 1 and 5.4 years, and all studies have been completed.

The comparisons presented by the company are unsuitable for the benefit assessment

The company descriptively compares the results of the studies on albutrepenonacog alfa with the results from the studies on eftrenonacog alfa regarding outcomes from the mortality, morbidity, health related quality of life, and side effects categories. For 2 of the studies, it additionally carried out selective matching-adjusted indirect comparison (MAIC) analyses for patients aged ≥ 12 years regarding the outcomes of bleeding rate and factor use in prophylaxis.

A purely descriptive comparison of the results from individual arms of different studies is not suitable for deriving added benefit. Furthermore, the MAIC analyses carried out by the company for several outcomes without a common comparator are generally not an adequate solution for confounder adjustment. In addition, in the present scenario of indirect comparison without a common comparator, the identified effects are not sufficiently large to rule out with certainty that they result solely from systematic bias due to confounders.

Results on added benefit

For the assessment of albutrepenonacog alfa in the therapy and prophylaxis of patients with haemophilia B (congenital factor IX deficiency), no suitable data are available for assessing added benefit in comparison with the ACT. This resulted in no hint of an added benefit of albutrepenonacog alfa versus the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

On the basis of the results presented, the probability and extent of the added benefit of the drug albutrepenonacog alfa in comparison with the ACT is assessed as follows:

Table 3 shows a summary of the probability and extent of the added benefit of albutrepenonacog alfa.

Table 3: Albutrepenonacog alfa – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Treatment and prevention of bleeding events in patients with haemophilia B (congenital factor IX deficiency)	**Recombinant** or human plasma-derived **coagulation factor IX products**[b]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Company's choice: eftrenonacog alfa.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of market access in 2016. In this assessment, the G-BA had determined a non-quantifiable added benefit of albutrepenonacog alfa; however, due to the special situation for orphan drugs, the added benefit had been regarded as proven by the approval irrespective of the underlying data.

2.2 Research question

The aim of the present report was to assess the added benefit of albutrepenonacog alfa compared with the ACT in the treatment and prevention of bleeding events in patients with haemophilia B (congenital factor IX deficiency).

The research question presented in Table 4 results from the ACT specified by the G-BA.

[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 4: Research question of the benefit assessment of albutrepenonacog alfa

Therapeutic indication	**ACT**[a]
Treatment and prevention of bleeding events in patients with haemophilia B (congenital factor IX deficiency)	**Recombinant** or human plasma-derived **coagulation factor IX products**[b]
a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold. b. Company's choice: eftrenonacog alfa. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification and selected the recombinant coagulation factor eftrenonacog alfa from among the presented options.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. The minimum study duration defined for prophylactic treatment is 6 months. A study duration of at least 50 exposure days must be ensured to assess episodic treatment. This deviates from inclusion criteria of the company, which used only a minimum study duration of 6 months.

2.3 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 lists on albutrepenonacog for the direct comparison (status: 6 October 2021) and on other investigations (status: 23 July 2021)
- bibliographical literature search on albutrepenonacog (last search on 21 July 2021)
- search in trial registries/trial results databases for studies on albutrepenonacog (last search on 9 August 2021)
- search on the G-BA website for albutrepenonacog (last search on 23 July 2021)
- bibliographical literature search on the ACT (last search on 21 July 2021)
- search in trial registries/trial results databases for studies on the ACT (last search on 3 August 2021)
- search on the G-BA website for the ACT (last search on 23 July 2021)

To check the completeness of the study pool:

- search in trial registries for studies on albutrepenonacog (last search on 9 November 2021); for search strategies, see Appendix A of the full dossier assessment

Direct comparison

In its information retrieval, the company identified no RCTs with a direct comparison of albutrepenonacog alfa versus the ACT. The check of completeness also produced no directly comparative RCT.

Other investigations

As the company identified no studies for a direct comparison, it conducted an information retrieval for further studies. Regarding the inclusion criteria, the company reportedly disregarded patients without prior treatment as well as studies on perioperative treatment with factor IX products. The company identified 5 non-active-controlled trials for the intervention and 3 for eftrenonacog alfa.

The approach of the company was not appropriate. The Summary of Product Characteristics (SPC) for albutrepenonacog alfa [3] does not restrict the use to treatment-experienced patients, and the drug's approval also covers perioperative episodic treatment. However, the company's approach remains without consequence because the check of completeness of the study pool did not identify any additional, potentially relevant study on albutrepenonacog alfa. A check of the completeness of the study pool for the ACT was omitted because the comparison of individual arms from different studies as presented by the company is generally unsuitable for drawing conclusions on the added benefit of albutrepenonacog alfa for patients in the present therapeutic indication. This is explained below.

Study pool of the company

Below, the studies presented by the company are described only briefly and in summarized form. A detailed presentation is found in the company's Module 4.

Studies with albutrepenonacog alfa

On the side of albutrepenonacog alfa, the company included the open-label, non-controlled multicentre studies CSL654_2004 [4], CSL654_3001 [5], CSL654_3002 [6], CSL654_3003 [7], and CSL654_5005 [8]. All studies included treatment-experienced male haemophilia B-patients: studies CSL654_2004 and CSL654_2004 each included adults and adolescents aged 12 to 65 years; the CSL654_3002 study included children < 12 years, and CSL654_3003 and CSL654_5005 included all age groups. The smallest study enrolled 17 patients, and the largest study, 83 patients. Treatment with albutrepenonacog alfa for bleeding prevention and any episodic treatment necessary was largely in accordance with the SPC [3]. The primary outcomes were either inhibitor development, spontaneous bleeding, or treatment-associated adverse events (AE). The study durations were between 4 months and 3 years. Only the CSL654_5005 study is still ongoing.

Studies with eftrenonacog alfa

For eftrenonacog alfa, the company used the studies B-LONG [9], Kids B-LONG [10], and B-YOND [11]. The studies included treatment-experienced male haemophilia B patients: the

B-LONG study included adults and adolescents from 12 years of age, the Kids B-LONG study included children aged < 12 years, and the B-YOND study, an extension study of the two B-LONG studies, included all age groups. The smallest study enrolled 30 patients, and the largest study, 123 patients. Treatment with eftrenonacog alfa for bleeding prophylaxis as well as any necessary episodic treatment was in accordance with the SPC [12]. The primary outcome was either annualized bleeding rate or inhibitor development. The study durations were between 1 and 5.4 years. All studies have been completed.

Comparisons presented by the company

The company descriptively compares the results of the studies on albutrepenonacog alfa versus the results from the studies on eftrenonacog alfa regarding the outcome categories of mortality, morbidity, health related quality of life, and side effects. It did not present any effect estimators for the comparison of the intervention versus comparator therapy.

Furthermore, the company presents MAIC analyses for the outcomes of annualized bleeding rate and factor use. Regarding albutrepenonacog alfa, the company uses individual patient data for the MAIC analysis and aggregated data for the studies on eftrenonacog alfa. The MAIC analyses each investigate only the results of the CSL654_3001 study for albutrepenonacog alfa and the B-LONG study for eftrenonacog alpha in patients ≥ 12 years of age. The company did not justify its approach.

Comparisons of individual arms of different studies are not suitable for the benefit assessment

The purely descriptive comparison of results from individual arms of different studies is unsuitable for deriving added benefit, particularly since the company did not investigate the similarity of the studies for the intervention and comparator.

Further, MAIC analyses without a common comparator are generally not an adequate option for confounder adjustment [1]. In case of non-randomized comparisons without a common comparator, meaningful approaches towards confounder adjustment are usually only those that - unlike the MAIC analysis - involve the use of individual patient data [13]. The MAIC analysis, in contrast, takes confounding into account on the basis of aggregate data. Hence, the results presented by the company on the basis of MAIC analyses are unsuitable for assessing the added benefit of albutrepenonacog alfa. Furthermore, the company's approach of carrying out the MAIC analyses only selectively for individual outcomes is not appropriate.

Irrespective of the company's approach, in the present scenario of indirect comparison without a common comparator, the identified effects are not sufficiently large to rule out with certainty that they are based solely on systematic bias due to confounders.

2.4 Results

For the assessment of albutrepenonacog alfa in the therapy and prophylaxis of patients with haemophilia B (congenital factor IX deficiency), no suitable data are available for assessing

any added benefit in comparison with the ACT. This resulted in no hint of an added benefit of albutrepenonacog alfa versus the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Since no data for the assessment of added benefit are available for albutrepenonacog alfa versus the ACT in the treatment and prevention of bleeding events in patients with haemophilia B (congenital factor IX deficiency), an added benefit of albutrepenonacog alfa is not proven for these patients.

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

Table 5: Albutrepenonacog alfa – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Treatment and prevention of bleeding events in patients with haemophilia B (congenital factor IX deficiency)	**Recombinant** or human plasma-derived **coagulation factor IX products**[b]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA. In cases where the ACT specified by the G-BA allows the company to choose a comparator therapy from several options, the respective choice of the company is printed in bold.
b. Company's choice: eftrenonacog alfa

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above deviates from the company's assessment, which derived a considerable added benefit of albutrepenonacog alfa without specifying the certainty of results.

The G-BA decides on the added benefit.

Supplementary note

The result of the assessment deviates from the result of the G-BA's assessment in the context of market access in 2016, In the latter assessment, the G-BA had determined a non-quantifiable added benefit of albutrepenonacog alfa. however, due to the special situation for orphan drugs, the added benefit had been regarded as proven by the approval irrespective of the underlying data.

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/a21-137.html.