IQWiG Reports – Commission No. A18-23

Bezlotoxumab (Clostridium difficile infection) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Bezlotoxumab (Clostridium-difficile-Infektion) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 June 2018). 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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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) 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 bezlotoxumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 29 March 2018.

Research question

The aim of this report is to assess the added benefit of bezlotoxumab in comparison with the ACT in the prevention of recurrent *Clostridium difficile* infection (CDI) in adult patients at high risk of CDI recurrence.

Table 2 presents the indication to be assessed and the respective ACT specified by the G-BA.

Table 2[2]: Research question of the benefit assessment of bezlotoxumab

Indication	**ACT[a]**
Prevention of CDI recurrence in adults at high risk of CDI recurrence	Watchful waiting
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; CDI: *Clostridium difficile* infection; G-BA: Federal Joint Committee	

The company followed the G-BA's specification of the ACT.

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) with a minimum duration of 10 weeks were used for the derivation of the added benefit.

Results

The RCTs MODIFY I and MODIFY II were included for the assessment of the added benefit of bezlotoxumab.

Study design

MODIFY I and MODIFY II are randomized, multicentre, double-blind studies. Both studies included patients with a primary or recurrent CDI episode, regardless of their recurrence risk. The CDI diagnosis had to be confirmed by diarrhoea and a positive stool test for toxigenic CDI. In addition, patients had to currently receive or plan to receive 10 to 14 days of standard-of-care (SOC) antibiotic therapy for CDI. The studies offered the following options for SOC antibiotic therapy: oral metronidazole (metronidazole stratum), oral vancomycin or oral vancomycin +

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

intravenous (IV) metronidazole (vancomycin stratum), as well as oral fidaxomicin or oral fidaxomicin + IV metronidazole (fidaxomicin stratum).

The MODIFY I study included a total of 1452 patients, which were randomized at a 1:1:1:1 ratio to the 4 study arms bezlotoxumab, actoxumab + bezlotoxumab, actoxumab, or placebo, stratified by stratum of SOC antibiotic therapy and hospitalization status. After randomization, study participants were observed for a maximum of 12 weeks. The MODIFY II study included a total of 1203 patients, who were randomized at a 1:1:1 ratio to the 3 study arms bezlotoxumab, actoxumab + bezlotoxumab, or placebo, stratified by stratum of SOC antibiotic therapy and hospitalization status. Like in MODIFY I, the randomized observation period was 12 weeks, but an additional 9-month extension phase was added to the end of that period in this study. The extension phase of MODIFY II was disregarded because only 183 patients of the bezlotoxumab and placebo arms participated in the extension phase, and no re-randomization took place.

Of relevance to the benefit assessment were only the study arms bezlotoxumab and placebo, and from each of these arms, only a subpopulation of patients at high risk of recurrence. High risk of recurrence was defined by the presence of at least 1 of the following risk factors: age ≥ 65 years, prior history of one or more episodes of CDI in the past 6 months, immunosuppressed, severe CDI, infected with hypervirulent strain (ribotype 027, 078 or 244), and infected with ribotype 027. At 1175 patients, this population equalled about 73% of the total population of randomized patients in the relevant treatment arms.

Due to the measures to be taken in the studies (e.g., close patient monitoring, option to switch the antibiotic agent in case of insufficient effectiveness), the placebo arms of both studies overall represent an adequate implementation of the ACT specified by the G-BA (watchful waiting).

The primary outcome of the studies was CDI recurrence; patient-relevant secondary outcomes assessed a priori were global cure and outcomes on adverse events, which included the assessment of all-cause mortality. All outcomes except for adverse events (AEs) were monitored for 12 weeks; the outcome AEs was monitored for only 4 weeks.

Risk of bias and summary assessment of reliability

The risk of bias on the study level was rated as low for both MODIFY I and MODIFY II.

The risk of bias for the outcomes all-cause mortality and discontinuation due to AEs was rated as low. Since a relevant percentage of patients had no stool test for *Clostridium difficile* after diarrhoea recurrence, there is a high risk of bias for the primary analyses of the outcomes global cure and CDI recurrence. To check the robustness of results for these two outcomes, secondary analyses with different assumptions for patients without stool test were additionally carried out. If the primary analysis resulted in a statistically significant effect for global cure and CDI

recurrence and this effect was confirmed by the secondary analysis, reliability was not downgraded for the outcomes global cure and CDI recurrence despite the high risk of bias.

For the outcome serious adverse events (SAEs), the available analyses were not usable since events related to CDI recurrence were included. For the outcomes pain and CDI-related hospitalization, no relevant data were available. For these outcomes, the risk of bias was therefore not assessed.

The quality of the available data allows deriving at most proof, e.g., of an added benefit, for all examined outcomes.

Mortality

All-cause mortality

For the outcome all-cause mortality, the meta-analysis of the studies does not show a statistically significant difference between treatment groups. This resulted in no hint of an added benefit of bezlotoxumab + antibacterial therapy in comparison with watchful waiting + antibacterial therapy; an added benefit is therefore not proven.

Morbidity

Global cure and CDI recurrence

For the outcomes global cure and CDI recurrence, the meta-analysis of the studies (primary analysis) shows a statistically significant difference in favour of bezlotoxumab + antibacterial therapy.

The results of the primary analyses may be highly biased due to unverifiable assumptions regarding patients for whom no stool test results for *Clostridium difficile* are available after diarrhoea recurrence. To check the robustness of results, the result of the secondary analyses is additionally considered. The result of the secondary analyses still shows a statistically significant difference in favour of bezlotoxumab + antibacterial therapy and hence confirms the result of the primary analyses.

From the joint consideration of the outcomes global cure and CDI recurrence, proof of added benefit of bezlotoxumab + antibacterial therapy is derived in comparison with watchful waiting + antibacterial therapy.

Pain

No relevant data are available for the outcome pain. This resulted in no hint of an added benefit of bezlotoxumab + antibacterial therapy in comparison with watchful waiting + antibacterial therapy; an added benefit is therefore not proven.

CDI-related hospitalization

For the outcome CDI-related hospitalization, no relevant data were available. This resulted in no hint of an added benefit of bezlotoxumab + antibacterial therapy in comparison with watchful waiting + antibacterial therapy; an added benefit is therefore not proven.

Health-related quality of life

No outcomes from this category were assessed in either study.

Adverse events

SAEs

Since SAEs included events associated with CDI recurrence, the existing analyses on SAEs are not useful. On the basis of the available data, however, greater or lesser harm of bezlotoxumab can be ruled out for the outcome SAEs (excluding events associated with CDI recurrence).

Hence for the outcome SAEs, there was no hint of greater or lesser harm from bezlotoxumab + antibacterial therapy in comparison with watchful waiting + antibacterial therapy; greater or lesser harm is therefore not proven.

Discontinuation due to AEs

One patient in the bezlotoxumab arm and no patient in the placebo arm discontinued the infusion of the study drug due to AEs.

Hence for the outcome discontinuation due to AEs, there was overall no hint of greater or lesser harm from bezlotoxumab + antibacterial therapy in comparison with watchful waiting + antibacterial therapy; greater or lesser harm is therefore not proven.

Specific AEs

This benefit assessment reveals no conspicuous differences regarding specific AEs not obviously affected by the underlying disease (such as the System Organ Classes [SOCs] Infections and Infestations as well as Gastrointestinal Disorders).

For the SOCs Infections and Infestations as well as Gastrointestinal Disorders, no conspicuous differences were found either. The results of common AEs and SAEs show, however, that under the SOCs Gastrointestinal Disorders and Infections and Infestations, symptoms of CDI such as abdominal pain or diarrhoea or of CDI recurrence itself were recorded as well. Despite the inclusion of events which may result from CDI recurrence, the bezlotoxumab arm had more events in the SOC Gastrointestinal Disorders than did the placebo arm. Therefore, a negative effect of bezlotoxumab on gastrointestinal AEs cannot be ruled out. This pattern is not observed in the SOC Infections and Infestations, however. No specific AEs were selected from the SOC Infections and Infestations.

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 bezlotoxumab compared with the ACT is assessed as follows:

Overall, the effect of bezlotoxumab + antibacterial therapy in comparison with watchful waiting + antibacterial therapy in the prevention of CDI recurrence was exclusively positive; the probability of the effect was categorized as "proof" and the extent as "non-quantifiable", but at most "considerable". A negative effect of bezlotoxumab on gastrointestinal AEs cannot be ruled out on the basis of the data.

In summary, there is proof of a non-quantifiable added benefit of bezlotoxumab in comparison with the ACT of watchful waiting for the prevention of CDI recurrence in patients at high risk of CDI recurrence.

Table 3 presents a summary of the probability and extent of the added benefit of bezlotoxumab.

Table 3: Bezlotoxumab – probability and extent of added benefit

Indication	**ACT[a]**	**Probability and extent of added benefit**
Prevention of CDI recurrence in adults at high risk of CDI recurrence	Watchful waiting	Proof of non-quantifiable (at most considerable) added benefit
a: Presentation of the ACT specified by the G-BA. ACT: appropriate comparator therapy; CDI: *Clostridium difficile* infection; G-BA: Federal Joint Committee		

The approach for deriving the overall conclusion on added benefit is a suggestion from IQWiG. 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].

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 04 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-23-bezlotoxumab-clostridium-difficile-infection-benefit-assessment-according-to-35a-social-code-book-v.9396.html.