IQWiG Reports – Commission No. A21-125

Ravulizumab (paroxysmal nocturnal haemoglobinuria, paediatric patients) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Ravulizumab (paroxysmale nächtliche Hämoglobinurie, pädiatrische Patientinnen und Patienten) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 21 December 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.

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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 available for the present dossier assessment.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Ulrike Göbel.

IQWiG thanks the respondent for participating in the written exchange about how she experienced the disease and its treatment, and about treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Christina Keksel
- Moritz Felsch
- Stefan Kobza
- Prateek Mishra
- Daniela Preukschat
- Cornelia Rüdig
- Dorothea Sow
- Kathrin Wohlhöfner

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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
AE	adverse event
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PNH	paroxysmal nocturnal haemoglobinuria
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 ravulizumab. 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 30 September 2021.

Research question

The aim of this report is to assess the added benefit of ravulizumab in comparison with eculizumab as the appropriate comparator therapy (ACT) in paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH)

- with haemolysis along with clinical symptom(s) indicative of high disease activity
- who are clinically stable after having been treated with eculizumab for at least the past 6 months.

The research questions shown in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of ravulizumab

Research question	Therapeutic indication	ACT[a]
Paediatric patients with a body weight of 10 kg or above with PNH		
1	with haemolysis along with clinical symptom(s) indicative of high disease activity[b]	Eculizumab[c]
2	who are clinically stable after having been treated with eculizumab for at least the past 6 months[b].	Eculizumab[c]

a. Presented is the respective ACT specified by the G-BA.
b. The presented therapeutic indication is assumed to include only patients requiring therapy who have PNH and clinical symptoms of haemolysis. Patients with concomitant bone marrow failure – including in the context of aplastic anaemia – are disregarded in this assessment. For the present therapeutic indication, allogeneic stem cell transplantation is assumed not to be indicated at the time point of treatment with ravulizumab.
c. Supportive measures are assumed to be conducted as a pre-requisite both in the intervention arm and in the control arm. The continuation of an inadequate therapy does not represent an ACT. Any dose modifications which may be needed in the treatment with eculizumab are assumed to be exhaustively covered by way of adjustments to the dosing interval.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PNH: paroxysmal nocturnal haemoglobinuria

The company followed the GBA's specification on the ACT. While the company used 2 separate cohorts to analyse patients with high disease activity versus patients who are

clinically stable after at least 6 months of eculizumab treatment, it did not investigate the 2 research questions separately.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data submitted by the company and was carried out separately for research questions 1 and 2. The minimum study duration in the therapeutic indication is 24 weeks.

Study pool and study design

In the present therapeutic indication, no direct comparative randomized controlled trial (RCT) was identified for the comparison of ravulizumab with the ACT.

Due to a lack of direct comparative RCTs, the company submitted, as the intervention, the two single-arm studies ALXN1210-PNH-304 on ravulizumab and M07-005 on eculizumab. The company's dossier compares the results of these studies purely descriptively.

For the present benefit assessment, the comparison of the studies was unsuitable. Since treatment with eculizumab or ravulizumab typically takes the form of long-term therapy, a minimum study duration of 24 weeks is deemed necessary for the present research questions. In the M07-005 study with eculizumab, patients were treated for only 12 weeks. The M07-005 study's treatment duration is therefore too short for a comparison with the ALXN1210-PNH-304 study, in which patients were treated and observed for 26 weeks.

Results

No suitable data are available for assessing the added benefit of ravulizumab in comparison with the ACT for the treatment of paediatric patients with a body weight of 10 kg or above with PNH

- with haemolysis along with clinical symptom(s) indicative of high disease activity
- who are clinically stable after having been treated with eculizumab for at least the past 6 months

. In each case, this resulted in no hint of an added benefit of ravulizumab in comparison with the ACT; an added benefit is therefore not proven for either of them.

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

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

[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

Table 3: Ravulizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Paediatric patients with a body weight of 10 kg or above with PNH			
1	with haemolysis along with clinical symptom(s) indicative of high disease activity[b]	Eculizumab[c]	Added benefit not proven
2	who are clinically stable after having been treated with eculizumab for at least the past 6 months[b].	Eculizumab[c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The presented therapeutic indication is assumed to include only patients requiring therapy who have PNH and clinical symptoms of haemolysis. Patients with concomitant bone marrow failure – including in the context of aplastic anaemia – are disregarded in this assessment. For the present therapeutic indication, allogeneic stem cell transplantation is assumed not to be indicated at the time point of treatment with ravulizumab.
c. Supportive measures are assumed to be conducted as a prerequisite both in the intervention arm and in the control arm. The continuation of an inadequate therapy does not represent an ACT. Any dose modifications which may be needed in the treatment with eculizumab are assumed to be exhaustively covered by way of adjustments to the dosing interval.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PNH: paroxysmal nocturnal haemoglobinuria

The G-BA decides on the added benefit.

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

The aim of this report is to assess the added benefit of ravulizumab in comparison with eculizumab as the ACT in paediatric patients with a body weight of 10 kg or above with PNH

- with haemolysis along with clinical symptom(s) indicative of high disease activity
- who are clinically stable after having been treated with eculizumab for at least the past 6 months.

The research questions shown in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of ravulizumab

Research question	Therapeutic indication	ACT[a]
Paediatric patients with a body weight of 10 kg or above with PNH		
1	with haemolysis along with clinical symptom(s) indicative of high disease activity[b]	Eculizumab[c]
2	who are clinically stable after having been treated with eculizumab for at least the past 6 months[b].	Eculizumab[c]

a. Presented is the respective ACT specified by the G-BA.
b. The presented therapeutic indication is assumed to include only patients requiring therapy who have PNH and clinical symptoms of haemolysis. Patients with concomitant bone marrow failure – including in the context of aplastic anaemia – are disregarded in this assessment. For the present therapeutic indication, allogeneic stem cell transplantation is assumed not to be indicated at the time point of treatment with ravulizumab.
c. Supportive measures are assumed to be conducted as a prerequisite both in the intervention arm and in the control arm. The continuation of an inadequate therapy does not represent an ACT. Any dose modifications which may be needed in the treatment with eculizumab are assumed to be exhaustively covered by way of adjustments to the dosing interval.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PNH: paroxysmal nocturnal haemoglobinuria

The company followed the G-BA's specification by identifying eculizumab as the ACT.

While the company analysed separately patients with high disease activity versus patients who are clinically stable after at least 6 months of eculizumab treatment, it did not investigate the 2 research questions separately. The present assessment was conducted separately for research questions 1 and 2.

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 in the therapeutic indication is 24 weeks. This departs from the inclusion criteria used by the company, which applied no restrictions of study duration.

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 list on ravulizumab (status: 21 September 2021)
- bibliographical literature search on ravulizumab (last search on 12 August 2021)
- search in trial registries / trial results databases for studies on ravulizumab (last search on 28 August 2021)
- search on the G-BA website for ravulizumab (last search on 8 September 2021)
- study list on the ACT (status: 21 September 2021)
- bibliographical literature search on the ACT (last search on 12 August 2021)
- search in trial registries / trial results databases for studies on the ACT (last search on 28 August 2021)
- search on the G-BA website for the ACT (last search on 8 September 2021)

To check the completeness of the study pool:

- search in trial registries for studies on ravulizumab (last search on 15 October 2021); for search strategies, see Appendix A of the full dossier assessment

Concurring with the company, the check of the study pool did not identify any study which would allow a direct comparison of ravulizumab with the ACT specified by the G-BA.

To assess medical benefit and added benefit of ravulizumab, the company therefore used two 1-arm studies. However, the submitted data are unsuitable for the derivation of an added benefit of ravulizumab. This is explained below.

Usability of the data presented by the company

Due to a lack of direct comparative RCTs in the present therapeutic indication, the company submitted, as the intervention, the 1-arm studies ALXN1210-PNH-304 on ravulizumab and M07-005 on eculizumab. The company's dossier presents the results of these studies purely descriptively and indicates that due to the small size of the study populations, an indirect comparison is statistically impossible.

In the descriptive comparison of the studies ALXN1210-PNH-304 on ravulizumab and M07-005 on eculizumab, the company deems the effectiveness of the 2 drugs to be equal. Regarding adverse events (AEs), the company sees a numerical advantage in individual outcomes because fewer AEs and fewer serious adverse events (SAEs) were observed during a longer follow-up period of 26 weeks in comparison with the ACT of eculizumab, which was subject to a follow-up period of 12 weeks. Overall, however, the company did not derive any added benefit for ravulizumab in comparison with the ACT of eculizumab.

All told, the data presented by the company are unsuitable for deriving an added benefit. This is explained below.

Study with ravulizumab: ALXN1210-PNH-304

The ALXN1210-PNH-304 study [3] is an ongoing 1-arm, phase III study in patients under the age of 18 years with PNH. A total of 12 patients were included. Of these patients, 4 match research question 1. The remaining 8 patients had received prior eculizumab treatment. However, it is unclear whether these patients were in fact stable and had received eculizumab for ≥ 6 months, thereby meeting the requirements of research question 2. All patients received ravulizumab for 26 weeks. This was followed by a 4-year extension phase. The primary analysis was conducted after 26 weeks of treatment.

Study with the ACT: M07-005

The M07-005 study [4] is an ongoing 1-arm, phase I/II study in patients with PNH aged 2 to < 18 years. A total of 7 patients were included, with all of them meeting the profile of research question 1. Patients received eculizumab for 12 weeks.

M07-005 study too short for the benefit assessment

In the evaluation of interventions for the treatment of chronic diseases, short-term studies are typically unsuitable for a complete benefit assessment [1]. This applies in particular when treatment is required for several years, or even lifelong. Since eculizumab or ravulizumab treatment typically takes the form of long-term therapy [5], a minimum study duration of 24 weeks is deemed necessary for the present research questions. The treatment duration of 12 weeks in the M07-005 study is therefore too short for a comparison with the ALXN1210-PNH-304 study in the assessment of added benefit. The comparison between the two studies ALXN1210-PNH-304 and M07-005 submitted by the company is therefore unsuitable for deriving added benefit.

2.4 Results on added benefit

No suitable data are available for assessing the added benefit of ravulizumab in comparison with the ACT for the treatment of paediatric patients with a body weight of 10 kg or above with PNH

- with haemolysis along with clinical symptom(s) indicative of high disease activity
- who are clinically stable after having been treated with eculizumab for at least the past 6 months.

In each case, this resulted in no hint of an added benefit of ravulizumab in comparison with the ACT; an added benefit is therefore not proven for either of them.

2.5 Probability and extent of added benefit

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

Table 5: Ravulizumab – probability and extent of added benefit

Research question	Therapeutic indication	ACT[a]	Probability and extent of added benefit
Paediatric patients with a body weight of 10 kg or above with PNH			
1	with haemolysis along with clinical symptom(s) indicative of high disease activity[b]	Eculizumab[c]	Added benefit not proven
2	who are clinically stable after having been treated with eculizumab for at least the past 6 months[b].	Eculizumab[c]	Added benefit not proven

a. Presented is the respective ACT specified by the G-BA.
b. The presented therapeutic indication is assumed to include only patients requiring therapy who have PNH and clinical symptoms of haemolysis. Patients with concomitant bone marrow failure – including in the context of aplastic anaemia – are disregarded in this assessment. For the present therapeutic indication, allogeneic stem cell transplantation is assumed not to be indicated at the time point of treatment with ravulizumab.
c. Supportive measures are assumed to be conducted as a prerequisite both in the intervention arm and in the control arm. The continuation of an inadequate therapy does not represent an ACT. Any dose modifications which may be needed in the treatment with eculizumab are assumed to be exhaustively covered by way of adjustments to the dosing interval.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; PNH: paroxysmal nocturnal haemoglobinuria

The assessment described above concurs with that by the company, which considers the added benefit for the entire patient population as not proven.

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/a21-125.html