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Ravulizumab (atypical haemolytic uraemic syndrome) –

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 (atypisches hämolytisch-urämisches Syndrom) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 29 October 2020). 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.

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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
aHUS	atypical haemolytic uraemic syndrome
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HUS	haemolytic uraemic syndrome
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDH	lactate dehydrogenase
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
STEC-HUS	Shiga toxin-related haemolytic uraemic syndrome
TMA	thrombotic microangiopathy

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 was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 28 July 2020.

Due to the working conditions during the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.

Research question

The aim of the present report is the assessment of the added benefit of ravulizumab in comparison with eculizumab as appropriate comparator therapy (ACT) in patients with a body weight of 10 kg or above with atypical haemolytic uraemic syndrome (aHUS) who are complement inhibitor treatment-naive or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

Table 2 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of ravulizumab

Therapeutic indication	**ACT**[a]
Patients with a body weight of 10 kg or above with aHUS who are complement inhibitor treatment-naive or have received eculizumab for at least 3 months and have evidence of response to eculizumab	Eculizumab[b]
a. Presentation of the ACT specified by the G-BA. b. It is assumed that supportive measures are conducted both in the intervention and in the control arm. ACT: appropriate comparator therapy; aHUS: atypical haemolytic uraemic syndrome; G-BA: Federal Joint Committee	

In accordance with the G-BA, it is additionally assumed that supportive measures are conducted both in the intervention and in the control arm.

The company followed the G-BA's specification of the ACT and cited eculizumab as ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

Results

Concurring with the company, no relevant randomized controlled trials (RCTs) enabling a direct comparison or an adjusted indirect comparison with the ACT via a common comparator were identified from the check of the study pool.

Data presented by the company

Due to the lack of directly comparative data, the company presented comparisons of individual arms from different studies. These refer exclusively to patients who have not previously been treated with complement inhibitors (complement inhibitor treatment-naive patients).

For ravulizumab, the company included the 2 ongoing, single-arm, multicentre approval studies 311 and 312. Study 311 included 58 complement inhibitor treatment-naive adult patients with aHUS. In study 312, children and adolescents under 18 years of age and with a body weight of 5 kg or above with aHUS were enrolled in 2 cohorts. Cohort 1 consisted of 21 complement inhibitor treatment-naive patients. Cohort 2 included 10 patients who had been previously treated with eculizumab for at least 90 days and had shown evidence of response to eculizumab. Patients in both studies had to have evidence of thrombotic microangiopathy (TMA) during the screening period or within 28 days before. This was determined based on defined laboratory parameters.

For eculizumab, the company included the single-arm, multicentre studies C10-003 in 22 paediatric aHUS patients with a body weight of 5 kg or above, and C10-004 with 41 adult aHUS patients. Patients had to present with TMA based on defined laboratory parameters to be eligible for study inclusion.

Treatment with ravulizumab in study 311 and treatment with eculizumab in the studies C10-003 and C10-004 was carried out in compliance with the respective Summary of Product Characteristics (SPC). In study 312, the administration of ravulizumab was largely in compliance with the SPC. All 4 studies implemented supportive measures to different extents.

Comparisons of individual arms from different studies

The company considered paediatric and adult patients separately. The comparison with paediatric patients included the studies 312 and C10-003; the comparison with adult patients included the studies 311 and C10-004.

Although the studies presented by the company correspond overall to the research question, some information on comparability within the paediatric or adult patient populations is missing. There are differences, for example, in the use of plasma therapy: While plasma therapy was not allowed as part of the study treatment in the ravulizumab studies, some of the patients in the eculizumab studies received such treatment.

The company initially compared the results of the individual study arms descriptively for both paediatric and adult patients. In order to adjust for differences in the patient populations, the

company, in addition to the "descriptive comparison", conducted a comparison of the single-arm studies for each of the 2 populations based on selected patient characteristics using propensity score matching. It did not present these analyses for all outcomes it considered, e.g. they are missing for the adverse event (AE) outcomes. To derive the added benefit of ravulizumab, the company used the descriptive comparison for the AE outcomes, and the comparisons according to propensity score matching (date of analysis at the end of the initial evaluation period, week 26) for the outcomes on the benefit side.

The comparison of the studies with paediatric patients, 312 and C10-003, showed no statistically significant difference between the treatments for any outcome. When comparing the studies in adult patients, 311 and C10-004, individual statistically significant differences observed in favour of ravulizumab were in no case large enough that they could not be explained by systematic bias alone.

Overall, the data presented by the company for patients with a body weight of 10 kg or above with aHUS who are complement inhibitor treatment-naive or have received eculizumab for at least 3 months and have evidence of response to eculizumab are unsuitable for the derivation of an added benefit of ravulizumab in comparison with the ACT.

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 ravulizumab.

Table 3: Ravulizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with a body weight of 10 kg or above with aHUS who are complement inhibitor treatment-naive or have received eculizumab for at least 3 months and have evidence of response to eculizumab	Eculizumab[b]	Added benefit not proven
a. Presentation of the ACT specified by the G-BA. b. It is assumed that supportive measures are conducted both in the intervention and in the control arm. ACT: appropriate comparator therapy; aHUS: atypical haemolytic uraemic syndrome; G-BA: Federal Joint Committee		

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

The aim of the present report is the assessment of the added benefit of ravulizumab in comparison with eculizumab as ACT in patients with a body weight of 10 kg or above with aHUS who are complement inhibitor treatment-naive or have received eculizumab for at least 3 months and have evidence of response to eculizumab.

Table 4 shows the research question of the benefit assessment and the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of ravulizumab

Therapeutic indication	**ACT**[a]
Patients with a body weight of 10 kg or above with aHUS who are complement inhibitor treatment-naive or have received eculizumab for at least 3 months and have evidence of response to eculizumab	Eculizumab[b]
a. Presentation of the ACT specified by the G-BA. b. It is assumed that supportive measures are conducted both in the intervention and in the control arm. ACT: appropriate comparator therapy; aHUS: atypical haemolytic uraemic syndrome; G-BA: Federal Joint Committee	

In accordance with the G-BA, it is additionally assumed that supportive measures are conducted both in the intervention and in the control arm.

The company followed the G-BA's specification of the ACT and cited eculizumab as ACT.

For better readability in the running text, the following designation is used for patients who have not previously been treated with complement inhibitors: complement inhibitor treatment-naive patients.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier.

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: 13 May 2020)
- bibliographical literature search on ravulizumab (last search on 8 May 2020)
- search in trial registries/trial results databases for studies on ravulizumab (last search on 25 May 2020)
- search on the G-BA website for ravulizumab (last search on 26 May 2020)
- study list on the ACT (status: 13 May 2020)

- bibliographical literature search on the ACT (last search on 8 May 2020)
- search in trial registries/trial results databases for the ACT (last search on 25 May 2020)

To check the completeness of the study pool:

- search in trial registries for studies on ravulizumab (last search on 10 August 2020)
- search in trial registries for studies on the ACT (last search on 17 August 2020)

Concurring with the company, no relevant RCTs enabling a direct comparison or an adjusted indirect comparison with the ACT via a common comparator were identified from the check of the study pool.

Due to the lack of directly comparative data, the company presented comparisons of individual arms from different studies. To this end, it identified 2 studies each on the ravulizumab side and the eculizumab side. The check of the completeness of the company's study pool did not identify any additional potentially relevant studies on ravulizumab or eculizumab. The data presented by the company are unsuitable for the derivation of an added benefit of ravulizumab. This is justified below.

Data presented by the company

Table 5 shows an overview of the studies included by the company.

Table 5: Study pool of the company – comparison of individual arms of different studies: ravulizumab vs. eculizumab

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
Studies with ravulizumab						
ALXN1210-aHUS-311[c] (311[e])	Yes	Yes	No	No[d]	Yes [3-5]	Yes [6]
ALXN1210-aHUS-312[f] (312[e])	Yes	Yes	No	No[d]	Yes [7,8]	No
Studies with eculizumab						
C10-003[f]	No	Yes	No	No[d]	Yes [9-12]	Yes [13]
C10-004[c]	No	Yes	No	No[d]	Yes [14-17]	Yes [18]

a. Study for which the company was sponsor.
b. Citation of the study registry entries and, if available, of the reports on study design and/or results listed in the study registries.
c. Study with adult patients with aHUS.
d. Due to the coronavirus pandemic, the present assessment was conducted without the use of strictly confidential data presented in Module 5 of the company's dossier.
e. In the following tables, the study is referred to with this abbreviated form.
f. Study with paediatric patients (< 18 years of age) with aHUS.

aHUS: atypical haemolytic uraemic syndrome; CSR: clinical study report; vs.: versus

For ravulizumab, the company included the 2 approval studies 311 and 312 conducted within the investigated therapeutic indication of aHUS. For the ACT eculizumab, the company identified the studies C10-003 and C10-004.

The company presented comparisons of individual arms from different studies with complement inhibitor treatment-naive patients separately for paediatric and adult patient populations. The comparison with paediatric patients included the studies 312 and C10-003; the comparison with adult patients included the studies 311 and C10-004. The company did not present any comparative data for the subpopulation that has received eculizumab for at least 3 months and has evidence of response to eculizumab.

Due to the very similar study design, the studies on ravulizumab and eculizumab included by the company are described together below.

Studies on ravulizumab (study 311, study 312)

The 2 studies 311 and 312 are ongoing, single-arm, multicentre approval studies of ravulizumab in the present therapeutic indication. Study 311 included complement inhibitor treatment-naive adult patients with aHUS. In study 312, children and adolescents under 18 years of age and with a body weight of 5 kg or above with aHUS were enrolled in 2 cohorts. Cohort 1 consisted of

complement inhibitor treatment-naive patients. Cohort 2 included patients who had been previously treated with eculizumab for at least 90 days and had shown evidence of response to eculizumab. Since no comparative data are available for the subpopulation with eculizumab pretreatment and evidence of response to therapy (see below), the following information on study 312 is limited to cohort 1, unless otherwise stated.

Both studies included patients with evidence of TMA during the screening period or within 28 days before. This was determined based on defined laboratory parameters on platelet count, lactate dehydrogenase (LDH) and haemoglobin concentration, and serum creatinine level (for the exact definition, see Appendix A, Table 10, of the full dossier assessment).

Excluded from participation were patients with other causes of TMA (e.g. Shiga toxin-related haemolytic uraemic syndrome [STEC-HUS]), dialysis on a regular basis for end stage renal disease, and plasma therapy for ≥ 28 days prior to the start of screening for the current TMA.

Study 312 included 31 children and adolescents, 21 of them in cohort 1. 3 patients from cohort 1 were subsequently excluded from the study because they did not meet the inclusion criteria, and were not included in the analysis. Study 311 included 58 adults, 2 of whom were subsequently excluded from the study analysis because they did not meet the inclusion criteria.

In both studies, treatment with ravulizumab was largely in compliance with the requirements of the SPC [19]. However, according to the SPC, ravulizumab may only be administered to patients with a body weight of 10 kg or above. Deviating from this, study 312 included 4 (cohort 1: n = 3, cohort 2: n = 1) of 31 patients (12.9%) with a body weight < 10 kg.

The primary outcome of both studies was complete TMA response during the 26-week initial evaluation period, as evidenced by normalization of haematological parameters (platelet count and LDH) and ≥ 25% improvement in serum creatinine from baseline. Secondary outcomes were further morbidity outcomes and AEs.

After the initial evaluation period, patients could continue to receive ravulizumab for an extension period of up to 2 years (study 311) and 4.5 years (study 312) or until commercial availability.

Further details on the characteristics of the studies, interventions and patients included can be found in Appendix A of the full dossier assessment.

Studies on eculizumab (C10-003, C10-004)

Adults and paediatric patients with aHUS with a body weight of 5 kg or above were included in the single-arm, multicentre studies C10-003 and C10-004 and treated with eculizumab. Patients had to present with TMA based on defined laboratory parameters to be eligible for study inclusion (see Appendix A, Table 10, of the full dossier assessment).

Excluded from participation in study C10-003 were patients with other causes of TMA (e.g. STEC-HUS), dialysis on a regular basis for end stage renal disease, and plasma therapy for > 5 weeks prior to the start of screening for the current TMA.

Studies C10-003 and C10-004 included 22 paediatric and 41 adult patients, respectively. In study C10-003, one patient was subsequently deemed unsuitable for the study and excluded from the analyses.

Treatment was in compliance with the requirements of the SPC [20].

The primary outcome of the studies C10-003 and C10-004 was complete TMA response during the 26-week initial evaluation period, as operationalized in the studies with ravulizumab (see also Appendix A, Table 10, of the full dossier assessment). Secondary outcomes were further morbidity outcomes and AEs.

After the initial evaluation period, patients could continue to receive eculizumab for an extension period of up to 2 years or until commercial availability. Further information on the characteristics of the studies C10-003 and C10-004 can be found in Appendix A of the full dossier assessment.

Supportive measures in the studies presented by the company

According to the guideline for haemolytic uraemic syndrome (HUS) in childhood, and recommendations of international consensus bodies and clinical experts, supportive measures are part of the therapy of HUS, regardless of its aetiology [21-24]. These include therapy for acute renal failure with adequate fluid management, as well as close monitoring of electrolytes and blood pressure and, if necessary, renal replacement therapy. In the case of haemolytic anaemia, the transfusion of packed red blood cells is recommended and erythropoietin therapy may be considered. Transfusion of a platelet concentrate is recommended for clinical signs of bleeding and, if necessary, before interventional procedures. Plasma exchange and plasma infusion may be indicated in certain patients [24].

All 4 studies allowed supportive measures in principle, but partly with restrictions. For example, patients in the ravulizumab studies were not allowed to receive plasma therapy during the study, whereas in the eculizumab studies, plasma therapy was allowed (see Appendix A, Table 11, of the full dossier assessment). Whether there were restrictions regarding non-pharmacological supportive therapy for the eculizumab studies, cannot be inferred in detail from the information available in Module 4 A. It is therefore unclear whether transfusion of packed red blood cells or platelets was possible in the eculizumab studies.

Supportive measures in the form of concomitant medication such as antihypertensives (see Appendix A, Table 14 to Table 17, of the full dossier assessment) were carried out in all 4 studies included by the company. The use of non-pharmacological supportive therapies was also possible. In Study 312, 15 of 21 patients (71.4%) received a transfusion of packed red

blood cells and 2 of the 21 patients (9.5%) received a platelet transfusion. In study 311, 16 of 58 patients (27.6%) were treated with a blood transfusion, while an unspecified transfusion was reported for 10 patients (17.2%). In the eculizumab studies, 2 of 22 (9.1%) of the paediatric patients and 13 of 41 (31.7%) of the adult patients received plasma therapy.

Comparisons of individual arms from different studies

Complement inhibitor treatment-naive patients

To compare ravulizumab with eculizumab, the company presented data separately for the paediatric and adult patient populations. As described above, the comparison with adults included the single-arm studies 311 and C10-004; for paediatric patients, the company used cohort 1 of study 312 and study C10-003. For the derivation of the added benefit on outcomes on the benefit side, the company used the analysis date at the end of the initial evaluation period (week 26) for each of the different studies. For outcomes on the harm side, the company considered the entire period up to the respective data cut-off.

Comparability of the studies can only be partially assessed

Although the studies presented by the company correspond overall to the research question, some information on comparability within the paediatric or adult patient populations is missing. For example, there is no information on medical history available for the ravulizumab study 311 with adult patients. Furthermore, information on extrarenal signs and symptoms of the aHUS before study start is missing for both studies with eculizumab (see Appendix A, Table 12 and Table 13, of the full dossier assessment). Furthermore, it remains unclear whether the implementation of supportive measures in addition to treatment with ravulizumab or eculizumab is comparable in the studies, as different levels of detail are available on this issue (see Appendix A, Table 14 to Table 17, of the full dossier assessment). Differences between the 2 therapies include the use of plasma therapy during treatment with the study medication, for example: While plasma therapy was not allowed in the ravulizumab studies, it was possible in the eculizumab studies, and some patients received this treatment (see above).

Unsuitable approach of the company

The company initially compared the results of the individual study arms descriptively for both paediatric and adult patients. In order to adjust for differences in the patient populations, the company, in addition to the "descriptive comparison", conducted a comparison of the single-arm studies for each of the 2 populations based on selected patient characteristics using propensity score matching. It did not present these analyses for all outcomes it considered, e.g. they are missing for the AE outcomes. To derive the added benefit of ravulizumab, the company used the descriptive comparison for the AE outcomes (see above), and the comparisons according to propensity score matching (date of analysis at the end of the initial evaluation period, week 26) for the outcomes on the benefit side.

Although an adjustment was made in the analysis with regard to potentially relevant effect modifiers or prognostic factors, the results from a comparison of individual arms from different

studies are subject to inherent uncertainty due to the lack of randomization, so an added benefit can only be derived if the effects are sufficiently large.

The comparison of the studies with paediatric patients, 312 and C10-003, showed no statistically significant difference between the treatments for any outcome.

When comparing the studies in adult patients, 311 and C10-004, statistically significant differences in individual analyses of different outcomes in favour of ravulizumab can be observed at the end of the initial evaluation period. The company provided neither effect estimations nor confidence intervals for the analyses. On the basis of the available results from the statistical tests, however, the observed effects were in no case large enough that they could not be explained by systematic bias alone. In addition, various outcomes, e.g. the complete TMA response operationalized solely on the basis of laboratory parameters, are not considered to be directly patient-relevant (for the definition of TMA, see Table 10 in Appendix A of the full dossier assessment). The company itself also did not derive an added benefit of ravulizumab in comparison with eculizumab on the basis of its analyses.

Patients pretreated with eculizumab

The company presented only data from cohort 2 of the paediatric ravulizumab study 312 for the subpopulation with aHUS that has received eculizumab for at least 3 months and has evidence of response to eculizumab. The company provided a purely descriptive presentation of their results as supplementary information. The company did not provide any data on this subpopulation for the ACT. The data were not used for the benefit assessment.

Summary

Overall, the data presented by the company for patients with a body weight of 10 kg or above with aHUS who are complement inhibitor treatment-naive or have received eculizumab for at least 3 months and have evidence of response to eculizumab are unsuitable for the derivation of an added benefit of ravulizumab in comparison with the ACT.

2.4 Results on added benefit

The comparisons using individual arms from different studies presented by the company for the assessment of the added benefit of ravulizumab in comparison with the ACT in patients with a body weight of 10 kg or above with aHUS who are complement inhibitor treatment-naive or have received eculizumab for at least 3 months and have evidence of response to eculizumab, are unsuitable for deriving an added benefit of ravulizumab in comparison with eculizumab. There is no hint of an added benefit of ravulizumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 6 summarizes the result of the assessment of the added benefit of ravulizumab in comparison with the ACT.

Table 6: Ravulizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients with a body weight of 10 kg or above with aHUS who are complement inhibitor treatment-naive or have received eculizumab for at least 3 months and have evidence of response to eculizumab	Eculizumab[b]	Added benefit not proven
a. Presentation of the ACT specified by the G-BA. b. It is assumed that supportive measures are conducted both in the intervention and in the control arm. ACT: appropriate comparator therapy; aHUS: atypical haemolytic uraemic syndrome; G-BA: Federal Joint Committee		

The assessment described above corresponds to that of the company, which also derived no added benefit separately for paediatric and adult patients with aHUS in the overall consideration.

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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