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Ravulizumab (paroxysmal nocturnal haemoglobinuria) –

Addendum to Commission A19-59[1]

Addendum

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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

IQWiG employees involved in the addendum

- Regine Potthast
- Lars Beckmann
- Volker Vervölgyi

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Table of contents

Page

List of tables ..... **iv**
List of abbreviations ..... **v**
1 Background **1**
2 Assessment **2**
3 References **4**

List of tables

Page

Table 1: Results (morbidity, dichotomous) – RCT, direct comparison: ravulizumab vs. eculizumab 3

List of abbreviations

Abbreviation	Meaning
BTH	breakthrough haemolysis
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
Hb	haemoglobin
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LDH	lactate dehydrogenase
MAVE	major adverse vascular event
PNH	paroxysmal nocturnal haemoglobinuria
ULN	upper limit of normal

1 Background

On 10 December 2019, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A19-59 (Ravulizumab – Benefit assessment according to §35a Social Code Book V) [1].

In the benefit assessment on ravulizumab [1] in patients with paroxysmal nocturnal haemoglobinuria (PNH), Study 301 was included for research question 1 (high disease activity) and Study 302 was included for research question 2 (clinically stable after at least 6 months of eculizumab treatment).

The outcome "breakthrough haemolysis (BTH)" was recorded in both studies (301 and 302). This was defined a priori as at least one new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia [haemoglobin (Hb) < 10 g/dL], major adverse vascular event [MAVE], dysphagia, or erectile dysfunction). At the same time, the patients had to have elevated lactate dehydrogenase (LDH) ≥ 2 × upper limit of normal (ULN), after prior LDH reduction to < 1.5 × ULN on therapy.

It was explained in the benefit assessment that the symptoms that eventually result in BTH are patient-relevant. On the basis of the data available for the benefit assessment, it was assessed that the complete recording of the symptoms described above was not guaranteed. For this reason, the BTH was not used for the benefit assessment of ravulizumab.

The G-BA commissioned IQWiG with the assessment of the results of the outcome "BTH" in the studies 301 (research question 1) and 302 (research question 2).

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

No new findings regarding the relevance of the outcome "BTH" resulted from the comments and the oral hearing [2]. In line with the evaluation described in the dossier assessment, the outcome "BTH" is therefore still rated as unsuitable due to the connection with LDH levels. In accordance with the commission, the results on this outcome are presented below.

For the outcome "BTH", it had been planned in the studies 301 and 302 to analyse the proportions of patients with BTH according to the definition described in Section 1. In Module 4 A of the dossier [3], the company additionally presented further analyses defined post hoc to investigate the robustness of the results. On the one hand, the company presented analyses on the number of events per 100 patient years as well as on the time to first event using the definition of BTH mentioned above. On the other, the company presented the results of an alternative definition of BTH, which only included the elevated LDH $\geq 2 \times$ ULN, after prior LDH reduction to $< 1.5 \times$ ULN on therapy without considering the presence of symptoms.

The definition of BTH defined a priori for the studies 301 and 302 (see Section 1) and the analysis planned a priori were considered for the addendum. The results of both studies are shown in Table 1. Further information on both studies (including study characteristics, patient characteristics, concomitant medications) can be found in benefit assessment A19-59 [1].

The operationalization of this outcome contains subjective components such as fatigue, abdominal pain, dyspnoea, dysphagia and erectile dysfunction. Since both studies, 301 and 302, had an open-label study design, the risk of bias of the results was rated as high.

For the outcome "BTH", a statistically significant advantage in favour of ravulizumab was shown both in Study 301 (research question 1) and in Study 302 (research question 2).

Table 1: Results (morbidity, dichotomous) – RCT, direct comparison: ravulizumab vs. eculizumab

Study Outcome category Outcome Time point	Ravulizumab N	Ravulizumab Patients with event n (%)	Eculizumab N	Eculizumab Patients with event n (%)	Ravulizumab vs. eculizumab RR [95% CI]; p-value[a]
Study 301 (research question 1; high disease activity)					
Morbidity					
BTH until day 183[b]	125	5 (4.0)	121	13 (10.7)	0.37 [0.14; 1.01]; 0.045
Study 302 (research question 2; clinically stable after at least 6 months of eculizumab treatment)					
Morbidity					
BTH until day 183[b]	97	0 (0.0)	98	5 (5.1)	0.09 [0.01; 1.64]; 0.025

a. Institute's calculation of RR, CI (asymptotic) and p-value (unconditional exact test, CSZ method according to [4]). In case of 0 events in one study arm, the correction factor 0.5 was used in both study arms for the calculation of effect and CI. Discrepancy between p-value (exact) and CI (asymptotic) due to different calculation methods.

b. Defined as at least one new or worsening symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, dyspnoea, anaemia [Hb < 10 g/dL], MAVE, dysphagia, or erectile dysfunction) and presence of elevated LDH ≥ 2 × ULN, after prior LDH reduction to < 1.5 × ULN on therapy; day 183 corresponds to week 26.

BTH: breakthrough haemolysis; CI: confidence interval; CSZ: convexity, symmetry, z score; Hb: haemoglobin; LDH: lactate dehydrogenase; MAVE: major adverse vascular event; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; ULN: upper limit of normal; vs.: versus

3 References

The reference list contains citations provided by the company in which bibliographical information may be missing.

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