Gemeinsamer Bundesausschuss

Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a SGB V Ravulizumab (new therapeutic indication: paroxysmal haemoglobinuria, paediatric patients)

of 18 March 2022

Contents

1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. approved therapeutic indications,
2. medical benefit,
3. additional medical benefit in relation to the appropriate comparator therapy,
4. number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. treatment costs for the statutory health insurance funds,
6. requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient ravulizumab (Ultomiris) was listed for the first time on 1 August 2019 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

On 1 September 2021, ravulizumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2 number 2 letter a to Regulation (EC) No. 1234/2008 of the European Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12.12.2008, p. 7).

On 28 September 2021, i.e. at the latest within four weeks after the notification of the pharmaceutical company of the approval of a new therapeutic indication, the pharmaceutical company has submitted a dossier in due time in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in

conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient ravulizumab with the new therapeutic indication (treatment of paediatric patients with paroxysmal nocturnal haemoglobinuria).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 3 January 2022, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of ravulizumab compared to the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of ravulizumab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA has come to the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of Ravulizumab (Ultomiris) according to product information

Ultomiris is indicated in the treatment of adult and paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH):

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

Therapeutic indication of the resolution (resolution of 18 March 2022):

Ultomiris is indicated in the treatment of paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH):

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

[1] General Methods, version 6.1 from 24.01.2022. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

Appropriate comparator therapy:

- Eculizumab

b) Paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH) who are clinically stable after having been treated with eculizumab for at least the past 6 months

Appropriate comparator therapy:

- Eculizumab

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication in accordance with the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the Federal Joint Committee has already determined the patient-relevant benefit shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

on 1. In addition to ravulizumab, the active ingredient eculizumab is approved for the treatment of paediatric patients with PNH.

on 2. For the present therapeutic indication, it is assumed that an allogeneic stem cell transplantation is not indicated at the time of therapy with ravulizumab. Non-medicinal treatments are therefore not considered as an appropriate comparator therapy.

on 3. There are no relevant resolutions on medicinal applications or non-medicinal treatments.

on 4. The general state of medical knowledge in the present therapeutic indication was represented by a systematic search for guidelines and reviews of clinical studies. The scientific-medical societies and the Drugs Commission of the German Medical Association (AkdÄ) were also involved in writing on questions relating to the comparator therapy in the present therapeutic indication according to Section 35a paragraph 7 SGB V.

The approved therapeutic indication of ravulizumab results in two distinct treatment settings, each with a different therapeutic goal. On the one hand, the treatment of haemolysis with clinical symptom(s) indicative of high disease activity, on the other, the maintenance of a clinically stable state achieved under a prior therapy with eculizumab.

The evidence of treatment options for these treatment settings is extremely limited. The systematic research of guidelines and reviews of clinical studies identified only one systematic review that generally indicated eculizumab as a treatment option for paediatric patients with PNH.

According to the written statements of the scientific-medical societies, there is an indication for therapy with eculizumab in paediatric patients with haemolysis with clinical symptom(s) indicative of high disease activity. With regard to paediatric patients who are clinically stable after having been treated with eculizumab for at least the past 6 months, therapy with eculizumab can be continued according to the statements of the scientific-medical societies.

Overall, the G-BA therefore considers it appropriate to determine eculizumab as an appropriate comparator therapy both for paediatric patients with a body weight of 10 kg or above with haemolysis with clinical symptom(s) indicative of high disease activity (patient group a)) and for those who are clinically stable after having been treated with eculizumab for at least the past 6 months (patient group b)).

In addition to therapy with eculizumab, supportive measures should be carried out (e.g. substitution of red blood cell concentrates, folic acid, vitamin B12 and iron, prophylactic anticoagulation, early antibiotic therapy of bacterial infections).

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment mandate.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of ravulizumab is assessed as follows:

a) <u>Paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH) with haemolysis with clinical symptom(s) indicative of high disease activity</u>

An additional benefit is not proven.

b) <u>Paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH) who are clinically stable after having been treated with eculizumab for at least the past 6 months</u>

An additional benefit is not proven.

Justification:

In the absence of direct comparator studies of ravulizumab versus the appropriate comparator therapy, the pharmaceutical company presents the two single-arm studies ALXN1210-PNH-304 (with the intervention ravulizumab) and M07-005 (with the intervention eculizumab) and compares the results of these two studies in purely descriptive terms.

ALXN1210-PNH-304 study

The ALXN1210-PNH-304 study is a single-arm, ongoing, phase III study. A total of 12 patients under 18 years of age with PNH were included, four of whom were assigned to patient group a). For the remaining eight patients, it can be assumed that they are basically to be assigned to patient group b), taking into account the statements of the pharmaceutical company. In particular, since seven of the eight patients (87.5%) had been pretreated with eculizumab for longer than six months prior to study enrolment or had an LDH value below one and a half times the upper normal range with regard to clinical stability at the time of screening.

All patients in the ALXN1210-PNH-304 study received ravulizumab for 26 weeks, followed by an extension phase of up to four years. The primary analysis was done after 26 weeks of treatment.

M07-005 study

The M07-005 study is a single-arm, phase I / II study. A total of seven patients from two to < 18 years of age with PNH were enrolled, all of whom belong to patient group a). The patients received eculizumab for 12 weeks.

Assessment

PNH is a chronic disease. Accordingly, treatment with eculizumab or ravulizumab is also recommended as lifelong treatment according to the relevant product information. Against this background, short-term studies (with a treatment duration of less than 24 weeks) are considered unsuitable for the benefit assessment in the therapeutic indication of PNH. Consequently, the 12-week treatment period chosen by the pharmaceutical company for the M07-005 study is not long enough for comparison with the ALXN1210-PNH-304 study, in which patients were treated and observed for 26 weeks. The presented comparison of the two studies is therefore inappropriate for the present assessment on patient group a).

Since all patients in the M07-005 study belong to patient group a), no comparator data are available for the evaluation of patient group b) compared to the appropriate comparator therapy.

An additional benefit of ravulizumab compared to the appropriate comparator therapy is therefore not proven for patient groups a) and b).

2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the medicinal product Ultomiris with the active ingredient ravulizumab.

The therapeutic indication assessed here is as follows:

Ultomiris is indicated in the treatment of paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH):

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

This results in the following patient groups:

a) Paediatric patients with a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH) and haemolysis with clinical symptom(s) indicative of high disease activity

and

b) Paediatric a body weight of 10 kg or above with paroxysmal nocturnal haemoglobinuria (PNH) who are clinically stable after having been treated with eculizumab for at least the past 6 months.

For patient groups a) and b)

In the absence of direct comparator studies of ravulizumab versus the appropriate comparator therapy for patient groups a) and b), the pharmaceutical company presents the two single-arm studies ALXN1210-PNH-304 (with the intervention ravulizumab) and M07-005 (with the intervention eculizumab) and compares the results of these two studies in purely descriptive terms.

The 12-week treatment duration in the M07-005 study is too short for comparison with the ALXN1210-PNH-304 study, given the chronic nature of the disease and the lifelong treatment recommended for patients. The comparison of the two studies is therefore inappropriate for the present assessment on patient group a).

Since all patients in the M07-005 study belong to patient group a), no comparator data are available for the evaluation of patient group b) compared to the appropriate comparator therapy.

An additional benefit of ravulizumab compared to the appropriate comparator therapy is therefore not proven for patient groups a) and b).

2.2 Number of patients or demarcation of patient groups eligible for treatment

The information on the number of patients is based on the target population in statutory health insurance (SHI).

In the dossier, the pharmaceutical company does not provide any information on the number of patients separated into patient groups a) and b). The resolution is therefore based on IQWiG's calculations from the dossier assessment with regard to the upper limits. The lower limits correspond in each case to the information provided by the pharmaceutical company in the dossier.

It is assumed to be an underestimate with regard to the lower limits, as the number of patients in the lower limit is higher according to several sources. For example, in the procedure for ravulizumab in adults with PNH, the pharmaceutical company had put the percentage of patients with PNH who were under 18 years of age at the onset of the disease at 6.3%.

The upper limits are also subject to uncertainties, in particular because, when determining the respective percentage values on which the calculation of the upper limits is based, it remains unclear whether the patients who were treated with eculizumab at least once but did not fulfil the criteria of high disease activity at the start of treatment are actually those who are clinically stable after being treated with eculizumab for at least the past six months.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Ultomiris (active ingredient: ravulizumab) at the following publicly accessible link (last access: 9 February 2022):

https://www.ema.europa.eu/en/documents/product-information/ultomiris-epar-product-information_en.pdf

Treatment with ravulizumab should only be initiated and monitored by specialists who are experienced in the treatment of patients with haematological diseases.

In accordance with the European Medicines Agency (EMA) requirements regarding additional risk minimisation measures, the pharmaceutical company must provide training material that contains information for medical professionals and patients. In particular, the training material contains instructions regarding the increased risk of meningococcal infection under ravulizumab.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 March 2022).

In general, initial induction regimens are not taken into account for the cost representation, since the present indication is a disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration. The costs are calculated on the basis of the maintenance doses.

This resolution relates to the treatment of paediatric patients with a body weight of 10 kg or above with PNH. The doses of the medicinal product under assessment with the active ingredient ravulizumab and the appropriate comparator therapy eculizumab (for a body weight < 40 kg) follow a body-weight-based dosing scheme. The annual treatment costs are given accordingly on the basis of a body weight range between 10 kg and 67 kg. The upper limit is the average body weight of 17 to under 18-year-olds according to the average body measurements from the official representative statistics "Microcensus 2017 - Body weights of the population".[2]

Treatment period:

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-

[2] Federal Statistical Office, Wiesbaden: http://www.gbe-bund.de/

individual and/or is shorter on average. The time unit "days" is used to calculate the "number of treatments/ patient/ year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Designation of the therapy	Treatment mode	Number of treatments/ patient /year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Ravulizumab ≥ 10 to < 20 kg BW ≥ 60 to < 100 kg BW	 1 x every 28 days 1 x every 56 days	 13.0 6.5	 1 1	 13.0 6.5
Appropriate comparator therapy				
Patient population a) and b)				
Eculizumab ≥ 10 to < 20 kg BW ≥ 40kg BW	 1 x every 14 days 1 x every 14 days	 26.1 26.1	 1 1	 26.1 26.1

<u>Consumption:</u>

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Ravulizumab ≥ 10 to < 20 kg BW ≥ 60 to < 100 kg BW	 600 mg 3300 mg	 600 mg 3300 mg	 2 x 300 mg 3 x 1100 mg	 13.0 6.5	 26.0 x 300 mg 19.5 x 1100 mg
Appropriate comparator therapy					
Patient population a) and b)					
Eculizumab					

Designation of the therapy	Dosage/ application	Dose/ patient/ treatment days	Consumption by potency/ treatment day	Treatment days/ patient/ year	Average annual consumption by potency
≥ 10 to < 20 kg BW	300 mg	300 mg	1 x 300 mg	26.1	26.1 x 300 mg
≥ 40kg BW	900 mg	900 mg	3 x 300 mg	26.1	78.3 x 300 mg

Costs:

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Ravulizumab 300 mg	1 CIS	€ 5,266.08	€ 1.77	€ 0.00	€ 5,264.31
Ravulizumab 1100 mg	1 CIS	€ 19,281.15	€ 1.77	€ 0.00	€ 19,279.38
Appropriate comparator therapy					
Patient population a) and b)					
Eculizumab	1 CIS	€ 5,877.85	€ 1.77	€ 335.09	€ 5,540.99
Abbreviations: CIS = concentrate for the preparation of an infusion solution					

LAUER-TAXE® last revised: 1 March 2022

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed the standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be evaluated and the appropriate comparator therapy in accordance with the product information, no costs for additionally required SHI services had to be taken into account.

Other SHI services:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe) (Sections 4 and 5 of the Pharmaceutical Price Ordinance) from 01.10.2009 is not fully used to

calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131 paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the currently valid version of the special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe), surcharges for the production of parenteral preparations containing cytostatic drugs a maximum amount of € 81 per ready-to-use preparation, and for the production of parenteral solutions containing monoclonal antibodies a maximum of € 71 per ready-to-use unit are to be payable. These additional other costs are not added to the pharmacy sales price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredient, the invoicing of discards, the calculation of application containers, and carrier solutions in accordance with the regulations in Annex 3 of the Hilfstaxe.

3. Bureaucratic costs calculation

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

At its session on 12 October 2021, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 September 2021, the pharmaceutical company submitted a dossier for the benefit assessment of ravulizumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 29 September 2021 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient ravulizumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 21 December 2021, and the written statement procedure was initiated with publication on the website of the G-BA on 3 January 2022. The deadline for submitting written statements was 24 January 2022.

The oral hearing was held on 7 February 2022.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing was discussed at the session of the subcommittee on 9 March 2022, and the proposed resolution was approved.

At its session on 18 March 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal product	12 October 2021	Determination of the appropriate comparator therapy
Working group Section 35a	2 February 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal product	7 February 2022	Conduct of the oral hearing
Working group Section 35a	16 February 2022 2 March 2022	Consultation on the dossier assessment by the IQWiG, assessment of the written statement procedure
Subcommittee Medicinal product	9 March 2022	Concluding discussion of the draft resolution
Plenum	18 March 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 18 March 2022

Federal Joint Committee (G-BA)
in accordance with Section 91 SGB V
The Chair

Prof. Hecken