

# Justification



## to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Ravulizumab

of 6 February 2020

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## 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 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 shall pass a resolution on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

## 2. Key points of the resolution

The relevant date for the first placing on the market of the active ingredient ravulizumab in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 August 2019. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 1 VerfO on 1 August 2019.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 November 2019 on the website of the G-BA ([www.g-ba.de](http://www.g-ba.de)), 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 with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. 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 <sup>1</sup> 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 arrived at 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®) in accordance with the product information**

Ultomiris is indicated in the treatment of adult patients 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 (see section 5.1).

### **2.1.2 Appropriate comparator therapy**

The appropriate comparator therapy was determined as follows:

- a) Adult patients with paroxysmal nocturnal haemoglobinuria (PNH) with a high disease activity characterised by clinical symptoms of haemolysis

**Appropriate comparator therapy:**

Eculizumab

- b) Adult patients 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 according to 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.

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<sup>1</sup> General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee 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 the therapeutic indication of paroxysmal nocturnal haemoglobinuria (PNH), the antibody eculizumab is approved for the treatment of adults, children, and adolescents. In accordance with the product information of Soliris<sup>®</sup>, the clinical benefit in patients with haemolysis with clinical symptom(s) indicative of high disease activity is demonstrated independent of the transfusion history.
- On 2. Non-medicinal treatment that can be provided within the framework of the SHI system is not considered in the present therapeutic indication.
- On 3. No resolutions of the G-BA have been made in the therapeutic indication considered here.
- On 4. The general state of medical knowledge on which the decision of the G-BA are based was illustrated by systematic research for guidelines and reviews of clinical studies in the present indication.

It is assumed that the therapeutic indication presented covers only patients with PNH and clinical symptoms of haemolysis in need of treatment. Patients with concomitant bone marrow failure – also in the context of aplastic anaemia – are not considered further here. Accordingly, an allogenic stem cell transplantation is not to be considered in this case.

In the present therapeutic indication, only the antibody eculizumab is approved for patients with clinical symptoms of haemolysis. In addition to therapy with eculizumab, supportive measures (e.g. substitution of erythrocyte concentrates, folic acid, vitamin B12, and iron as well as prophylactic anticoagulation, early antibiotic therapy of bacterial infections) should be implemented.

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

### **2.1.3 Extent and probability of the additional benefit**

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

- a) Adult patients with paroxysmal nocturnal haemoglobinuria (PNH) with a high disease activity characterised by clinical symptoms of haemolysis

For adult PNH patients with high disease activity characterised by the clinical symptoms of haemolysis, the additional benefit compared with eculizumab is not proven.

Justification:

The pharmaceutical company has submitted the results of Study 301 to demonstrate the additional benefit of ravulizumab in patient population a).

Study 301 is a randomised, open-label, controlled, double-arm, parallel group study investigating ravulizumab in comparison with eculizumab in adult PNH patients who have never received treatment with a complement inhibitor.

Patients had to show at least one PNH-associated symptom indicating high disease activity (e.g. fatigue, haemoglobinuria, history, or presence of a major adverse vascular event (MAVE)) within the 3 months prior to screening. Only patients with a lactate dehydrogenase (LDH) value of  $\geq 1.5$ -fold the upper limit of the normal range were included in the study.

In Study 301, 246 patients were randomised at a ratio of 1:1 to the study arms ravulizumab (N = 125) or eculizumab (N = 121). In the study, the patients were stratified according to LDH value at screening and transfusion history (number of red cell concentrate units in the year before the 1st dose of the study medication). The study included a 26-week open-label treatment phase.

The co-primary endpoints in Study 301 were transfusion avoidance and haemolysis, which were operationalised as normalisation of LDH levels. Patient relevant secondary endpoints were overall mortality, morbidity endpoints (MAVE, fatigue, transfusion avoidance, breakthrough haemolysis), quality of life assessed by EORTC QLQ-C30, and side effects.

Accompanying treatment was permitted if it was necessary as part of the therapy or to treat AEs. The documentation of the concomitant medication shows that supportive measures were used to a comparable extent in both study arms.

#### Extent and probability of the additional benefit

##### Mortality

Until week 26, no deaths occurred in Study 301.

##### Morbidity

###### *Major adverse vascular events (MAVE)*

For the endpoint MAVE, the proportion of patients with a MAVE was based on the survey of adverse events. In Study 301, a MAVE was defined *a priori* as one of the following events: Thrombophlebitis/deep vein thrombosis, pulmonary embolism, myocardial infarction, transient ischaemic attack, unstable angina pectoris, renal vein thrombosis, peripheral artery disease, mesenteric/visceral venous thrombosis or infarction, mesenteric/visceral arterial thrombosis or infarction, hepatic vein/portal vein thrombosis (Budd-Chiari syndrome), cerebral artery occlusion/stroke, cerebral vein occlusion, renal artery thrombosis, gangrene (non-traumatic, non-diabetic), amputation (non-traumatic, non-diabetic), dermal thrombosis, other.

For the endpoint MAVE, there was no statistically significant difference between the treatment groups.

### *Fatigue (FACIT fatigue)*

The endpoint fatigue was assessed using the FACIT Fatigue Scale (Version 4.0). The FACIT-Fatigue Scale is a validated self-assessment tool consisting of 13 items that measure the intensity of fatigue as well as weakness and difficulty in performing daily activities because of fatigue within the last seven days. The items are answered on a numerical 5-point scale (0 = not at all; 4 = very much). The evaluation was based on the total score of all 13 items in the form of a responder analysis of the number of patients with an improvement of at least 3 points at week 26.

For the endpoint fatigue, there was no statistically significant difference between the treatment groups.

### *Transfusion avoidance*

For the endpoint transfusion avoidance, the proportion of patients who remained transfusion-free and did not require a transfusion until the end of the study according to the guidelines specified in the study protocol is used.

For the endpoint transfusion avoidance, there was no statistically significant difference between the treatment groups.

### *Breakthrough haemolysis (BTH)*

For the endpoint, the proportion of patients with BTH at week 26 is considered. The occurrence of BTH is defined as the recurrence or worsening of at least one symptom or sign of intravascular haemolysis (fatigue, haemoglobinuria, abdominal pain, shortness of breath, anaemia, MAVE, including thrombosis, dysphagia, or erectile dysfunction) as well as an LDH level  $\geq 2$  times above the upper limit of the normal range after a reduction of the LDH level to  $< 1.5$  times the upper limit of the normal range had been observed under therapy.

In general, BTH associated symptoms are patient-relevant. The applied operationalisation of this endpoint links the collection of symptoms to a simultaneous increase in LDH levels. The LDH value represents a surrogate parameter. The causes for an increase in this laboratory value can be manifold and are not exclusively limited to or specific for a PNH disease. Based on the data presented in the benefit assessment procedure, it is not clear to what extent all symptoms that may occur in the context of a BTH have been fully assessed decoupled from the LDH value. For a comprehensive interpretation of the effects of ravulizumab on the occurrence of BTH, a complete assessment of the individual symptoms would be necessary. With the described uncertainties regarding the operationalisation as well as the choice of the laboratory parameter, the endpoint BTH is not considered patient-relevant in the present operationalisation and is thus not used when assessing the additional benefit of ravulizumab.

### Quality of life

In Study 301, the functional scales of the disease-specific questionnaire EORTC QLQ-C30 were used to assess the health-related quality of life. The EORTC QLQ-C30 is primarily used to assess the quality of life of cancer patients. In general, it seems to be sufficient for assessing the quality of life of PNH patients. However, a query of additional aspects could increase the relevance of EORTC QLQ-C30 for patients with PNH.

In Study 301, there was no statistically significant difference between the treatment groups in the six different functional scales of the EORTC QLQ30-C30.

### Side effects

By week 26 of Study 301, there were no discontinuations because of AEs or meningococcal infections. For the SAEs endpoint, there was no statistically significant difference between the treatment groups.

#### Overall assessment/conclusion

For the assessment of the additional benefit of ravulizumab for the treatment of adult patients with PNH with high disease activity characterised by clinical symptoms of haemolysis, data on mortality, morbidity, quality of life, and side effects are available.

In Study 301, the additional benefit is assessed on the basis of a randomised, open, and directly comparative Phase III study. Only therapy naïve patients were included in the study. There is thus no data available for patients who show high disease activity despite pretreatment.

No deaths occurred in the study presented; thus, no difference was observed between treatment groups with regard to the mortality endpoint.

There is no difference between ravulizumab and eculizumab with regard to the patient-relevant endpoints MAVE, fatigue, and transfusion avoidance of the morbidity category.

There are neither advantages nor disadvantages with regard to health-related quality of life measured with the EORTC-QLQ-C30.

The data presented show no statistically significant difference with respect to the occurrence of adverse events.

There are neither positive nor negative effects of ravulizumab compared with eculizumab; there is thus overall no proof of additional benefit for ravulizumab for the treatment of adult PNH patients with high disease activity characterised by the clinical symptoms of haemolysis.

#### b) Adult patients with paroxysmal nocturnal haemoglobinuria (PNH) who are clinically stable after having been treated with eculizumab for at least the past 6 months

For adult PNH patients who have received eculizumab for  $\geq 6$  months and are clinically stable, the additional benefit compared with eculizumab is not proven.

Justification:

The pharmaceutical company has submitted the results of Study 302 to demonstrate the additional benefit of ravulizumab in patient population b).

Study 302 is a randomised, open-label, controlled, double-arm, parallel group study investigating ravulizumab in comparison with eculizumab in adult PNH patients who were previously  $\geq$  treated with eculizumab for 6 months and were clinically stable.

The patients had to have an LDH value of  $\leq 1.5$  times above the normal range at the time of screening. The LDH value also should not have been  $> 2$  times above the normal range in the 6 months before the first treatment with the study medication. In addition, no MAVE should have occurred in patients in the 6 months before the first treatment with the study medication.

In Study 302, 197 patients were randomised at a ratio of 1:1 to the study arms ravulizumab (N = 98) or eculizumab (N = 99). In the study, patients were stratified according to transfusion history (transfusion received in the year before the 1st study medication: yes or

no). The study included a 26-week open-label treatment phase. This was followed by an extension phase in which all patients received ravulizumab. For the assessment of the additional benefit, only the randomized study phase up to week 26 is used.

Haemolysis, which was operationalised as a mean change in LDH levels at week 26, was the primary endpoint in Study 302. Patient relevant secondary endpoints were morbidity endpoints (MAVE, fatigue, transfusion avoidance, breakthrough haemolysis), quality of life (EORTC QLQ-C30), and side effects.

Accompanying treatment was permitted if it was necessary as part of the therapy or to treat AEs. The documentation of the concomitant medication shows that supportive measures were used to a comparable extent in both study arms.

#### Extent and probability of the additional benefit

The respective operationalisations of the endpoints in Study 302 were performed analogously to the survey of the respective endpoints in Study 301. The explanations on the individual endpoints therefore apply to Study 302 as described above.

#### Mortality

Until week 26, no deaths occurred in Study 302.

#### Morbidity

##### *MAVE*

In study 301, no MAVE occurred by week 26.

##### *Fatigue (FACIT fatigue)*

For fatigue, measured using the FACIT Fatigue Scale, there is no statistically significant difference between treatment groups.

##### *Transfusion avoidance*

For the endpoint transfusion avoidance, there was no statistically significant difference between the treatment groups.

##### *Breakthrough haemolysis (BTH)*

Because of the uncertainties in the operationalisation of the BTH endpoint described above, the endpoint is not included in the present assessment of additional benefit.

#### Quality of life

For 5 of 6 items of the EORTC QLQ-C30 functional scales (physical function, role function, emotional function, cognitive function, social function), there is no statistically significant difference between the treatment groups. For the item global health status, a statistically significant advantage in favour of ravulizumab is shown compared with eculizumab. (1.8 vs -2.7; MD 4.52 [95% CI 0.17; 8.87]; p = 0.042). However, the clinical relevance of this effect cannot be conclusively assessed because the 95% CI of the standardised mean difference is not completely outside the irrelevance range of -0.2 to 0.2 (Hedges' g: 0.29 [0.01; 0.57]).

#### Side effects



By week 26 of Study 302, there were no discontinuations because of AEs or meningococcal infections. For the SAEs endpoint, there was no statistically significant difference between the treatment groups.

#### Overall assessment/conclusion

For the assessment of the additional benefit of ravulizumab for the treatment of adult PNH patients who have received eculizumab for  $\geq 6$  months and are clinically stable, data on mortality, morbidity, quality of life, and side effects are available.

In Study 302, the additional benefit is assessed on the basis of a randomised, open, and directly comparative Phase III study.

No deaths occurred in the studies presented; thus, no difference was observed between treatment groups with regard to the mortality endpoint.

There is no difference between ravulizumab and eculizumab with regard to the MAVE, fatigue, and transfusion avoidance endpoints of the morbidity category.

There are neither advantages nor disadvantages with regard to health-related quality of life measured with the EORTC-QLQ-C30.

The data presented show no statistically significant difference with respect to the occurrence of adverse events.

There are neither positive nor negative effects of ravulizumab compared with eculizumab; there is thus overall no proof of additional benefit for ravulizumab for the treatment of adult PNH patients who have received eculizumab for  $\geq 6$  months and who are clinically stable.

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

The number of patients is the target population in the statutory health insurance (SHI). In the dossier submitted, the pharmaceutical company does not distinguish PNH patients into therapy naïve patients with high disease activity (patient population a)) and pre-treated patients ( $\geq 6$  months eculizumab, stable) (patient population b)).

Overall, the number of patients in the SHI target population indicated is uncertain because of the limited data availability on the prevalence of PNH in Germany (information on the upper limit). Furthermore, the methodological derivation of the proportion with high disease activity or with eculizumab pre-treatment without high disease activity is subject to uncertainties.

The information on the number of patients in patient populations a) and b) is based on the calculations of the IQWiG in the benefit assessment.

## 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: 4 December 2019):

[https://www.ema.europa.eu/documents/all-authorized-presentations/ultomiris-epar-all-authorized-presentations\\_de.pdf](https://www.ema.europa.eu/documents/all-authorized-presentations/ultomiris-epar-all-authorized-presentations_de.pdf)

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

In accordance with the specifications of the European Medicines Agency (EMA) regarding additional measures for risk minimisation, the pharmaceutical company must provide training materials to all doctors and patients expected to use ravulizumab.

In addition to the product information, the training material for doctors contains a guide for the prescribing doctor. In addition to the package insert, the training material for patients contains a guide for patients as well as a patient card.

## 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: 15 January 2020).

In general, initial induction schemes are not taken into account for the cost representation because the present indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

For the calculation of the dosages as a function of body weight, the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population" were used as a basis (average body weight): 77.0 kg)<sup>2</sup>.

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<sup>2</sup> German Federal Office For Statistics, Wiesbaden 2018: <http://www.gbe-bund.de/>

Treatment duration:

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	every 8 weeks	6	1	6
Appropriate comparator therapy				
Patient population a) and b)				
Eculizumab	every 12–16 days	22–30	1	22–30

Usage and consumption:

Designation of the therapy	Dosage/application	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/patient/year	Mean annual consumption by potency
Medicinal product to be assessed					
Ravulizumab	3300 mg	3300 mg	11 x 300 mg	6	66 x 300 mg
Appropriate comparator therapy					
Patient population a) and b)					
Eculizumab	900 mg	900 mg	3 x 300 mg	22–30	66–90 x 300 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy retail price level and also deducting the statutory rebates in accordance with Sections 130 and 130 a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

### Costs of the medicinal product:

Designation of the therapy	Package size	Costs (pharmacy selling price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Ravulizumab	1	€ 5,694.98	€ 1.77	€ 324.66	€ 5,368.55
Appropriate comparator therapy					
Eculizumab	1	€ 5,877.61	€ 1.77	€ 335.09	€ 5,540.75

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 15 January 2020

### 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 standard expenditure in the course of the treatment are not shown.

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

### Other services covered by SHI funds:

The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy selling 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 special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. These additional costs are not added to the pharmacy retail 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 production 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 ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

### 3. Bureaucratic costs

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

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 29 January 2019.

On 1 August 2019, 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 1, sentence 2 VerfO.

By letter dated 1 August 2019 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 30 October 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 1 November 2019. The deadline for submitting written statements was 22 November 2019.

The oral hearing was held on 10 December 2019.

By letter dated 10 December 2019, the IQWiG was commissioned with a supplementary assessment of data submitted in the dossier. The addendum prepared by IQWiG was submitted to the G-BA on 16 January 2020.

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 were discussed at the session of the subcommittee on 28 January 2020, and the proposed resolution was approved.

At its session on 6 February 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

### Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	29 January 2019	Determination of the appropriate comparator therapy
Working group Section §35a	3 December 2019	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	10 December 2019	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents

Working group Section §35a	17 December 2019 21 January 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	28 January 2020	Concluding consultation of the proposed resolution
Plenum	6 February 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 6 February 2020

Federal Joint Committee  
in accordance with Section 91 SGB V  
The Chair

Prof. Hecken