Gemeinsamer Bundesausschuss

# Justification

to 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
Garadacimab (hereditary angioedema, prophylaxis, ≥ 12 years)

of 21 August 2025

**Contents**

## 1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assess the benefit of all 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 studies the pharmaceutical company have 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.
7. Number of study participants who participated in the clinical studies at study sites within the scope of SGB V, and total number of study participants.

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 relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient garadacimab on 3 March 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. 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 28 March 2025.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 2 June 2025 on the G-BA website (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 garadacimab 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, and the statements submitted in the written statement and oral hearing procedure, as well of the addendum drawn up by the IQWiG on the benefit assessment. In order to determine the extent of the additional benefit, the G-BA have 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 garadacimab.

In the light of the above, and taking into account the statements received and the oral hearing, the G-BA have 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 Garadacimab (Andembry) in accordance with the product information

ANDEMBRY is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adult and adolescent patients aged 12 years and older.

**Therapeutic indication of the resolution (resolution of 21 August 2025):**

See therapeutic indication according to marketing authorisation.

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adolescents aged 12 and older and adults with recurrent attacks of hereditary angioedema

**Appropriate comparator therapy for garadacimab for routine prevention:**

- Routine prevention with a C1 esterase inhibitor or lanadelumab or berotralstat

Criteria according to Chapter 5 Section 6 of the Rules of Procedure of the G-BA and Section 6 paragraph 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV):

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.

[1] General Methods, version 7.0 from 19.09.2023. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

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 patient-relevant benefit has already been determined by the G-BA 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.

According to Section 6, paragraph 2, sentence 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the determination of the appropriate comparator therapy must be based on the actual medical treatment situation as it would be without the medicinal product to be assessed. According to Section 6, paragraph 2, sentence 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV), the G-BA may exceptionally determine the off-label use of medicinal products as an appropriate comparator therapy or as part of the appropriate comparator therapy if it determines by resolution on the benefit assessment according to Section 7, paragraph 4 that, according to the generally recognised state of medical knowledge, this is considered a therapy standard in the therapeutic indication to be assessed or as part of the therapy standard in the medical treatment situation to be taken into account according to sentence 2, and

1. for the first time, a medicinal product approved in the therapeutic indication is available with the medicinal product to be assessed,
2. according to the generally recognised state of medical knowledge, the off-label use is generally preferable to the medicinal products previously approved in the therapeutic indication, or
3. according to the generally recognised state of medical knowledge, the off-label use for relevant patient groups or indication areas is generally preferable to the medicinal products previously approved in the therapeutic indication.

An appropriate comparator therapy may also be non-medicinal therapy, the best possible add-on therapy including symptomatic or palliative treatment, or monitoring wait-and-see approach.

<u>Justification based on the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO and Section 6, paragraph 2 AM-NutzenV:</u>

On 1. In addition to the active ingredient garadacimab, the plasma kallikrein inhibitors lanadelumab and berotralstat, C1 esterase inhibitors and the antifibrinolytic tranexamic acid are approved in the present therapeutic indication.

On 2. No non-medical measures are considered as the appropriate comparator therapy for the routine prevention of recurrent attacks of hereditary angioedema.

On 3. The following resolutions of the G-BA on the early benefit assessment according to Section 35a SGB V of medicinal products with new active ingredients are available for

the therapeutic indication to be assessed in adolescents aged 12 years and older and adults (Annex XII of the Pharmaceuticals Directive):

- Lanadelumab from 4 November 2021
- Berotralstat from 2 December 2021.

On 4. The generally recognised state of medical knowledge was illustrated by a systematic search for guidelines as well as systematic reviews of clinical studies in the present indication and is presented in the "Research and synopsis of the evidence to determine the appropriate comparator therapy according to Section 35a SGB V".

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.

Hereditary angioedema (HAE) is divided into different subtypes, depending on the underlying genetic variant. The most common subtypes are HAE type I and type II, which are characterised by a deficiency of C1 esterase inhibitor (C1-INH) or by a functional insufficiency of the same due to a C1-INH gene defect. In contrast, HAE type III occurs only very rarely. These are patients with normal C1-INH in whom HAE is associated with a number of mutations in other genes. In addition, in many cases no gene mutation can be foun, so that the pathogenesis of HAE type III remains to be clarified in detail.

Overall, most patients are found to have HAE type I or II. In addition, the guideline recommendations and the currently available therapeutic options mainly address these two subtypes. Accordingly, the focus in the determination of the appropriate comparator therapy is on patients with HAE type I and II.

The goal of treating affected patients is to reduce the occurring angioedema or HAE attacks. If acute treatment of HAE attacks alone is no longer sufficient, the current guidelines and scientific-medical societies recommend long-term prevention with either a C1 esterase inhibitor or a plasma kallikrein inhibitor such as lanadelumab or berotralstat. These therapies can reduce the number, duration and severity of HAE attacks. However, according to guideline recommendations, prevention with an antifibrinolytic such as tranexamic acid is a secondary therapy option.

An early benefit assessment was conducted for the active ingredients lanadelumab and berotralstat respectively. An additional benefit was not proven for either active ingredient compared with the appropriate comparator therapy.

Based on the available evidence, both C1 esterase inhibitors and the active ingredients lanadelumab and berotralstat are therefore equally appropriate therapy options.

In the overall assessment, routine prophylaxis with a C1 esterase inhibitor or with lanadelumab or berotralstat is therefore determined as the appropriate comparator therapy for adolescents aged 12 years and older and for adults with recurrent attacks of hereditary angioedema. The appropriate comparator therapy determined here includes several therapy options. These therapeutic alternatives are equally appropriate for the comparator therapy. The additional benefit can be demonstrated compared to one of the therapeutic alternatives mentioned.

The marketing authorisation and the dosage information in the product information of the active ingredients must be taken into account.

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

A change in the appropriate comparator therapy requires a resolution by the G-BA linked to the prior review of the criteria according to Chapter 5 Section 6, paragraph 3 Rules of Procedure.

### 2.1.3 Extent and probability of the additional benefit

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

Adolescents aged 12 and older and adults with recurrent attacks of hereditary angioedema

Hint for a considerable additional benefit.

Justification:

Adjusted indirect comparison

For the proof of additional benefit of garadacimab compared with the appropriate comparator therapy of berotralstat, the pharmaceutical company used an adjusted indirect comparison according to the procedure by Bucher et al. For the adjusted indirect comparison via the bridge comparator placebo, the VANGUARD study is available on the intervention side and the APeX-2 and APeX-J studies on berotralstat are available on the appropriate comparator therapy side.

VANGUARD study (pivotal study on garadacimab)

The VANGUARD study is a double-blind, randomised controlled trial comparing garadacimab versus placebo in adolescents aged 12 years and older and adults with HAE type I or II. The placebo-controlled treatment phase lasted 6 months.

According to the inclusion criteria, a documented clinical history of HAE was requires, which was defined as episodes of subcutaneous or mucosal swelling without concomitant urticaria, as well as C1 esterase inhibitor (C1-INH) deficiency and/or reduced functional C1-INH activity in the range ≤ 50% of the normal value should, among others. Diagnosis of any other form of angioedema or HAE type III led to exclusion from the study. Another prerequisite for enrolment in the study was a minimum number of 3 HAE attacks within 3 months prior to screening, and at least 2 HAE attacks during the run-in phase in a period of 1 to 2 months were required for the transition to the double-blind treatment phase.

In the VANGUARD study, 64 patients were randomised and assigned in a 3:2 ratio to the 200 mg garadacimab treatment arm (39 subjects) or the placebo arm (26 subjects).

Treatment on demand of HAE attacks with C1-INH, among other things, and short-term prevention with C1-INH before medically indicated interventions were permitted. Adults must not have received therapy for long-term prevention of HAE attacks within 2 weeks prior to the run-in phase. For children and adolescents, any long-term prevention prior to screening was not permitted.

The primary endpoint of the study was the rate of medically confirmed HAE attacks during the 6-month treatment phase. In addition, other endpoints in the categories of morbidity, health-related quality of life and side effects were examined.

APeX-2 and APeX-J studies (pivotal studies on berotralstat)

The APeX-2 and APeX-J studies are double-blind, randomised studies comparing berotralstat versus placebo in adolescents aged 12 years and older and in adults with HAE type I or II. The first placebo-controlled treatment phase with a duration of 24 weeks and the treatment arm with berotralstat at a dosage of 150 mg, respectively, are relevant for the present benefit assessment.

According to the inclusion criteria of the studies, a clinical diagnosis of HAE type I or II was required, which was attributable to C1-INH deficiency or reduced functional C1-INH activity in the range < 50% of the normal value, among other things. During the run-in phase in the period from 14 to 56 days, at least 2 HAE attacks should have occurred.

In the placebo-controlled treatment phase of the APeX-2 study, 40 subjects were randomised and assigned to the 150 mg berotralstat arm and another 40 subjects to the placebo arm. In the APeX-J studies, there were 7 subjects in the 150 mg berotralstat arm and 6 subjects in the placebo arm.

In the studies, treatment on demand of HAE attacks was permitted with C1-INH, among others. In addition, prevention with C1-INH was permitted due to an unplanned intervention. Patients were not allowed to have received androgens or tranexamic acid within 28 days prior to the screening or C1-INH for the prevention of HAE attacks within 14 days prior to the screening.

The primary endpoint of the studies was the rate of HAE attacks confirmed by doctors or independent experts during the 24-week treatment phase. In addition, other endpoints in the categories of morbidity, health-related quality of life and side effects were examined.

Similarity of the studies for an adjusted indirect comparison

The VANGUARD study and the two APeX studies have a very similar study design. The duration of the placebo-controlled treatment phase is considered to be sufficiently comparable in the studies. The patient populations are also sufficiently similar. Differences in the individual demographic and clinical patient characteristics as well as differences in the possible concomitant treatments with regard to oestrogen-containing medicinal products between the VANGUARD study and the APeX-2 and APeX-J studies do not call into question the sufficient similarity of the studies and thus the performance of an adjusted indirect comparison via the bridge comparator placebo overall.

In summary, the presented adjusted indirect comparison was used for the assessment of the additional benefit of garadacimab versus the appropriate comparator therapy of berotralstat as part of the benefit assessment.

Extent and probability of the additional benefit

Mortality

*Overall mortality*

No deaths occurred in the VANGUARD, APeX-2 and APeX-J studies.

Morbidity

*HAE attacks (monthly rate)*

In the VANGUARD, APeX-2 and APeX-J studies, HAE attacks were collected via entries made by patients in an electronic diary. The presence of an attack was confirmed by the principal investigators or by independent experts.

In the VANGUARD study, an HAE attack was defined as such if at least one symptom or localisation or a combination of several symptoms / localisations with a perceptible swelling or corresponding conditions occured. A new attack had to be separated in time from a previous attack and therefore could not begin within 24 hours of the end of the previous HAE attack.

In the APeX 2 and APeX-J studies, an HAE attack was defined as such if it was accompanied by symptoms of swelling. In addition to visible swelling, these included conditions in the oropharyngeal or abdominal region, indicating internal swelling. The HAE attack must either have been treated, required healthcare or have demonstrably led to a functional impairment. A new attack was only categorised as such if it occurred at least 48 hours after the end of the previous HAE attack.

Overall, the collection of HAE attacks in the studies analysed here is considered to be sufficiently similar. Nevertheless, it remains unclear to what extent the categorisation of the severity grade was comparable in the studies. In addition, information on localisation was only collected in the studies on berotralstat. Therefore, no conclusions can be drawn on the additional benefit with regard to the severity grade and localisation of HAE attacks. Consequently, evaluations of all HAE attacks are used for the benefit assessment, regardless of severity grade and localisation.

The monthly rate of HAE attacks was operationalised as the number of HAE attacks divided by the duration of observation of the participants (in days) from the start of treatment multiplied by 30.4375 days (VANGUARD study) or 28 days (APeX-2 and APeX-J studies).
For the endpoint "monthly rate of HAE attacks", the adjusted indirect comparison showed a statistically significant difference in favour of garadacimab compared to berotralstat.

*Attack-free status*

The most important therapeutic goal in HAE is complete control of the disease and thus, attack-free status. In the studies, the endpoint "attack-free status" was defined as the percentage of patients without HAE attacks during the treatment phase of 26 weeks in the VANGUARD study and 24 weeks in the APeX-2 and APeX-J studies.

For the endpoint "attack-free status", the adjusted indirect comparison showed no statistically significant difference between garadacimab and berotralstat.

*Activity impairment (assessed using WPAI question 6)*

The Work Productivity and Activity Impairment (WPAI) is used to collect impairments to work productivity and activities. Health economic aspects such as the endpoints of absenteeism and presenteeism collected by the WPAI are not considered patient-relevant and are therefore not taken into account in this benefit assessment. However, activity impairment due to the disease (question 6) addresses a patient-relevant aspect.

For the present benefit assessment, the data on activity impairment according to question 6 of the WPAI are therefore considered. The scale range comprises the values 0 to 10, with lower

values indicating better symptomatology. Here, the evaluations subsequently submitted as part of the written statement procedure are used for the change at week 26 for the VANGUARD study and at week 24 for the APeX-2 and APeX-J studies, in each case in comparison to the baseline value.

For the endpoint of activity impairment (assessed using WPAI question 6), the adjusted indirect comparison showed a statistically significant difference in favour of garadacimab compared to berotralstat.

*Health status (EQ-5D, visual analogue scale)*

The health status was assessed in the studies using the visual analogue scale (VAS) of the EQ-5D questionnaire. The VAS of the EQ-5D is a visual analogue scale from 0 to 100 on which patients rate their health status. A value of 0 corresponds to the worst possible health status and a value of 100 to the best possible health status. For the benefit assessment, the presented evaluations of the change at the end of treatment compared to the start of the study are used.

For the endpoint of health status, assessed using the VAS of the EQ-5D, the adjusted indirect comparison showed a statistically significant difference in favour of garadacimab compared to berotralstat.

Quality of life

*Angioedema - Quality of Life (AE-QoL)*

The AE-QoL is a disease-specific instrument for assessing the quality of life of adults with recurrent angioedema. The questionnaire contains a total of 17 questions in the 4 domains of function, fatigue / mood, anxiety / shame and nutrition, which are answered using a 5-point Likert scale (from 1 (never) to 5 (very often)). Possible scores ranging from 0 to 100 make up the total score of the AE-QoL. An improvement in health-related quality of life is shown by a reduction in the score in the AE-QoL. For the benefit assessment, the presented evaluations of the change at the end of treatment compared to the start of the study in adults are used.

For the endpoint of health-related quality of life assessed using AE-QoL, the total score in the adjusted indirect comparison showed a statistically significant difference in favour of garadacimab compared to berotralstat.

Side effects

*SAEs and discontinuation due to AEs*

For the endpoint of SAEs, the adjusted indirect comparison showed no statistically significant difference between garadacimab and berotralstat.

For the endpoint of therapy discontinuation due to AEs, the adjusted indirect comparison also showed no statistically significant difference between garadacimab and berotralstat.

*Severe AEs*

In the VANGUARD study, the severity grade of AEs was assessed by the principal investigators as mild, moderate or severe, taking into account the need for treatment and impairment of activities of daily living. This is an inadequate operationalisation of severe AEs in demarcation from non-severe AEs.

In the APeX studies, the severity grade of AEs was classified according to the toxicity tables for adults of the Division of Microbiology and Infectious Diseases (DMID), version November 2007. Severe AEs were predefined in the study protocol and operationalised as DMID grade 3 (severe) or DMID grade 4 (life-threatening).

Therefore, no suitable data are available for the indirect comparison for the endpoint of severe AEs for the garadacimab intervention from the VANGUARD study.

Overall assessment

Results from an adjusted indirect comparison are available for the assessment of the additional benefit of garadacimab for use in the routine prevention of recurrent attacks of hereditary angioedema (HAE). For this purpose, data on garadacimab from the VANGUARD study was compared with berotralstat from the APeX-2 and APeX-J studies via the bridge comparator placebo. These studies are sufficiently similar and overall suitable for conducting an adjusted indirect comparison.

Only patients with HAE type I and type II were examined. Accordingly, no statements on the additional benefit in patients with HAE type III can be derived.

No deaths occurred in the mortality endpoint category in the studies analysed.

In the morbidity endpoint category, all confirmed HAE attacks were considered for the endpoint "HAE attacks", regardless of severity grade and localisation. Data are available for this endpoint in two operationalisations for the adjusted indirect comparison. For the operationalisation as "monthly rate of HAE attacks", there was a statistically significant difference in favour of garadacimab compared to berotralstat. For the further operationalisation described as "attack-free status", which defines the percentage of subjects without HAE attacks during the treatment phase, there were no statistically significant differences between garadacimab and berotralstat.

Furthermore, the adjusted indirect comparison in the morbidity endpoint category showed statistically significant differences for the endpoint "activity impairment" (assessed using WPAI question 6) and for the endpoint "health status" (assessed using EQ-5D VAS) in favour of garadacimab over berotralstat in each case.

In the health-related quality of life endpoint category, data from the disease-specific Angioedema - Quality of Life (AE-QoL) questionnaire were used. For the total score of the AE-QoL, the adjusted indirect comparison showed a statistically significant difference in favour of garadacimab compared to berotralstat.

In the side effects endpoint category, the adjusted indirect comparison showed no statistically significant differences between garadacimab and berotralstat.

In the overall assessment, it was found that an adjusted indirect comparison showed positive effects of garadacimab compared to berotralstat for the endpoints "monthly rate of HAE attacks", "activity impairment", "health status" and "health-related quality of life". Overall, the extent of the additional benefit of garadacimab compared to berotralstat is classified as considerable.

Reliability of data (probability of additional benefit)

No direct comparator data are available for the assessment of the additional benefit of garadacimab compared with the appropriate comparator therapy. Therefore, the results of the placebo-controlled VANGUARD as well as APeX-2 and APeX-J studies were considered in

an adjusted indirect comparison of garadacimab versus berotralstat. Due to the limitations in the reliability of data associated with the performance of an adjusted indirect comparison, a hint for the identified additional benefit of garadacimab can be assumed at most.

### 2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product ANDEMBRY with the active ingredient garadacimab, approved for use in the routine prevention of recurrent attacks of hereditary angioedema in adolescents aged 12 years and older and adults.

Routine prevention with a C1 esterase inhibitor or lanadelumab or berotralstat was determined as the appropriate comparator therapy.

In the absence of direct comparator studies, an adjusted indirect comparison of garadacimab versus berotralstat via the bridge comparator placebo was used. The presented VANGUARD study is sufficiently similar to the APeX-2 and APeX-J studies so that the adjusted indirect comparison is considered appropriate for the benefit assessment.

Only patients with HAE type I and type II were examined. Accordingly, no statements on the additional benefit in patients with HAE type III can be derived.

There were no deaths in the studies.

In the morbidity endpoint category, there were statistically significant advantages in favour of garadacimab for the endpoints "monthly rate of HAE attacks", "activity impairment" and "health status". There were no statically significant differences for the endpoint "attack-free status".

In the category of health-related quality of life, there was a statistically significant advantage in favour of garadacimab.

In terms of side effects, there were no statistically significant differences between garadacimab and berotralstat.

In the overall assessment, an adjusted indirect comparison showed only advantages of garadacimab over berotralstat, which are classified as considerable overall. However, the overall reliability of data is limited as the results are based on an adjusted indirect comparison.

A hint for a considerable additional benefit of garadacimab over berotralstat was therefore identified for use in the routine prevention of recurrent attacks of hereditary angioedema in adolescents aged 12 years and older and adults.

## 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).

The resolution is based on the patient numbers stated in the pharmaceutical company's dossier. It is assumed that the patient numbers are underestimated. This is mainly due to the fact that the patient numbers were derived on the basis of a survey from 2018, in which patients who underwent routine prevention at the time of the survey were assessed. However, the number of patients eligible for routine prevention in the current year under consideration may be higher.

## 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 Andembry (active ingredient: garadacimab) at the following publicly accessible link (last access: 4 July 2025):

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

Treatment with garadacimab should only be initiated and monitored by specialists who are experienced in the treatment of patients with hereditary angiooedema.

According to the product information, therapy discontinuation should be considered in patients with normal C1-INH-HAE (nC1-INH) who have shown insufficient reduction in attacks after 3 months of treatment with garadacimab.

## 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 August 2025).

For the cost representation, only the dosages of the general case are considered. Patient-individual dose adjustments (e.g. because of side effects or comorbidities) are not taken into account when calculating the annual treatment costs.

In general, initial induction regimens are not taken into account for the cost representation, since 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.

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 varies from patient to patient 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 | | | | |
| Garadacimab | 1 x every 30.4 days | 12.0 | 1.0 | 12.0 |
| Appropriate comparator therapy | | | | |
| Routine prevention with C1 esterase inhibitor or lanadelumab or berotralstat | | | | |
| C1 esterase inhibitor | Continuously, every 3 – 4 days | 91.3 – 121.7 | 1.0 | 91.3 – 121.7 |
| Lanadelumab | Continuously, every 14 – 28 days | 13.0 - 26.1 | 1.0 | 13.0 - 26.1 |
| Berotralstat | Continuously, 1 x daily | 365.0 | 1.0 | 365.0 |

Consumption:

| 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 | | | | | |
| Garadacimab | 200 mg | 200 mg | 1 x 200 mg | 12.0 | 12 x 200 mg |
| Appropriate comparator therapy | | | | | |
| Routine prevention with C1 esterase inhibitor or lanadelumab or berotralstat | | | | | |
| C1 esterase inhibitor | 1000 I.U. | 1000 I.U. | 2 x 500 I.U. | 91.3 – 121.7 | 182.6 x 500 I.U. – 243.4 x 500 I.U. |
| Lanadelumab | 300 mg | 300 mg | 1 x 300 mg | 13.0 – 26.1 | 13.0 x 300 mg – 26.1 x 300 mg |
| Berotralstat | 150 mg | 150 mg | 1 x 150 mg | 365.0 | 365 x 150 mg |

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a 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. Any reference prices shown in the cost representation may not represent the cheapest available alternative.

**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 | | | | | |
| Garadacimab 200 mg | 3 SFI | € 69,113.59 | € 1.77 | € 3,943.80 | € 65,168.02 |
| Appropriate comparator therapy | | | | | |
| $C_1$ esterase inhibitor, 500 I.U. | 2 PSI | € 2,209.62 | € 1.77 | € 122.90 | € 2,084.95 |
| Lanadelumab 300 mg | 6 SPF | € 64,521.81 | € 1.77 | € 3,681.56 | € 60,838.48 |
| Berotralstat 150 mg | 98 HC | € 51,632.54 | € 1.77 | € 2,945.45 | € 48,685.32 |
| Abbreviations: HC = hard capsules; SPF = solution for injection in a pre-filled syringe; SFI = solution for injection; PSI = powder and solvent for solution for injection | | | | | |

LAUER-TAXE® last revised: 1 August 2025

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.

## 2.5 Designation of medicinal products with new active ingredients according to Section 35a, paragraph 3, sentence 4 SGB V that can be used in a combination therapy with the assessed medicinal product

According to Section 35a, paragraph 3, sentence 4, the G-BA designate all medicinal products with new active ingredients that can be used in a combination therapy with the assessed medicinal product for the therapeutic indication to be assessed on the basis of the marketing authorisation under Medicinal Products Act.

Basic principles of the assessed medicinal product

A designation in accordance with Section 35a, paragraph 3, sentence 4 SGB V requires that it is examined based on the product information for the assessed medicinal product whether it can be used in a combination therapy with other medicinal products in the assessed therapeutic indication. In the first step, the examination is carried out on the basis of all sections of the currently valid product information for the assessed medicinal product.

If the assessed medicinal product contains an active ingredient or a fixed combination of active ingredients in the therapeutic indication of the resolution (assessed therapeutic indication) and is approved exclusively for use in monotherapy, a combination therapy is not considered due to the marketing authorisation under Medicinal Products Act, which is why no designation is made.

A designation is also not considered if the G-BA have decided on an exemption as a reserve antibiotic for the assessed medicinal product in accordance with Section 35a, paragraph 1c, sentence 1 SGB V. The additional benefit is deemed to be proven if the G-BA have decided on an exemption for a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V; the extent of the additional benefit and its therapeutic significance are not to be assessed by the G-BA. Due to the lack of an assessment mandate by the G-BA following the resolution on an exemption according to Section 35a, paragraph 1c, sentence 1 SGB V with regard to the extent of the additional benefit and the therapeutic significance of the reserve antibiotic to be assessed, there is a limitation due to the procedural privileging of the pharmaceutical companies to the effect that neither the proof of an existing nor an expected at least considerable additional benefit is possible for exempted reserve antibiotics in the procedures according to Section 35a paragraph 1 or 6 SGB V and Section 35a paragraph 1d SGB V. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V must therefore also be taken into account at the level of designation according to Section 35a, paragraph 3, sentence 4 SGB V in order to avoid valuation contradictions.

With regard to the further examination steps, a differentiation is made between a "determined" or "undetermined" combination, which may also be the basis for a designation.

A "determined combination" exists if one or more individual active ingredients which can be used in combination with the assessed medicinal product in the assessed therapeutic indication are specifically named.

An "undetermined combination" exists if there is information on a combination therapy, but no specific active ingredients are named. An undetermined combination may be present if the information on a combination therapy:

- names a product class or group from which some active ingredients not specified in detail can be used in combination therapy with the assessed medicinal product, or
- does not name any active ingredients, product classes or groups, but the assessed medicinal product is used in addition to a therapeutic indication described in more detail in the relevant product information, which, however, does not include information on active ingredients within the scope of this therapeutic indication.

Concomitant active ingredient

The concomitant active ingredient is a medicinal product with new active ingredients that can be used in combination therapy with the assessed medicinal product for the therapeutic indication to be assessed.

For a medicinal product to be considered as a concomitant active ingredient, it must be classified as a medicinal product with new active ingredients according to Section 2 paragraph 1 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with the corresponding regulations in Chapter 5 of the Rules of Procedure of the G-BA as of the date of the present resolution. In addition, the medicinal product must be approved in the assessed therapeutic indication, whereby a marketing authorisation is sufficient only for a sub-area of the assessed therapeutic indication.

Based on an "undetermined combination", the concomitant active ingredient must be attributable to the information on the product class or group or the therapeutic indication according to the product information of the assessed medicinal product in the assessed therapeutic indication, whereby the definition of a product class or group is based on the corresponding requirements in the product information of the assessed medicinal product.

In addition, there must be no reasons for exclusion of the concomitant active ingredient from a combination therapy with the assessed medicinal product, in particular no exclusive marketing authorisation as monotherapy.

In addition, all sections of the currently valid product information of the eligible concomitant active ingredient are checked to see whether there is any information that excludes its use in combination therapy with the assessed medicinal product in the assessed therapeutic indication under marketing authorisation regulations. Corresponding information can be, for example, dosage information or warnings. In the event that the medicinal product is used as part of a determined or undetermined combination which does not include the assessed medicinal product, a combination with the assessed medicinal product shall be excluded.

Furthermore, the product information of the assessed medicinal product must not contain any specific information that excludes its use in combination therapy with the eligible concomitant active ingredient in the assessed therapeutic indication under marketing authorisation regulations.

Medicinal products with new active ingredients for which the G-BA have decided on an exemption as a reserve antibiotic in accordance with Section 35a, paragraph 1c, sentence 1 SGB V are ineligible as concomitant active ingredients. The procedural privileging of the reserve antibiotics exempted according to Section 35a, paragraph 1c, sentence 1 SGB V also applies accordingly to the medicinal product eligible as a concomitant active ingredient.

Designation

The medicinal products which have been determined as concomitant active ingredients in accordance with the above points of examination are named by indicating the relevant active ingredient and the invented name. The designation may include several active ingredients, provided that several medicinal products with new active ingredients may be used in the same combination therapy with the assessed medicinal product or different combinations with different medicinal products with new active ingredients form the basis of the designation.

If the present resolution on the assessed medicinal product in the assessed therapeutic indication contains several patient groups, the designation of concomitant active ingredients shall be made separately for each of the patient groups.

Exception to the designation

The designation excludes combination therapies for which - patient group-related - a considerable or major additional benefit has been determined by resolution according to Section 35a, paragraph 3, sentence 1 SGB V or it has been determined according to Section 35a, paragraph 1d, sentence 1 SGB V that at least considerable additional benefit of the combination can be expected. In this context, the combination therapy that is excluded from the designation must, as a rule, be identical to the combination therapy on which the preceding findings were based.

In the case of designations based on undetermined combinations, only those concomitant active ingredients - based on a resolution according to Section 35a, paragraph 3, sentence 1 SGB V on the assessed medicinal product in which a considerable or major additional benefit

had been determined - which were approved at the time of this resolution are excluded from the designation.

Legal effects of the designation

The designation of combinations is carried out in accordance with the legal requirements according to Section 35a, paragraph 3, sentence 4 and is used exclusively to implement the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. The designation is not associated with a statement as to the extent to which a therapy with the assessed medicinal products in combination with the designated medicinal products corresponds to the generally recognised state of medical knowledge. The examination was carried out exclusively on the basis of the possibility under Medicinal Products Act to use the medicinal products in combination therapy in the assessed therapeutic indication based on the product information; the generally recognised state of medical knowledge or the use of the medicinal products in the reality of care were not the subject of the examination due to the lack of an assessment mandate of the G-BA within the framework of Section 35a, paragraph 3, sentence 4 SGB V.

The findings made neither restrict the scope of treatment required to fulfil the medical treatment mandate, nor do they make statements about expediency or economic feasibility.

Justification for the findings on designation in the present resolution:

Adolescents aged 12 and older and adults with recurrent attacks of hereditary angioedema

No medicinal product with new active ingredients that can be used in a combination therapy that fulfils the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:

Product information for garadacimab (ANDEMBRY); ANDEMBRY 200 mg solution for injection in a pre-filled syringe; last revised: February 2025.

## 2.6 Percentage of study participants at study sites within the scope of SGB V in accordance with Section 35a, paragraph 3, sentence 5 SGB V

The medicinal product Andembry is a medicinal product placed on the market from 1 January 2025.

In accordance with Section 35a, paragraph 3, sentence 5 SGB V, the G-BA must determine whether a relevant percentage of the clinical studies on the medicinal product were conducted within the scope of SGB V. This is the case if the percentage of study participants who have participated in the clinical studies on the medicinal product to be assessed in the therapeutic indication to be assessed at study sites within the scope of SGB V is at least five per cent of the total number of study participants.

The calculation is based on all studies that were submitted as part of the benefit assessment dossier in the therapeutic indication to be assessed in accordance with Section 35a, paragraph 1, sentence 3 SGB V in conjunction with Section 4, paragraph 6 AM-NutzenV. Approval studies include all studies submitted to the regulatory authority in the authorisation dossier for the assessment of the clinical efficacy and safety of the medicinal product in the therapeutic indication to be assessed.

The percentage of study participants in the clinical studies of the medicinal product conducted or commissioned by the pharmaceutical company in the therapeutic indication to be assessed who participated at study sites within the scope of SGB V (German Social Security Code) is ≥ 5% of the total number of study participants.

The clinical studies of the medicinal product in the therapeutic indication to be assessed were therefore conducted to a relevant extent within the scope of SGB V.

## 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 their session on 23 April 2024, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 28 February 2025, the pharmaceutical company submitted a dossier for the benefit assessment of garadacimab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 3 March 2025 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefit 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 garadacimab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 May 2025, and the written statement procedure was initiated with publication on the G-BA website on 2 June 2025. The deadline for submitting statements was 23 June 2025.

The oral hearing was held on 7 July 2025.

By letter dated 8 July 2025, the IQWiG was commissioned with a supplementary assessment. The addendum prepared by IQWiG was submitted to the G-BA on 29 July 2025.

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 12 August 2025, and the proposed draft resolution was approved.

At their session on 21 August 2025, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee on Medicinal Products | 23 April 2024 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 1 July 2025 | Information on written statements received; preparation of the oral hearing |
| Subcommittee on Medicinal Products | 7 July 2025 | Conduct of the oral hearing, commissioning of the IQWiG with the supplementary assessment of documents |
| Working group Section 35a | 15 July 2025<br>5 August 2025 | Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure |
| Subcommittee on Medicinal Products | 12 August 2025 | Concluding discussion of the draft resolution |
| Plenum | 21 August 2025 | Adoption of the resolution on the amendment of the Pharmaceuticals Directive |

Berlin, 21 August 2025

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

Prof. Hecken