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
Sebetralstat (hereditary angioedema, acute treatment, ≥ 12 years)

of 2 April 2026

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.

For medicinal products for the treatment of rare diseases (orphan drugs) that are approved according to Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999, the additional medical benefit is considered to be proven through the grant of the marketing authorisation according to Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V. Evidence of the medical benefit and the additional medical benefit in relation to the appropriate comparator therapy do not have to be submitted (Section 35a, paragraph 1, sentence 11, 2nd half of the sentence SGB V). Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V thus guarantees an additional benefit of an approved orphan drug, although an assessment of the orphan drug in accordance with the principles laid down in Section 35a, paragraph 1, sentence 3, Nos. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seqq. of the Rules of Procedure (VerfO) of the G-BA has not been carried out. In accordance with Section 5, paragraph 8 AM-NutzenV, only the extent of the additional benefit is to be quantified indicating the significance of the evidence.

However, the restrictions on the benefit assessment of orphan drugs resulting from the statutory obligation to the marketing authorisation do not apply if the turnover of the medicinal product with the SHI at pharmacy sales prices and outside the scope of SHI-accredited medical care, including VAT exceeds € 30 million in the last 12 calendar months. In accordance with Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company shall provide evidence - within three months of being requested to do so by the G-BA - in accordance with Chapter 5 Section 5, paragraphs 1 to 6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy specified by the G-BA in accordance with Chapter 5 Section 6 VerfO, and in this evidence, demonstrate the additional benefit over the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decide whether to carry out the benefit assessment itself or to commission the Institute for Quality and Efficiency in Health Care (IQWiG). Based on the legal requirement in Section 35a, paragraph 1, sentence 11 SGB V that the additional benefit of an orphan drug is considered to be proven through the grant of the marketing authorisation, the G-BA modified the procedure for the benefit assessment of orphan drugs at their session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determine an appropriate comparator therapy as the basis for the solely legally permissible assessment of the extent of an additional benefit to be assumed by law. Rather, the extent of the additional benefit is assessed exclusively on the basis of the approval studies by the G-BA indicating the significance of the evidence .

Accordingly, at their session on 15 March 2012, the G-BA amended the mandate issued to the IQWiG by the resolution of 1 August 2011 for the benefit assessment of medicinal products with new active ingredients in accordance with Section 35a, paragraph 2 SGB V to that effect that, in the case of orphan drugs, the IQWiG is only commissioned to carry out a benefit assessment in the case of a previously defined comparator therapy when the sales volume of the medicinal product concerned has exceeded the turnover limit according to Section 35a, paragraph 1, sentence 12 SGB V and is therefore subject to an unrestricted benefit assessment. According to Section 35a paragraph 2 SGB V, the assessment by the G-BA 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 decide 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 sebetralstat on 15 October 2025 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO). Pursuant to Section 4, paragraph 3, No. 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, No. 1 Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 14 October 2025.

Sebetralstat for the treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999.

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the approval studies by the G-BA.

The G-BA carried out the benefit assessment and commissioned the IQWiG to evaluate the information provided by the pharmaceutical company in Module 3 of the dossier on treatment costs and patient numbers. The benefit assessment was published on 15 January 2026 together with the IQWiG assessment 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 adopted their resolution on the basis of the pharmaceutical company's dossier, the dossier assessment carried out by the G-BA, the IQWiG assessment of treatment costs and patient numbers (IQWiG G25-30) and the statements made in the written statement and oral hearing procedure, as well of the amendment drawn up by the G-BA on the benefit assessment.

In order to determine the extent of the additional benefit, the G-BA have assessed the studies relevant to the marketing authorisation on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 to 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of sebetralstat.

[1] General Methods, version 8.0 from 19.12.2025. Institute for Quality and Efficiency in Health Care (IQWiG), Cologne.

2.1 Additional benefit of the medicinal product

2.1.1 Approved therapeutic indication of Sebetralstat (Ekterly) in accordance with the product information

Ekterly is indicated for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

Therapeutic indication of the resolution (resolution of 2 April 2026):

See the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

Adults and adolescents aged 12 years and older with an acute attack of hereditary angioedema

Hint for a non-quantifiable additional benefit since the scientific data does not allow quantification.

Justification:

The pharmaceutical company submitted the label-enabling phase III KONFIDENT study for the benefit assessment of sebetralstat for the symptomatic treatment of acute attacks of hereditary angioedema (HAE).

KONFIDENT study

The KONFIDENT study was conducted as a multicentre, double-blind, placebo-controlled study with a three-way crossover design between February 2022 and December 2023. The administration of 300 mg and 600 mg sebetralstat was compared with placebo for the treatment of acute HAE attacks in adults and adolescents aged 12 years and older.

The enrolled subjects were randomised and assigned in a 1:1:1:1:1:1 ratio to six different treatment sequences. The sequence of the specified study medication – 300 mg sebetralstat, 600 mg sebetralstat and placebo – for the treatment of the first, second and third HAE attacks, respectively, varied depending on the treatment sequence. Only the on-label dosage of 300 mg sebetralstat and the comparison with placebo are relevant for the benefit assessment, not the off-label dose of 600 mg sebetralstat.

For enrolment in the study, subjects had to have a documented genetic or clinical diagnosis of type I or type II HAE, defined as subcutaneous or mucosal episodes of non-pruritic swelling without accompanying urticaria, as well as reduced functional activity of C1 esterase inhibitor (C1-INH) below the normal range[2]. The enrolled patients had to have experienced at least two HAE attacks within the three months prior to randomisation. If long-term preventive treatment for HAE with C1-INH, lanadelumab or berotralstat had been completed prior to the start of the study, the dosage had to have been stable for at least three months prior to

[2] C1-INH < 40% or C1-INH between 40% and 50% with a C4 level below the normal reference value

screening and must remain stable throughout the entire study duration. Furthermore, access to conventional HAE on-demand medication had to be available.

In the KONFIDENT study, a total of 136 subjects were randomised; of these, 110 had experienced HAE attacks which were treated with the study medication at least once, and could therefore be analysed (analysis population with regard to the HAE attacks that occurred and were treated during the study).

Conventional on-demand medication

The administration of C1-INH, icatibant and ecallantide was defined as conventional on-demand medication.

In the case of non-laryngeal attacks where symptoms were still estimated to be severe after taking the first dose of the study medication, a second dose of the study medication could be taken after three hours. If symptoms were still estimated to be severe after the second dose, the on-demand medication could be taken after a further hour. In contrast, in the case of laryngeal HAE attacks, on-demand medication could be administered as soon as the first dose of the study medication had been taken, provided that the symptoms were estimated to be severe after one hour. An exception applied to severe attacks affecting the airways; these attacks could be treated at any time with on-demand medication.

Patients who received conventional on-demand medication in addition to the study medication were excluded from the analyses.

Analysis strategy

The analysis was not carried out on the basis of the randomised patients in the conventional sense, but on the basis of the HAE attacks treated with the study medication. According to the study protocol, HAE attacks had to be classified as "eligible[3] attacks" in order to be treated with the study medication. However, during the course of the study, SAP version 2 of 1 December 2023 established further criteria for the characterisation of attacks that would qualify for inclusion in the analyses. Only those eligible attacks which had actually been treated with the study medication were classified as "qualifying attacks". Accordingly, only "qualifying attacks" were documented and considered for the analysis. Consequently, no data are available on how many randomised subjects experienced an on-study HAE attack that was eligible for treatment with the study medication but did not receive the study medication to treat their attack. In this respect, no data could be provided on the number of eligible HAE attacks that actually occurred in the study. Similarly, no data are available on how many HAE attacks occurred without compliance with all criteria for the definition of an "eligible attack".

A total of 264 qualifying HAE attacks were considered for the analysis; of these, 87 were treated with the on-label dosage of 300 mg sebetralstat, and 84 with placebo.

Study duration

The KONFIDENT study was conducted on an event-driven basis. According to the study protocol, each randomised subject should have undergone a complete treatment sequence for three different attacks, and accordingly been treated with 300 mg sebetralstat, 600 mg sebetralstat and placebo respectively. According to the study documents, the initial plan was

[3] The following criteria, amongst others, had to be met for the definition of an "eligible attack": - no severe laryngeal attack; - the onset of the attack had to be identifiable; - a washout phase of at least 48 hours had to be observed between treatment with conventional on-demand medication or study medication; for further criteria, see the benefit assessment, Chapter 2.2.

for each one of the 84 subjects to receive all three test preparations in order to complete the study. However, according to the pharmaceutical company's statements during the written statement procedure, the occurrence of at least 84 qualifying attacks per treatment was used as the criterion for study termination. This minimum number of qualifying attacks ultimately led to premature termination of the study, regardless of whether the treated subjects had completed the full treatment sequence or not. The analysis in the study report was carried out after 264 qualifying HAE attacks had occurred, regardless of the subject concerned or the treatment sequence. By this point in time, a total of 42 of the 110 treated subjects (just under 40 %) had withdrawn from the study prematurely; they had experienced fewer than 3 qualifying attacks and were therefore unable to complete the treatment sequence to which they had been randomised.

It is not known how long the patients were followed up in the study overall.

Relevant sub-population for the benefit assessment

According to the study report, 71 subjects – representing 64.5 % of the analysis population – were treated with both the on-label dosage of 300 mg sebetralstat and placebo. Data correlation can be assumed in these subjects. Since the data from the dossier did not take into account the correlation of the sample, the data, which were submitted subsequently during the written statement procedure and take into account the 2x2 crossover design and the data correlation, are used here. However, the data submitted subsequently only include analyses for 61 subjects who received both test preparations – 300 mg sebetralstat and placebo. It is unclear why these data differ from the figure of 71 subjects stated in the study report.

With regard to the analysis of the endpoints collected, acceptable return rates of just over 70% are available for the period up to four hours after baseline, such that these data are used for the benefit assessment.

Mortality

Deaths were documented as part of the safety assessment throughout the study duration. There were no deaths in the KONFIDENT study. Due to its study design, the KONFIDENT study is unsuitable for investigating endpoints in the mortality category.

Morbidity

Patient Global Impression of Change (PGI-C)

The PGI-C was used for patient-reported assessment of the extent of change in the HAE attack compared with the onset of the attack with intake of the study medication. The question regarding change in the symptoms of the HAE attack was answered using a 7-point scale – "Very Much Improved"; "Much Improved"; "Minimally Improved", "No Change"; "Minimally Worse"; "Much Worse"; "Very Much Worse".

The PGI-C endpoint was pre-specified as the primary endpoint in the KONFIDENT study. For analysis purposes, a (confirmed) improvement in the PGI-C was defined as at least "Minimally Improved" at two consecutive survey time points. Responder analyses up to four hours after baseline are taken into account here.

For the endpoint of confirmed symptom improvement, assessed using the PGI-C within four hours, there was a statistically significant advantage of sebetralstat over placebo.

Patient Global Impression of Severity (PGI-S)

The PGI-S was used for patient-reported assessment of the severity of the HAE attack after intake of the study medication. The question regarding the current assessment of the severity of symptoms was answered using a 5-point scale – "none"; "mild"; "moderate"; "severe"; "very severe".

Improvement in the severity of the attack was defined as the improvement by at least one category compared with the baseline assessment. Responder analyses up to four hours after baseline are taken into account here.

For the endpoint of reduction in attack severity, assessed using the PGI-S within four hours, there was a statistically significant advantage of sebetralstat over placebo.

HAE symptoms: Abdominal pain, skin pain, skin swelling

The endpoint of HAE symptoms comprises the HAE symptoms "abdominal pain", "skin pain" and "skin swelling", each of which was assessed using a separate 101-point visual analogue scale (VAS). A score of "0" meant no pain or symptoms, and a score of "100" meant very severe pain or symptoms.

The baseline value was defined as the last non-missing value prior to or at the time of the first intake of the study medication. The responder analyses of the improvement with the relevant 15% clinical threshold up to four hours after baseline were considered here.

For the endpoint of HAE symptoms of abdominal pain, skin pain and skin swelling, assessed using the visual analogue scale within four hours, there was no statistically significant difference between sebetralstat and placebo.

General Anxiety – Numerical Rating Scale (GA-NRS)

The patient-reported GA-NRS questionnaire consists of a single question to assess patients' current anxiety triggered by an HAE attack. The endpoint is considered a patient-relevant endpoint in the present operationalisation.

The question regarding the severity of anxiety was answered using a numerical rating scale (NRS) with the scores: "0": "no anxiety"; "1 to 3": "mild anxiety"; "4 to 6": "moderate anxiety"; and "7 to 10": "extreme anxiety".

Improvement in anxiety was defined as the improvement by at least 2 points in accordance with the 15% clinical threshold, compared with the baseline assessment.

For the analysis, a threshold value of at least 2 points above baseline was set. Accordingly, the results for this endpoint were not taken into account for subjects who had a lower baseline score (no anxiety, mild anxiety). This results in such a selection of the study population during the analysis that data on the GA-NRS endpoint are available for only 34 subjects, representing 30% of the study population (N = 110). This approach violates the ITT principle. This endpoint is therefore not considered for the benefit assessment.

Quality of life

In the KONFIDENT study, no endpoints of the health-related quality of life category were assessed.

Side effects

In the KONFIDENT study, safety endpoints were collected for each qualifying attack, from the time the study medication was first taken until the final study visit or the end of treatment. The safety endpoints were collected during a teleconsultation following an HAE attack.

Adverse events (AEs) were attributed to the last study medication administered in accordance with the treatment sequence, and were monitored until resolution.

At least one AE occurred in the 17 HAE attacks treated with sebetralstat and the 17 HAE attacks treated with placebo respectively. Overall, one subject in the sebetralstat arm experienced a severe AE and an SAE. No subject discontinued the study due to an AE.

Overall, no analyses of the safety endpoints were submitted which adequately take into account the data correlation and incorporate the 2x2 crossover design at the subject level. Furthermore, no data are available on the median duration of observation for the enrolled patients. Further uncertainty arises from the method used for collection of the safety endpoints being linked to the occurrence of an HAE attack. Consequently, it cannot be ruled out with certainty that observation periods for subjects without qualifying attacks may not have been reported.

It should also be noted that the premature termination of the study was viewed critically by the regulatory authority (EMA). As a result, only 68 patients out of the originally planned 84 subjects were treated with all the allocated test preparations. Furthermore, due to the crossover study design, the small number of HAE attacks that occurred, and the short duration of exposure to sebetralstat, a long duration of observation of the patients whilst they were receiving the on-label dosage of sebetralstat was not possible.

Overall, it is not possible to make a definitive assessment of the safety endpoints on the basis of the available documents, given the uncertainty mentioned.

Overall assessment

This assessment is based on data from the label-enabling, 3x3 crossover KONFIDENT randomised controlled trial, comparing two doses of sebetralstat with placebo for the acute treatment of HAE attacks. The study investigated adults and adolescents aged 12 years and older with confirmed HAE diagnosis who had experienced two HAE attacks within three months prior to the start of the study.

The only relevant factor for the benefit assessment is the comparison of the on-label dosage of sebetralstat with placebo in a 2x2 crossover design, taking into account the correlation of the sample. Therefore, only the subsequently submitted analyses of the sub-population of 61 subjects (out of the 110 subjects treated in the study) are used for the benefit assessment.

There were no deaths in the KONFIDENT study.

In the morbidity endpoint category, the endpoints of symptom improvement (PGI-C), reduction in attack severity (PGI-S) and the HAE symptoms (VAS) of abdominal pain, skin pain and skin swelling were used for quantification of the additional benefit. For the endpoints of symptom improvement and reduction in attack severity, there was a statistically significant advantage in favour of sebetralstat over placebo in each case. For the aforementioned HAE symptoms in contrast, there was no statistically significant difference between sebetralstat and placebo.

Endpoints in the health-related quality of life category were not collected in the study.

In the KONFIDENT study, safety endpoints were assessed at the level of HAE attacks treated with the study medication, and not on the basis of the randomised patients. No data are available on the exact observation period for the treated subjects. Due to this method used for data collection, it cannot be ruled out with certainty that AEs may not have been reported for different observation periods. In addition, the regulatory authority criticised the very short duration of exposure to sebetralstat and the small number of attacks treated, which resulted from the premature termination of the study. The procedure followed in the study meant that patients treated with sebetralstat could not be monitored for a sufficiently long period. For this reason, it is not possible to make a definitive assessment of the safety endpoints on the basis of the KONFIDENT study.

Due to the study design, the overall analysis showed relevant findings on the additional benefit of sebetralstat in the morbidity endpoint category only for a sub-population of the enrolled subjects. For the endpoints of symptom improvement (PGI-C) and reduction in attack severity (PGI-S), there was a statistically significant advantage of sebetralstat over placebo in each case. The data presented are unsuitable overall for quantifying the extent of the additional benefit as no endpoints were collected in the other endpoint categories of mortality, quality of life and side effects, or a definitive assessment is not possible due to the method used for data collection and analysis.

A non-quantifiable additional benefit of sebetralstat is identified for the symptomatic treatment of acute HAE attacks, since the scientific data does not allow quantification.

Significance of the evidence

Due to the crossover design of the KONFIDENT study as well as methodological limitations in the conduct and analysis of the study, there is significant uncertainty that limit the significance of the evidence overall.

Only the "qualifying" attacks treated with the study medication were documented and analysed in the study, not the total number of HAE attacks that occurred. It is therefore not possible to make statements on how many of the total number of attacks that occurred were actually treated. Another point of criticism is the lack of information on the exact observation period for the enrolled patients. Furthermore, the pharmaceutical company's premature termination of the study is incomprehensible, as it meant that a significant percentage of the randomised patients were unable to complete the full treatment sequence with the three study medications as planned.

The transferability to the German healthcare context is also limited. Although patients were able to receive conventional therapy with C1 INH, icatibant and ecallantide for the treatment of HAE attacks, this was only permitted under predefined conditions. Furthermore, the administration of conventional therapy automatically resulted in the exclusion of these subjects from the analyses. This does not meet the currently recognised standard of care for the acute treatment of HAE attacks.

Taking into account the identified limitations and given the study's high risk of bias, the reliability of data is classified in the "hint"
category.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Ekterly with the active ingredient sebetralstat. Ekterly was approved as an orphan drug for symptomatic treatment of acute attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

For the benefit assessment, data from the label-enabling KONFIDENT study with a 2x2 crossover design, comparing the on-label dosage of sebetralstat with placebo for the treatment of acute HAE attacks in subjects aged 12 years and older, were used.

The analysis of the results relates to attacks treated with sebetralstat or placebo within 4 hours.

There were no deaths in the study. For the endpoints of symptom improvement, assessed using the PGI-C, and reduction in attack severity, assessed using the PGI-S, in the morbidity endpoint category, there was a statistically significant advantage in favour of sebetralstat over placebo. In contrast, for the symptoms of abdominal pain, skin pain and skin swelling, assessed using the VAS, there was no statistically significant difference between the treatment groups. No data were collected in the category of health-related quality of life. It is not possible to make a definitive assessment of the side effects due to methodological shortcomings. In the overall assessment, the presented data are unsuitable overall for quantifying the extent of the additional benefit. A "hint" is assumed with regard to the reliability of data due to the high risk of bias and other limitations.

In summary, there is a hint for a non-quantifiable additional benefit of sebetralstat for the acute treatment of HAE attacks in patients aged 12 years and older, since the scientific data does not allow quantification.

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. Most of the figures are mathematically comprehensible. The lower limit is within a plausible range overall. In contrast, the upper limit tends to be underestimated. With regard to the upper limit, the selection concept used to determine the patient number as part of the routine data analysis is not clear. According to the product information for sebetralstat, administration thereof is regardless of whether patients receive routine prophylaxis or not. By selecting prescribed active ingredients based on a defined threshold for acute or preventive treatment, patients whose documented prescriptions were assigned to preventive treatment may be overlooked, even though they also received the same active ingredient for acute treatment. This results in a possible underestimation of the upper limit.

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 Ekterly (active ingredient: sebetralstat) at the following publicly accessible link (last access: 4 February 2026):

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

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

According to the product information, therapy discontinuation should be considered in patients with normal C1-INH (nC1-INH) if no clinical response is observed.

2.4 Treatment costs

The treatment costs are based on the requirements in the product information and the information listed in the LAUER-TAXE® (last revised: 1 February 2026).

The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

The annual treatment costs are different from patient to patient depending on the frequency of attacks. According to the information in the EPAR, patients with hereditary angioedema (HAE) experience HAE attacks on average every 3 weeks or more[4] frequently, up to once a week. To ensure comparability, a representative range is established for the calculation of costs relating to the frequency of attacks. For the treatment duration within a year, the treatment of just one attack every three weeks is taken into account as the lower limit, and one attack every week as the upper limit.

[4] European Medicines Agency (EMA). Ekterly (sebetralstat): European public assessment report EMEA/H/C/006211/0000 [online]. Amsterdam (NED): EMA; 04.02.2026. [accessed on: 04.02.2026]. URL: https://www.ema.europa.eu/en/documents/assessment-report/ekterly-epar-public-assessment-report_en.pdf

According to the product information, a 300 mg tablet of sebetralstat is administered at the first sign of an impending attack; if the response is inadequate or if symptoms worsen or recur, a second 300 mg dose may be taken 3 hours after the first dose. With regard to consumption, the administration of 1 or 2 doses per attack is therefore taken into account.

Treatment period:

Designation of the therapy	Treatment mode	Number of treatments/ patient/ year	Treatment duration/ treatment (days)	Treatment days/ patient/ year
Medicinal product to be assessed				
Sebetralstat	1 – 2 x per HAE attack	17.4 – 52.1	1	17.4 – 52.1

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					
Sebetralstat	300 mg	300 mg – 600 mg	1 x 300 mg – 2 x 300 mg	17.4 – 52.1	17.4 x 300 mg – 104.2 x 300 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.

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					
Sebetralstat	6 FCT	€ 17,707.74	€ 1.77	€ 1,008.00	€ 16,697.97
Abbreviations: FCT = film-coated tablets					

LAUER-TAXE® last revised: 1 February 2026

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.

No additionally required SHI services are taken into account for the cost representation.

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 data from the product 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 statutory 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:

Adults and adolescents aged 12 years and older with an acute attack of hereditary angioedema

No medicinal product with new active ingredients for use in combination therapy in compliance with the requirements of Section 35a, paragraph 3, sentence 4 SGB V.

References:
Product information for sebetralstat (Ekterly); Ekterly 300 mg film-coated tablets; last revised: September 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 Ekterly 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 section 2.7.3 (Summary of Clinical Efficacy) and 2.7.4 (Summary of Clinical Safety) of the authorisation dossier in the therapeutic indication for which marketing authorisation has been applied for. In addition, studies, which were conducted in whole or in part within the therapeutic indication described in this document, and in which the company was a sponsor or is otherwise financially involved, must also be indicated.

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% (7.39%) of the total number of study participants according to the information provided by the pharmaceutical company.

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

On 14 October 2025, the pharmaceutical company submitted a dossier for the benefit assessment of sebetralstat to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 VerfO.

The benefit assessment of the G-BA was published on 15 January 2026 together with the IQWiG assessment of treatment costs and patient numbers on the G-BA website (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting written statements was 5 February 2026.

The oral hearing took place on 23 February 2026.

An amendment to the benefit assessment with a supplementary assessment was submitted on 13 March 2026.

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 Subcommittee's session on 24 March 2026, and the draft resolution was conclusively discussed.

At their session on 2 April 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee on Medicinal Products	13 January 2026	Information of the benefit assessment of the G-BA
Working group Section 35a	17 February 2026	Information on written statements received; preparation of the oral hearing
Subcommittee on Medicinal Products	23 February 2026	Conduct of the oral hearing
Working group Section 35a	3 March 2026 17 March 2026	Consultation on the dossier assessment by the G-BA, the assessment of treatment costs and patient numbers by the IQWiG, and the evaluation of the written statement procedure
Subcommittee on Medicinal Products	24 March 2026	Concluding discussion of the draft resolution
Plenum	2 April 2026	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 2 April 2026

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

Prof. Hecken