Gemeinsamer Bundesausschuss

# Justification

for 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
Donidalorsen (hereditary angioedema, prevention, ≥ 12 years)

From 20 August 2026

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## 1. Legal basis

According to Section 35a paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) 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.

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 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 donidalorsen on 1 March 2026 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, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Chapter 5, Section 8, paragraph 1, number 1 of the Rules of Procedure (VerfO), the pharmaceutical company submitted the final dossier to the G-BA on 27 February 2026.

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on 1 June 2026 on the G-BA website at (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 donidalorsen 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. 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 donidalorsen.

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

Dawnzera is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in adults and adolescents aged 12 years and older.

**Therapeutic indication of the resolution (resolution of 20.08.2026):**

See the approved therapeutic indication

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Adults and adolescents aged 12 years and older with recurrent attacks of hereditary angioedema for whom routine prevention is indicated

Appropriate comparator therapy for donidalorsen:

- Routine prevention with 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 according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

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

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

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 they determine 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 for 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 for 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 donidalorsen, berotralstat, C1 esterase inhibitors, garadacimab, lanadelumab and 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 (pursuant to Section 35a SGB V) of medicinal products with new active ingredients in adolescents aged 12 years and older and adults are available for the therapeutic indication under assessment (Annex XII of the Pharmaceuticals Directive):

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

– Garadacimab from 21 August 2025

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, the causative gene mutation cannot be identified in many cases, so that the pathogenesis of HAE type III has not yet been 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 applicable international guideline and involved scientific-medical societies recommend long-term prevention with either a C1 esterase inhibitor or a plasma kallikrein inhibitor such as lanadelumab or berotralstat as first-line therapy. These therapies can reduce the number, duration and severity of HAE attacks. The use of tranexamic acid for long-term prevention, by contrast, is not recommended. An early benefit assessment was conducted for the active ingredients lanadelumab and berotralstat respectively. An additional benefit of either active ingredient compared to the appropriate comparator therapy is not proven.

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

There are as yet no guideline-based recommendations for the active ingredient garadacimab, which was approved in February 2025. As part of the early benefit assessment, a hint of a considerable additional benefit of garadacimab compared with the appropriate comparator therapy (berotralstat) was identified. However, it is not yet possible to make a definitive assessment of the significance of garadacimab in healthcare. The active ingredient is therefore considered as not being part of the appropriate comparator therapy.

In the overall assessment, routine prevention with a C1 esterase inhibitor or lanadelumab or berotralstat is 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 therapy options are equally appropriate for the comparator therapy.

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

Any change to the appropriate comparator therapy requires a decision by the G-BA based on a prior review of the criteria set out in Chapter 5 Section 6, paragraph 3 VerfO.

### 2.1.3 Extent and probability of the additional benefit

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

There is a hint of a minor additional benefit for adults and adolescents aged 12 years and older with recurrent attacks of hereditary angioedema for whom routine prevention is indicated.

Justification:

In the absence of direct comparator studies versus the appropriate comparator therapy, the pharmaceutical company submitted an adjusted indirect comparison between donidalorsen and berotralstat via the placebo bridge comparator for this benefit assessment. They cite the OASIS-HAE study on the intervention side and the APeX-2 and APeX-J studies on berotralstat on the appropriate comparator therapy side.

OASIS-HAE study (study on donidalorsen)

The OASIS-HAE study is a double-blind, randomised study comparing donidalorsen at two different dosing intervals (monthly and every 2 months) with placebo in subjects aged 12 years and older with HAE type I or HAE type II. The placebo-controlled treatment phase lasted 24 weeks.

In accordance with the inclusion criteria, subjects were required to have a documented diagnosis of HAE type I or HAE type II. This diagnosis was characterised by episodes of subcutaneous or mucosal, non-itchy swelling, and was confirmed, among other factors, by a C1 esterase inhibitor (C1-INH) deficiency (reduced functional C1-INH activity in the range of < 40% of the normal value). At least 2 HAE attacks must have occurred within 56 days during the run-in phase.

In the OASIS-HAE study, 46 patients were randomised to receive treatment with donidalorsen once a month and 23 patients to receive donidalorsen every 2 months. 22 subjects were enrolled in the placebo arm; however, there is no information available on how many of them were treated with placebo once a month or every 2 months. The intervention arm with a dosing interval of every 2 months does not comply with the approved dosage and is therefore not considered further in this benefit assessment. The study permitted on-demand treatment of HAE attacks.

The primary endpoint of the study was the time-normalised number of medically confirmed HAE attacks per 4 weeks during the 24-week treatment phase. Secondary endpoints included additional endpoints in the categories of morbidity and health-related quality of life, as well as adverse events (AEs).

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

The APeX-2 and APeX-J studies are double-blind, randomised studies on berotralstat in subjects aged 12 years and older with HAE type I or type II. The first placebo-controlled

treatment phase lasting 24 weeks and the treatment arm with berotralstat at a dosage of 150 mg are relevant for this benefit assessment.

According to the inclusion criteria of the studies, subjects were required to have a clinical diagnosis of HAE type I or II, which could be confirmed, among other factors, by C1-INH deficiency (attributable to reduced functional C1-INH activity in the range < 50% of the normal value). At least 2 HAE attacks must have occurred during the run-in phase, within a period of 14 to 56 days (in APeX-2) or within 56 days (in APeX-J).

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

The studies permitted on-demand treatment of HAE attacks. 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 analysed.

The OASIS HAE, APeX-2 and APeX-J studies all have a similar study design. 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 androgens, tranexamic acid and oestrogen-containing medicinal products between the OASIS-HAE 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 placebo bridge comparator overall.

Extent and probability of the additional benefit

Mortality

The results on overall mortality are based on the data on fatal adverse events (AEs). No deaths occurred in the OASIS-HAE, APeX-2 and APeX-J studies.

Morbidity

*HAE attacks*

The occurrence of HAE attacks was reported by patients using the diary-like Angioedema Activity Score (AAS) questionnaire in the OASIS-HAE study and via entries in an electronic diary in the APeX-2 and APeX-J studies. The presence of an attack was confirmed by the principal investigators or independent experts.

In the OASIS-HAE study, an HAE attack was defined by the presence of at least one defined symptom at a minimum of one specific site. In the APeX-2 and APeX-J studies, an HAE attack was defined by the presence of swelling symptoms. 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 medical care or have demonstrably led to a functional impairment.

A new attack had to be distinct in time from a previous attack, i.e. it was not permitted to begin within 24 hours (in the OASIS-HAE study) or 48 hours (in the APeX-2 and APeX-J studies) following the end of the previous HAE attack.

Overall, HAE attacks were captured in the OASIS-HAE, APeX-2 and APeX-J studies in a sufficiently similar manner. The differences described do not call into question the performance of an adjusted indirect comparison via the placebo bridge comparator. However, the extent to which the severity grading was comparable across the studies remains unclear; consequently, given the present data basis, analyses of all HAE attacks were taken into account, regardless of severity.

The most important therapeutic goal in the present therapeutic indication is complete control of the disease and thus, attack-free status. However, the prevention of HAE attacks is also of crucial importance. Therefore, the operationalisation of the monthly rate of HAE attacks and the attack-free status are used here.

The patient's monthly rate of HAE attacks during the treatment phase was operationalised as the number of HAE attacks divided by the duration of observation (in days) of the study participants from the start of treatment, multiplied by 28 days.

For the endpoint "monthly rate of HAE attacks", the adjusted indirect comparison showed a statistically significant difference in favour of donidalorsen compared to berotralstat.

In the present analyses of the indirect comparison, attack-free status is defined as the percentage of study participants who did not experience any HAE attacks during the treatment phase. For this operationalisation, the adjusted indirect comparison did not show any statistically significant difference between donidalorsen and berotralstat.

In addition, the pharmaceutical company also presented analyses of the monthly rate of laryngeal HAE attacks in the dossier. Although laryngeal attacks are very rare and the monthly rate of laryngeal HAE attacks is already factored into the overall monthly rate of HAE attacks, the results are nevertheless presented here due to the potentially life-threatening course of laryngeal HAE attacks. For this endpoint, there was no statistically significant difference.

*Activity impairment (assessed using WPAI)*

The patient-relevant endpoint "activity impairment" was assessed using question 10 of the Work Productivity and Activity Impairment (WPAI) PLUS Classroom Impairment Questions: specific health problem (CIQ:SHP) in the OASIS-HAE study, and using question 6 of the WPAI in the APeX-2 and APeX-J studies. The two questions are considered sufficiently comparable for the indirect adjusted comparison.

The analyses of the change from the start of the study to the end of treatment (submitted by the pharmaceutical company for the WPAI) using a mixed model with repeated measures (MMRM) for the indirect comparison of donidalorsen with berotralstat are used for the present benefit assessment.

For the endpoint of activity impairment, there was no statistically significant difference.

*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. A value of 0 corresponds to the worst perceivable health status and a value of 100 to the best perceivable health status. The submitted analyses of the change from the start of the study to the end of treatment using the MMRM for an indirect comparison of donidalorsen with berotralstat are used for the benefit assessment.

For the endpoint of health status, there was no statistically significant difference.

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. The submitted analyses of the change from the start of the study to the end of treatment using the MMRM for an indirect comparison of donidalorsen with berotralstat in adults are used for the benefit assessment.

For the endpoint of health-related quality of life, as assessed using the AE-QoL, the adjusted indirect comparison showed a statistically significant difference in the AE-QoL total score in favour of donidalorsen over berotralstat. The 95% confidence interval of the standardised mean difference (SMD) is however not completely outside the irrelevance range from - 0.2 to 0.2, so that it cannot be concluded that the effect is clinically relevant.

Side effects

*Serious AEs (SAEs) and discontinuation due to AEs*

For the endpoints of SAEs and discontinuation due to AEs, the adjusted indirect comparison did not show any statistically significant difference between donidalorsen and berotralstat in either case.

*Severe AEs*

There was no suitable operationalisation for the "severe AEs" endpoint in the OASIS-HAE study. For some of the AEs, it is unclear how the severity grading was performed, whereas the severity of other AEs was assessed by the principal investigators as mild, moderate or severe, taking into account the need for treatment and the impairment of the activities of daily living. This is an inadequate operationalisation of severe AEs in demarcation from non-severe AEs.

For the endpoint of severe AEs, no suitable data are therefore available for the adjusted indirect comparison between donidalorsen and berotralstat.

Overall assessment

Results from an adjusted indirect comparison are available for the assessment of the additional benefit of donidalorsen for use in the routine prevention of recurrent attacks of hereditary angioedema (HAE). For this purpose, data on donidalorsen from the OASIS-HAE study was compared with berotralstat from the APeX-2 and APeX-J studies via the placebo bridge comparator. 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 category in the studies analysed.

In the morbidity category, all confirmed HAE attacks were considered for the endpoint "HAE attacks", regardless of severity grade and site. For the operationalisation as "monthly rate of

HAE attacks", there was a statistically significant advantage of donidalorsen over berotralstat. For the further operationalisation as "attack-free status", which defines the percentage of subjects without HAE attacks during the treatment phase, there were no statistically significant differences between donidalorsen and berotralstat.

For the other endpoints "activity impairment" (assessed using the WPAI) and "health status" (assessed using the EQ-5D VAS) in the endpoint category of morbidity, there was no statistically significant difference in either case.

In the endpoint category of health-related quality of life, as assessed using the disease-specific Angioedema Quality of Life (AE-QoL) questionnaire, an adjusted indirect comparison showed no clinically significant difference between donidalorsen and berotralstat.

For the endpoints of SAEs and discontinuation due to AEs in the endpoint category of side effects, the adjusted indirect comparison showed no statistically significant difference between donidalorsen and berotralstat in either case.

An advantage of donidalorsen was observed in terms of reducing the monthly rate of HAE attacks. There are no advantages in terms of other morbidity endpoints, such as general health status or health-related quality of life. In the overall assessment, the extent of the additional benefit is rated as minor.

Reliability of data (probability of the additional benefit)

No direct comparator data versus the appropriate comparator therapy are available for the assessment of the additional benefit of donidalorsen. Therefore, the results of the placebo-controlled OASIS-HAE as well as APeX-2 and APeX-J studies were considered in an adjusted indirect comparison between donidalorsen and berotralstat. Due to the limitations in the reliability of data associated with the performance of an adjusted indirect comparison, a hint of the identified additional benefit of donidalorsen is assumed.

### 2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Dawnzera with the active ingredient donidalorsen, 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 versus the appropriate comparator therapy, the pharmaceutical company submitted an adjusted indirect comparison between donidalorsen and berotralstat via the placebo bridge comparator. The OASIS-HAE study on donidalorsen is sufficiently similar to the APeX-2 and APeX-J studies on berotralstat, meaning that the adjusted indirect comparison is considered suitable for the benefit assessment and is used accordingly.

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.

For the "HAE attacks" endpoint operationalised as the "monthly rate of HAE attacks" In the endpoint category of morbidity, there was a statistically significant advantage of donidalorsen over berotralstat. For the further operationalisation "attack-free status" or for the endpoints

"activity impairment" (assessed using the WPAI) and "health status" (assessed using the EQ-5D VAS), there were no statistically significant differences.

In the endpoint category of health-related quality of life, as assessed using the disease-specific Angioedema Quality of Life (AE-QoL) questionnaire, an adjusted indirect comparison showed no clinically relevant difference between donidalorsen and berotralstat.

For the endpoints of SAEs and discontinuation due to AEs in the endpoint category of side effects, the adjusted indirect comparison showed no statistically significant differences between donidalorsen and berotralstat.

An advantage of donidalorsen was observed in terms of reducing the monthly rate of HAE attacks. There are no advantages in terms of other morbidity endpoints, such as general health status or health-related quality of life. In the overall assessment, the extent of the additional benefit is rated as minor.

The reliability of data is limited overall as the results are based on an adjusted indirect comparison. This provides a hint of a minor additional benefit.

## 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 an expert survey from 2018, in which patients who underwent routine prevention at the time of the survey were assessed.

The pharmaceutical company's approach to calculating the number of patients in the SHI target population is essentially the same as the approach taken in the benefit assessment procedure for garadacimab by resolution of 21 August 2025. However, this calculation of patient numbers is based on more recent population figures and the number of SHI-insured patients.

## 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 Dawnzera (active ingredient: donidalorsen) at the following publicly accessible link (last access: 11 August 2026):

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

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

Therapy discontinuation should be considered for patients with HAE with normal C1-INH (nC1-INH) who have shown an insufficient reduction in attacks after 4 months of treatment.

## 2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 June 2026). The calculation of treatment costs is generally based on the last revised LAUER-TAXE® version following the publication of the benefit assessment.

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.

Adults and adolescents aged 12 years and older with recurrent attacks of hereditary angioedema for whom routine prevention is indicated

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 | | | | |
| Donidalorsen<br>Year 1<br>Subsequent years | 1 x every 30.4 days, from month 4 onwards<br>1 x every 30.4 days or<br>1 x every 60.8 days | 7.5 – 12.0 | 1 | 7.5 – 12.0 |
| | 1 x every 30.4 days or<br>1 x every 60.8 days | 6.0 – 12.0 | 1 | 6.0 – 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 | 91.3 – 121.7 |
| Lanadelumab | Continuously, every 14 – 28 days | 13.0 – 26.1 | 1 | 13.0 – 26.1 |
| Berotralstat | Continuously, 1 x daily | 365.0 | 1 | 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 | | | | | |
| Donidalorsen 1st year | 80 mg | 80 mg | 1 x 80 mg | 7.5 - 12 | 7.5 x 80 mg – 12 x 80 mg |
| Subsequent years | 80 mg | 80 mg | 1 x 80 mg | 6 - 12 | 6 x 80 mg – 12 x 80 mg |
| Appropriate comparator therapy | | | | | |
| Routine prevention with C1 esterase inhibitor or lanadelumab or berotralstat | | | | | |
| C1 esterase inhibitor[2] | 1,000 I.U. | 1,000 I.U. | 2 x 500 I.U. | 91.3 – 121.7 | 182.6 x 500 I.U. – 243.4 x 500 I.U. |
| Lanadelumab[2] | 300 mg | 300 mg | 1 x 300 mg | 13.0 – 26.1 | 13.0 x 300 mg – 26.1 x 300 mg |
| Berotralstat[2] | 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.

[2] 1st year and subsequent years

**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 | | | | | |
| Donidalorsen 80 mg | 3 SFI | € 76,044.93 | € 1.77 | € 4,339.65 | € 71,703.51 |
| Appropriate comparator therapy | | | | | |
| C1 esterase inhibitor 500 I.U. | 2 PSI | € 2,209.62 | € 1.77 | € 122.90 | € 2,084.95 |
| Lanadelumab 300 mg | 6 SFI | € 63,877.17 | € 1.77 | € 3,644.75 | € 60,230.65 |
| Berotralstat 150 mg | 98 HC | € 51,632.54 | € 1.77 | € 2,945.45 | € 48,685.32 |
| Abbreviations: HC = hard capsules; SFI = solution for injection; PSI = powder and solvent for solution for injection | | | | | |

LAUER-TAXE® last revised: 15 June 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.

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.

## 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 11 March 2025, the Subcommittee on Medicinal Products determined the appropriate comparator therapy.

On 27 February 2026, the pharmaceutical company submitted a dossier for the benefit assessment of donidalorsen to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 VerfO.

By letter dated 27 February 2026 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 donidalorsen.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 May 2026, and the written statement procedure was initiated with publication on the G-BA website on 1 June 2026. The deadline for submitting written statements was 22 June 2026.

The oral hearing was held on 6 July 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 were discussed at the Subcommittee's session on 11 August 2026, and deliberation of the draft resolution was concluded.

At their session on 20 August 2026, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Gemeinsamer Bundesausschuss

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee on Medicinal Products | 11 March 2025 | Determination of the appropriate comparator therapy |
| Working group Section 35a | 1 July 2026 | Information on written statements received; preparation of the oral hearing |
| Subcommittee on Medicinal Products | 6 July 2026 | Conduct of the oral hearing |
| Working group Section 35a | 15 July 2026<br>5 August 2026 | Consultation on the dossier assessment by the IQWiG and evaluation of the written statement procedure |
| Subcommittee on Medicinal Products | 11 August 2026 | Concluding discussion of the draft resolution |
| Plenum | 20 August 2026 | Adoption of the resolution on the amendment of the Pharmaceuticals Directive |

Berlin, 20 August 2026

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

Dr Optendrenk