Gemeinsamer Bundesausschuss

# Justification

of the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive: Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients according to Section 35a (SGB V) Lanadelumab (new therapeutic indication: hereditary angioedema, prevention, 2 to < 12 years)

of 6 June 2024

**Contents**

## 1. Legal basis

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

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

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

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

## 2. Key points of the resolution

The active ingredient lanadelumab (Takhzyro) was listed for the first time on 1 October 2020 in the "LAUER-TAXE®", the extensive German registry of available drugs and their prices.

Takhzyro is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and of the Council of 16 December 1999.

Within the previously approved therapeutic indication, the sales volume of lanadelumab with the statutory health insurance at pharmacy sales prices, including value-added tax exceeded € 30 million. Evidence must therefore be provided for lanadelumab in accordance with Section 5, paragraph 1 through 6 VerfO, and the additional benefit compared with the appropriate comparator therapy must be demonstrated.

On 15 November 2023, lanadelumab received marketing authorisation for a new therapeutic indication to be classified as a major type 2 variation as defined according to Annex 2, number 2, letter a to Regulation (EC) No. 1234/2008 of the Commission of 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334 from 12.12.2008, sentence 7).

On 13 December 2023, the pharmaceutical company has submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient lanadelumab with the new therapeutic indication "TAKHZYRO is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 2 to < 12 years" in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication).

The G-BA commissioned the IQWiG to carry out the dossier assessment. The benefit assessment was published on 15 March 2024 on the G-BA website (www.g-ba.de), therefore initiating the written statement procedure. In addition, an oral hearing was held.

Based on 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 (if necessary, also the addendum to the benefit assessment prepared by IQWiG), the G-BA decided on the question on whether an additional benefit of lanadelumab compared with the appropriate comparator therapy could be determined – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V. In order to determine the extent of the additional benefit, the G-BA has evaluated the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7 VerfO. The methodology proposed by IQWiG according to the General Methods was not used in the benefit assessment of rucaparib – Annex XII - Resolutions on the benefit assessment of medicinal products with new active ingredients according to Section 35a SGB V.

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

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

### 2.1.1 Approved therapeutic indication of Lanadelumab (Takhzyro) in accordance with the product information

TAKHZYRO is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in patients aged 2 years and older.

**Therapeutic indication of the resolution (resolution of 6 June 2024):**

TAKHZYRO is indicated for routine prevention of recurrent attacks of hereditary angioedema (HAE) in children 2 to less than 12 years of age.

### 2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

<u>Children 2 to less than 12 years of age with recurrent attacks of hereditary angioedema</u>

Appropriate comparator therapy for routine prevention:

- C1 esterase inhibitor

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.

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.

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

on 1. In the present therapeutic indication, the active ingredients C1 esterase inhibitor (from the age of 6 years) and the antifibrinolytic tranexamic acid are approved for long-term prevention of hereditary angioedema in addition to the active ingredient to be assessed.

on 2. For the treatment of hereditary angiooedema, no non-medical measures can be considered as the appropriate comparator therapy.

on 3. There are no relevant resolutions by the G-BA for the age group in this therapeutic indication. For the therapeutic indication of hereditary angioedema in adults and adolescents, resolutions on the early benefit assessment of the active ingredient lanadelumab of 4 November 2021 (reassessment after exceeding the EUR 50 million turnover limit) and for the active ingredient berotralstat of 2 December 2021 are available.

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.

It is assumed that the patient population in this therapeutic indication of lanadelumab concerns patients who are characterised by a deficiency (HAE type I) or a defect (HAE type II) of the C1 esterase inhibitor and therefore require substitution.

The goal of treatment for affected patients is to reduce the resulting angioedema or HAE attacks.

If acute treatment of HAE attacks alone is no longer sufficient, the guidelines recommend long-term prevention with C1 esterase inhibitors, regardless of the patients' age (Maurer M. et al. 2022 guideline[1] and Betschel S et al. 2019 guideline[2]). This therapy can reduce the number, duration and severity of HAE attacks. For patients aged < 6 years, the antifibrinolytic tranexamic acid is the only approved therapy option, but is recommended as a secondary therapy option compared to C1 esterase inhibitors according to current guidelines (Maurer M. et al. 2022 guideline[3] and Betschel S et al. 2019 guideline[4]).

Accordingly, the off-label use of C1 esterase inhibitors is considered the therapy standard in the therapeutic indication to be assessed, according to the generally recognised state of medical knowledge, and is generally preferable to the medicinal product previously approved in the therapeutic indication, according to Section 6, paragraph 2, sentence 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV).

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1 Maurer M. et al. 2022*: "The preferred therapy in children younger than 12 years of age for long- term prophylaxis is pdC1- INH"*

2 Betschel S et al. 2019: *"When long-term prophylaxis is indicated in paediatric patients, pdC1-INH is the treatment of choice. (Level of Evidence: Consensus; Strength of recommendation: strong)"*

3 Maurer M. et al. 2022*: "Antifibrinolytics such as tranexamic acid are not recommended for long-term prophylaxis. Data for their efficacy are largely lacking, but some patients may find them helpful"*

4 Betschel S et al. 2019: *"Attenuated androgens and anti-fibrinolytics should not be used as first-line prophylaxis in patients with HAE-1/2. (Level of Evidence: Consensus; Strength of recommendation: strong)"*

Against this background, long-term prevention with C1 esterase inhibitors is determined as the appropriate comparator therapy for lanadelumab for long-term prevention in patients 2 to < 12 years of age with hereditary angioedema.

In addition to appropriate long-term prevention, acute treatment of HAE attacks should generally also be possible where necessary.

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 lanadelumab is assessed as follows:

For children 2 to < 12 years of age, an additional benefit of lanadelumab compared with the appropriate comparator therapy for routine prevention of recurrent attacks of hereditary angioedema is not proven.

Justification:

In its dossier for the assessment of the additional benefit of lanadelumab, the pharmaceutical company does not present any direct comparator studies versus the appropriate comparator therapy.

The pharmaceutical company additionally cites the label-enabling, single-arm SPRING study (24 children 2 to 11 years of age with a documented diagnosis of HAE (type I or II) over 12 weeks), which is unsuitable for the assessment of the additional benefit due to the lack of comparison with the appropriate comparator therapy.

Overall, no additional benefit can be derived for the routine prevention of recurrent attacks of hereditary angioedema in children 2 to < 12 years of age compared with the appropriate comparator therapy.

### 2.1.4 Summary of the assessment

The present assessment is the benefit assessment of a new therapeutic indication for the active ingredient lanadelumab. Lanadelumab (invented name: Takhzyro) was approved as an orphan drug but has exceeded the EUR 30 million turnover limit.

This resolution relates to the therapeutic indication "for the routine prevention of recurrent attacks of hereditary angioedema in children 2 to < 12 years of age".

The G-BA determined routine prophylaxis with C1 esterase inhibitors as the appropriate comparator therapy.

For the benefit assessment of lanadelumab, no direct comparator studies versus the appropriate comparator therapy were presented in the present therapeutic indication.

Against this background, an additional benefit of the routine prevention of recurrent attacks of hereditary angioedema in children 2 to < 12 years of age is therefore not proven.

## 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. The information is based on data provided by the pharmaceutical company in the dossier.

The lower limit of the patient numbers is based on an analysis that does not include patients 2 to 5 years of age in the healthcare data analysis due to a lack of approved therapy options, therefore representing an underestimate. The upper limit of the patient numbers is based on an expert survey and is subject to uncertainty, as the prevalence was determined independently of age and HAE type and therefore includes additional therapy options for patients 12 years and older that are not available for the target population 2 to < 12 years of age. For both the lower and upper limits, the values only refer to the period between 2020 and 2021, which does not take current fluctuations into account. Moreover, patients who are not currently receiving long-term prevention therapy, but for whom routine prevention is an option and who therefore belong to the target population, are not taken into account.

Overall, the figures are subject to uncertainties due to both underestimating and overestimating factors.

## 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 Takhzyro (active ingredient: lanadelumab) at the following publicly accessible link (last access: 28 May 2024):

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

Treatment with lanadelumab should only be initiated and monitored by doctors experienced in treating patients with hereditary angioedema (HAE).

## 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 May 2024).

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.

For dosages depending on body weight (BW), the average body measurements from the official representative statistics "Microcensus 2017 – body measurements of the population[5]" were used as a basis. The average body weight of a two-year-old child is 14.1 kg and that of an eleven-year-old child 42.1 kg.

[5] Federal Health Reporting. Average body measurements of the population (2017, both sexes, 1 year and older), www.gbe-bund.de

The recommended dose of lanadelumab for children between 10 and under 20 kg is 150 mg every 4 weeks according to the product information. The dose can be increased to 150 mg every 3 weeks in patients with inadequate control of attacks. According to the product information, children between 20 and under 40 kg receive 150 mg lanadelumab every 2 weeks. In patients who are free of attacks during treatment, a dose reduction of 150 mg lanadelumab every 4 weeks may be considered. Children weighing 40 kg or more receive 300 mg lanadelumab every 2 weeks according to the product information. In patients who are free of attacks during treatment, a dose reduction of 300 mg lanadelumab every 4 weeks may be considered.

Off-label use of C1 esterase inhibitors was determined to be the appropriate comparator therapy. The use of C1 esterase inhibitors for routine prophylaxis of angioedema attacks is approved for children from 6 to 11 years of age. For the therapeutic indication "Prevention of angioedema attacks prior to a medically indicated procedure", therapy with C1 esterase inhibitors is allowed for children from 2 to 11 years of age at a dose of 500 I.U. 24 hours before the medical procedure. For the cost representation of routine prophylaxis, the dosage of the approved therapeutic indication is used and presented as comparable.

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 | | | | |
| Lanadelumab | Continuously, every 14 - 28 days | 13.0 – 26.1 | 1 | 13.0 - 26.1 |
| Appropriate comparator therapy | | | | |
| C1 esterase inhibitor | Continuously, every 3 - 4 days | 91.3 – 121.7 | 1 | 91.3 – 121.7 |

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 | | | | | |
| Lanadelumab | Children 10 to under 20 kg | | | | |
| | 150 mg | 150 mg | 1 x 150 mg | 13.0 | 13.0 x 150 mg |

| Designation of the therapy | Dosage/ application | Dose/ patient/ treatment days | Consumption by potency/ treatment day | Treatment days/ patient/ year | Average annual consumption by potency |
|---|---|---|---|---|---|
| | Children 20 to under 40 kg | | | | |
| | 150 mg | 150 mg | 1 x 150 mg | 26.1 | 26.1 x 150 mg |
| | Children above 40 kg | | | | |
| | 300 mg | 300 mg | 1 x 300 mg | 26.1 | 26.1 x 300 mg |
| Appropriate comparator therapy | | | | | |
| C1 esterase inhibitor | 500 I.U. | 500 I.U. | 1 x 500 I.U. | 91.3 - 121.7 | 91.3 x 500 I.U. (91.3 x 5 ml) - 121.7 x 500 I.U. (121.7 x 5 ml) |

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 fixed reimbursement rates shown in the cost representation may not represent the cheapest available alternative.

The lowest annual treatment costs are for children with a body weight of 10 to under 20 kg. The highest annual treatment costs are for children with a body weight of 20 to under 40 kg. The annual treatment costs of € 264,646.39 for children with a body weight above 40 kg are within the range.

**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 | | | | | |
| Lanadelumab 150 mg | 1 SFIPFS | € 10,801.68 | € 2.00 | € 613.59 | € 10,186.09 |
| Lanadelumab 300 mg | 6 SFIPFS | € 64,521.81 | € 2.00 | € 3,681.56 | € 60,838.25 |
| Appropriate comparator therapy | | | | | |
| C1 esterase inhibitor 500 I.U. | 2 PSS | € 2,045.98 | € 2.00 | € 113.55 | € 1,930.43 |
| Abbreviations: SFIPFS = solution for injection in a pre-filled syringe; PSS = Powder and solvent for solution for injection, | | | | | |

LAUER-TAXE® last revised: 1 May 2024

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 need 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 designates 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 has 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 has 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 information 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 has 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:

Children 2 to less than 12 years of age 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.

## 3. Bureaucratic costs calculation

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

## 4. Process sequence

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

A review of the appropriate comparator therapy took place. The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 29 August 2023.

On 13 December 2023 the pharmaceutical company submitted a dossier for the benefit assessment of lanadelumab to the G-BA in due time in accordance with Chapter 5 Section 8, paragraph 1, number 2 VerfO.

By letter dated 14 December 2023 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 lanadelumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 07 March 2024, and the written statement procedure was initiated with publication on the G-BA website on 15 March 2024. The deadline for submitting statements was 5 April 2024.

The oral hearing was held on 22 April 2024.

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 28 May 2024, and the proposed resolution was approved.

At its session on 6 June 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

**Chronological course of consultation**

| Session | Date | Subject of consultation |
|---|---|---|
| Subcommittee Medicinal products | 12 October 2021 | Implementation of the appropriate comparator therapy |
| Subcommittee Medicinal products | 29 August 2023 | New implementation of the appropriate comparator therapy |
| Working group Section 35a | 16 April 2024 | Information on written statements received, preparation of the oral hearing |
| Subcommittee Medicinal products | 22 April 2024 | Conduct of the oral hearing, |
| Working group Section 35a | 29 April 2024<br>14 May 2024 | Consultation on the dossier evaluation by the IQWiG and evaluation of the written statement procedure |
| Subcommittee Medicinal products | 28 May 2024 | Concluding discussion of the draft resolution |
| Plenum | 6 June 2024 | Adoption of the resolution on the amendment of the Pharmaceuticals Directive |

Berlin, 6 June 2024

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

Prof. Hecken