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
Lonapegsomatropin (growth failure due to growth hormone deficiency, ≥ 3 to < 18 years)

of 7 March 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.

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 German Social Code, Book Five (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 for 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, No. 2 and 3 SGB V in conjunction with Chapter 5 Sections 5 et seq. 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. According to Section 35a, paragraph 1, sentence 12 SGB V, the pharmaceutical company must then, within three months of being requested to do so by the G-BA, submit evidence according to Chapter 5 Section 5, paragraphs 1–6 VerfO, in particular regarding the additional medical benefit in relation to the appropriate comparator therapy as defined by the G-BA according to Chapter 5 Section 6 VerfO and prove the additional benefit in comparison with the appropriate comparator therapy.

In accordance with Section 35a, paragraph 2 SGB V, the G-BA decides 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 its session on 15 March 2012 to the effect that, for orphan drugs, the G-BA initially no longer independently determines 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 its 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 threshold 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 decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and is part of the Pharmaceuticals Directive.

2. Key points of the resolution

The relevant date for the start of the benefit assessment procedure was the first placing on the (German) market of the active ingredient lonapegsomatropin on 15 September 2023 in accordance with Chapter 5 Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure (VerfO) of the G-BA. The pharmaceutical company submitted the final dossier to the G-BA in accordance with Section 4, paragraph 3, number 1 of the Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5 Section 8, paragraph 1, number 1 VerfO on 14 September 2023.

Lonapegsomatropin for the treatment of growth failure in children and adolescents aged from 3 years up to 18 years due to insufficient endogenous growth hormone secretion (growth hormone deficiency [GHD]) is approved as a medicinal product for the treatment of rare diseases in accordance with Regulation (EC) No. 141/2000 of the European Parliament and of 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 December 2023 together with the IQWiG assessment on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA has adopted its resolution on the basis of the dossier of the pharmaceutical company, the dossier evaluation carried out by the G-BA, the assessment of treatment costs and patient numbers (IQWiG G12-01) 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 has evaluated the studies relevant for the approval with regard to their therapeutic relevance (qualitative) in accordance with the criteria laid down in Chapter 5 Section 5, paragraph 7, sentence 1, numbers 1 – 4 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods 1 was not used in the benefit assessment of lonapegsomatropin.

1 General Methods, version 7.0 from 19.09.2023. 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 Lonapegsomatropin (Skytrofa) in accordance with the product information

Growth failure in children and adolescents aged from 3 years up to 18 years due to insufficient endogenous growth hormone secretion (growth hormone deficiency [GHD]).

Therapeutic indication of the resolution (resolution of 7 March 2024):

see the approved therapeutic indication

2.1.2 Extent of the additional benefit and significance of the evidence

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

<u>Children and adolescents aged from 3 years up to 18 years with growth failure due to insufficient growth hormone secretion</u>

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

Justification:
For the assessment of the additional benefit of lonapegsomatropin for children and adolescents aged 3 years and above with growth failure due to insufficient growth hormone secretion, the pharmaceutical company submitted the label-enabling heiGHt study and the CT-301-CN study, as well as a meta-analysis of both studies.

The heiGHt and CT-301-CN studies are randomised, open-label, actively controlled phase III studies comparing lonapegsomatropin with somatropin to be administered daily over 52 weeks.

The heiGHt study was conducted in 15 countries worldwide, primarily in Europe, the USA and Australia. It can therefore be assumed that the results are adequately transferable to the German healthcare context. The results of the CT-301-CN study conducted in China were also used for the benefit assessment due to comparable results and the lack of sufficient evidence of a lack of transferability.

At the start of the heiGHt and CT-301-CN studies, participants were randomised in a 2:1 ratio to the intervention arm (lonapegsomatropin; N = 106 and 101 respectively) or the comparator arm (somatropin; N = 56 and 53 respectively). Stratification was performed according to sex, age (≥ 3 to ≤ 6 years; > 6 years), and maximum hGH level in the stimulation test (≤ 5 ng/ml; > 5 ng/ml).

The studies are divided into an 6-week screening phase and a 52-week treatment phase. After successful completion of the 52-week treatment phase, study participants in the heiGHt study also had the opportunity to take part in the single-arm extension study.

Prepubertal children with GHD aged 3 to ≤ 12 years (boys) and 3 to ≤ 11 years (girls) were enrolled in the heiGHt study while children and adolescents aged 3 ≤ 17 years were enrolled in the CT-301-CN study.

The enrolled patients had to have either an isolated growth hormone deficiency (GHD) or a GHD as part of a multiple pituitary hormone deficiency. For diagnosis, a cut-off of ≤ 10 ng/ml in the highest measured growth hormone (GH) concentration in 2 different GH stimulation tests was defined in the studies presented and specified as an inclusion criterion. However, according to the current S2e guideline, a cut-off of < 8 ng/ml at the highest GH concentration measured in two GH stimulation tests is recommended for diagnosing growth hormone deficiency in childhood and adolescence.

Study participants had impaired body height (≥ 2.0 SD below the mean body height for chronological age and sex according to the 2000 CDC Growth Charts) and skeletal maturity that was at least 6 months below chronological age. In addition, the IGF-1 levels at baseline were ≥ 1.0 SD below the mean IGF-1 level standardised for age and sex (IGF-1 SDS ≤ -1.0) according to the reference values of the central laboratory.

Treatment with lonapegsomatropin in the intervention arm (0.24 mg/ kg/ week subcutaneous injection) and with somatropin in the control arm (0.034 mg/ kg/ day subcutaneous injection) of the heiGHT and CT-301-CN studies was carried out according to the respective product information.

The primary endpoint of the studies was the annualized growth rate in cm/ year after 12 months of treatment. Apart from the primary endpoint, endpoints of the categories mortality, morbidity and side effects were collected in the heiGHT and CT-301-CN studies.

Mortality

There were no deaths in the heiGHT and CT-301-CN studies.

Morbidity

Body height (SDS) – ANCOVA and MMRM

Anthropometric parameters can be assessed as patient-relevant morbidity parameters, especially in children with characteristic, disease-related growth failures. Data adjusted for age and sex are preferred to absolute values.

The standardised height was calculated using the Standard Deviation Score (SDS). The SDS of body height reflects the number of standard deviations (SD) from the age and sex-specific standard value. An SDS of zero indicates that the measured body height corresponds to the standard value of the reference population, while a positive SDS means a body height above the standard value and a negative SDS means a body height below the standard value.

The CT-301-CN study was analysed using ANCOVA. In the heiGHt study, in addition to the pre-specified evaluation using MMRM, a non-pre-specified evaluation was carried out using ANCOVA.

As part of the written statement procedure, the pharmaceutical company submitted data and information on the comparable statistical analysis procedure (analysis of covariance ANCOVA) for the evaluation of standardised body height in both the heiGHt and CT-301-CN studies. Due to the negligible heterogeneity of both studies, these data are also suitable for meta-analytical summarisation.

While the CT-301-CN study showed a statistically significant advantage in favour of lonapegsomatropin in the evaluation using ANCOVA, the heiGHt study only showed a statistically significant difference in the non-predefined evaluation using ANCOVA, but not using the predefined analysis using MMRM. The significant difference in favour of lonapegsomatropin was also shown in the meta-analysis of both studies using ANCOVA. However, the clinical relevance of the difference cannot be conclusively assessed.

For the subgroup feature "age", the CT-301-CN study showed a statistically significant effect modification for the endpoint "body height (SDS)". This showed a significant advantage in favour of lonapegsomatropin compared to somatropin for subjects under 6 years of age, while there was a smaller insignificant effect for subjects over 6 years of age. In the heiGHt study and in the meta-analysis of the two studies, the subgroup analyses performed showed no significant effect modification.

Annualized growth rate

The primary endpoint of growth rate describes the annual increase in standing height [cm/ year] and is only presented additionally, as it does not provide any information on growth other than body height for the benefit assessment.

In the heiGHt and CT-301-CN studies, there was a statistically significant advantage in favour of lonapegsomatropin for the growth rate endpoint.

Quality of life

No data on quality of life were assessed.

Side effects

Overall, only a few severe or serious adverse events (AEs) or therapy discontinuations due to AEs occurred.

For severe AEs, serious AEs and therapy discontinuations due to AEs, no statistically significant difference was detected between the treatment groups.

For the AEs of special interest, the heiGHt study showed a statistically significant disadvantage of lonapegsomatropin over somatropin for each of the endpoints abnormal reactions at the injection site and redness.

In the overall assessment, there are no advantages or disadvantages of lonapegsomatropin over somatropin in the side effects category.

Overall assessment

For the assessment of the additional benefit of lonapegsomatropin for children and adolescents aged 3 years and above with growth failure due to insufficient growth hormone secretion, the pharmaceutical company submitted the label-enabling heiGHt study as well as the CT-301-CN study.

The heiGHt and CT-301-CN studies yielded results on mortality, morbidity and side effects.

There were no deaths in the heiGHT and CT-301-CN studies.

For the endpoint in the morbidity category "body height (SDS)", the CT-301-CN study showed a statistically significant advantage in favour of lonapegsomatropin in the predefined evaluation using ANCOVA. The heiGHt study showed a statistically significant advantage of lonapegsomatropin in the non-predefined evaluation using ANCOVA, but not using the predefined evaluation using MMRM. The significant advantage in favour of lonapegsomatropin was also shown in the meta-analytic evaluation of both studies using

ANCOVA. Overall, however, the statistically significant difference in the endpoint "body height (SDS)" cannot be conclusively assessed with regard to its clinical relevance, so that no conclusions can be drawn on the extent of the additional benefit.

In addition, there are no long-term evaluations that allow an assessment of the further course of the increase in the extent.

In the overall assessment, there are no advantages or disadvantages of lonapegsomatropin in the side effects category.

In the overall assessment, in children and adolescents aged from 3 years up to 18 years with growth failure due to insufficient growth hormone secretion, there is therefore a non-quantifiable additional benefit of lonagpegsomatropin because the scientific data basis does not allow quantification.

Significance of the evidence

There is a high risk of bias at study level for the heiGHt and CT-301-CN studies presented due to the open-label study design.

For the endpoint of body height (SDS), the data and information subsequently submitted by the pharmaceutical company on the comparable analysis models for the heiGHt and CT-301-CN studies indicate a low risk of bias.

In the studies presented, a cut-off of ≤ 10 ng/ml in the highest measured growth hormone (GH) concentration in two different GH stimulation tests was specified as the inclusion criterion. However, according to the current S2e guideline, a cut-off of < 8 ng/ml is recommended for diagnosing growth hormone deficiency in childhood and adolescence. It therefore remains unclear whether all patients enrolled in the studies have GHD.

The results on patient-relevant endpoints from the studies and their meta-analytic summary do not allow quantification of the extent of additional benefit in the overall assessment. The overall significance of the results for the observed additional benefit is low, which is why the significance of the evidence is classified as a "hint".

In the overall assessment, the reliability of data is classified under the "hint" category.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Skytrofa with the active ingredient lonapegsomatropin.

Lonapegsomatropin was approved as an orphan drug for "growth failure in children and adolescents aged from 3 years up to 18 years due to insufficient endogenous growth hormone secretion (growth hormone deficiency [GHD])".

For the benefit assessment of lonapegsomatropin, the pharmaceutical company submitted the label-enabling heiGHt study as well as the CT-301-CN study. The heiGHt and CT-301-CN studies yielded results on mortality, morbidity and side effects.

There were no deaths in the heiGHT and CT-301-CN studies.

For the endpoint in the morbidity category "body height (SDS)", the CT-301-CN study showed a statistically significant advantage in favour of lonapegsomatropin in the predefined evaluation using ANCOVA. The heiGHt study showed a statistically significant advantage of lonapegsomatropin in the non-predefined evaluation using ANCOVA, but not using the predefined evaluation using MMRM. The significant advantage in favour of lonapegsomatropin was also shown in the meta-analysis of both studies using ANCOVA.

Overall, however, the statistically significant difference in the endpoint "body height (SDS)" cannot be conclusively assessed with regard to its clinical relevance, so that no conclusions can be drawn on the extent of the additional benefit. In addition, there are no long-term evaluations that allow an assessment of the further course of the increase in the extent.

In the overall assessment, there are no advantages or disadvantages in the side effects category.

In the overall assessment, in children and adolescents aged 3 to < 18 years with growth failure due to insufficient secretion of growth hormone, there is therefore a hint for a non-quantifiable additional benefit of lonagpegsomatropin because the scientific data basis does not allow quantification.

2.2 Eligible patient groups

The information on the number of patients is based on the target population in statutory health insurance (SHI).

There are methodological limitations and uncertainty factors for the range stated by the pharmaceutical company, so that the stated range is subject to uncertainties overall.

The SHI target population determined in the current procedure is of a similar order of magnitude as previous procedures, but is subject to uncertainties as described and therefore cannot be regarded as a better estimate. The number of patients from the benefit assessment procedure for somatrogon (resolution 15 September 2022) is therefore used.

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 Skytrofa (active ingredient: lonapegsomatropin) at the following publicly accessible link (last access: 10 January 2024):

https://www.ema.europa.eu/en/documents/product-information/skytrofa-previously-lonapegsomatropin-ascendis-pharma-epar-product-information_en.pdf

Treatment with lonapegsomatropin should only be initiated and monitored by doctors experienced in treating children and adolescents with growth hormone deficiency (GHD).

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 2024).

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				
Lonapegsomatropin	1 x every 7 days	52.1	1	52.1

Consumption:

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. The average body measurements were applied for dosages depending on body weight (bw) or body surface area (BSA) (average height of a 3-year-old child: 16.2 kg, average body weight of a 17-year-old adolescent: 67.2 kg)[2].

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					
Lonapegsomatropin	Patients ≥ 3 to under 4 years				
	0.24 mg[3] /BW	3.6 mg[4]	3.6 mg	52.1	52.1 x 3.6 mg
	Patients ≥ 17 to under 18 years				
	0.24 mg[3]/BW	15.2 mg[4]	2 x 7.6 mg	52.1	104.2 x 7.6 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.

[2]Federal Statistical Office, Wiesbaden 2021: http://www.gbe-bund.de/.
[3]The dosage information refers to the proportional somatropin quantity
[4]Recommended dose according to the product information based on the patient's body weight at prescribed doses of 0.24 mg somatropin/ kg/ week.

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					
Lonapegsomatropin 10.3 mg[5]	4 PSI	€ 1,162.68	€ 2.00	€ 63.75	€ 1096.93
Lonapegsomatropin 21.7 mg[6]	4 PSI	€ 2,414.06	€ 2.00	€ 134.58	€ 2277.48
Abbreviations: PSI = powder and solvent for solution for injection					

LAUER-TAXE® last revised: 1 February 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.

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

[5]Equivalent to 3.6 mg somatropin
[6]Equivalent to 7.6 mg somatropin

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 and adolescents aged from 3 years up to 18 years with growth failure due to insufficient growth hormone secretion

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

References:

Product information for lonapegsomatropin (Skytrofa); powder and solvent for solution for injection in a cartridge; last revised: January 2023

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 September 2023, the pharmaceutical company submitted a dossier for the benefit assessment of lonapegsomatropin 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 December 2023 together with the IQWiG assessment of treatment costs and patient numbers on the website of the G-BA (www.g-ba.de), thus initiating the written statement procedure. The deadline for submitting statements was 5 January 2024.

The oral hearing was held on 22 January 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 27 February 2024, and the proposed resolution was approved.

At its session on 7 March 2024, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	12 December 2023	Information of the benefit assessment of the G-BA
Working group Section 35a	9 January 2024	Information on written statements received, preparation of the oral hearing
Subcommittee Medicinal products	22 January 2024	Conduct of the oral hearing
Working group Section 35a	30 January 2024 13 February 2024	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 Medicinal products	27 February 2024	Concluding discussion of the draft resolution
Plenum	7 March 2024	Adoption of the resolution on the amendment of the Pharmaceuticals Directive

Berlin, 7 March 2024

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

Prof. Hecken