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 Somatrogon (growth disturbance due to growth hormone deficiency, ≥ 3 to < 18 years)

of 15 September 2022

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 € 50 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, subsection 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 legal limit of € 50 million and is therefore subject to an unrestricted benefit assessment (cf. Section 35a paragraph 1, sentence 12 SGB V). 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 first placing on the (German) market of the active ingredient somatrogon in accordance with Chapter 5, Section 8, paragraph 1, number 1, sentence 2 of the Rules of Procedure of the G-BA (VerfO) is 1 April 2022. 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 31 March 2022.

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

In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional benefit is considered to be proven through the grant of the marketing authorisation. The extent of the additional benefit and the significance of the evidence are assessed on the basis of the marketing authorisation 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 1 July 2022 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 G22-11) 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 has assessed the studies relevant for the marketing authorisation considering 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 somatrogon.

[1] General Methods, version 6.1 from 24.01.2022. 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 Somatrogon (Ngenla) in accordance with the product information

Ngenla is indicated for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone.

Therapeutic indication of the resolution (resolution of 15 September 2022):

see therapeutic indication according to marketing authorisation.

2.1.2 Extent of the additional benefit and significance of the evidence

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

<u>Children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone</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 somatrogon for children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone, the pharmaceutical company submitted the open-label, randomised, controlled phase III CP-4-006 pivotal study in a parallel-group design with data cut-off in month 12.

In the CP-4-006 study, somatrogon was compared to genotropin. Patients in the CP-4-006 study were randomised in a 1:1 ratio to the intervention arm (somatrogon; N = 109) or the comparator arm (genotropin; N = 115), stratified by the factors "region" (Western Europe, Israel, Australia, New Zealand, Canada, USA vs Central and Eastern Europe, Greece, Turkey, Latin America, Asia (excluding India and Vietnam) vs India, Vietnam), "highest measured GH concentration at screening (≤ 3 vs > 3 to ≤ 7 vs > 7 to ≤ 10 ng/ml)" and "chronological age (≥ 3 to ≤ 7 vs > 7 years).

The study is divided into a 2-month screening phase, a 12-month comparative treatment phase and a single-arm, open-label extension phase in which all study participants were treated with somatrogon.

The CP-4-006 study enrolled paediatric patients aged 3 to < 11 years (for girls) and < 12 years (for boys). The bone age of the study participants is not older than the chronological age and should be < 10 years for girls and < 11 years for boys.

The enrolled patients had to have either an isolated growth hormone deficiency (GHD) or a GHD as part of a multiple pituitary hormone deficiency. Confirmation of the diagnosis of GHD was made by two different GH stimulation tests at a maximum GH concentration of ≤ 10 ng/ml measured by a local or central laboratory. The following established examination procedures were used: Insulin tolerance test with a serum cortisol response to hypoglycaemia/ arginine test/ clonidine test/ glucagon test/ L-dopa test.

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 the diagnosis of growth hormone deficiency in childhood and adolescence.

The study participants were therapy naive for treatment with recombinant human growth hormone (r-hGH). In addition, the patients enrolled in the CP-4-006 study showed stunted body height and annualized growth velocity, as determined by the annualized growth velocity below the 25th percentile for chronological age (HV < -0.7 of the z score) and sex according to the OPKO HV (Tanner, Prader and Hermanussen) calculator.

Treatment with somatrogon in the intervention arm (0.66 mg/ kg/ week subcutaneous injection) and with genotropin in the control arm (0.034 mg/ kg/ day subcutaneous injection) in the CP-4-006 study was carried out according to the respective product information. Treatment with somatrogon should be stopped if there is evidence of closure of the epiphyseal joints and if the annualized growth velocity falls below 2 cm/ year or the bone age is > 14 years in girls or > 16 years in boys.

The primary endpoint was the annualized growth velocity in cm/ year after 12 months of treatment. Apart from the primary endpoint, endpoints of the categories mortality, morbidity, quality of life and side effects were collected in the CP-4-006 study.

Mortality

There were no deaths in the CP-4-006 study.

Morbidity

Body height (z score)

The anthropometric parameter of height is assessed as a patient-relevant morbidity parameter, especially in children with characteristic, disease-related growth disturbances. Data adjusted for age and sex (z scores) are preferred over absolute values.

Body height was recorded as standing height (not length) as well as age and sex-adjusted z scores were calculated. The z scores reflect the number of standard deviations (SD) of each score from the normal mean scores, standardised by age and sex. The data were presented as SD values above or below the age-specific reference (≙ 0). A sample of the US general population in the survey periods from 1963 to 1994 was used as comparator data for the z scores. Country-specific z scores were not taken into account.

For the endpoint of body height (z score), no statistically significant difference was detected between the treatment groups.

Annualized growth velocity

The primary endpoint 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 height for the benefit assessment.

In the CP-4-006 study, no statistically significant difference was found between the treatment groups for the endpoint of annualized growth velocity.

Quality of life

Quality of Life in Short Stature Youth Questionnaire (QoLISSY)

The QoLISSY questionnaire is an instrument for assessing the quality of life of short-stature youth, for which there is a version for direct questioning of children and adolescents in the age groups 8 to 12 years and 13 to 18 years and a version for questioning the parents of affected children and adolescents in the age groups 4 to 7 years, 8 to 12 years and 13 to 18 years. The versions contain three main domains (physical, emotional and social) which allow the calculation of a total score, as well as three further domains for coping, beliefs and treatment. The parent version also includes a domain on the child's future and a domain on the effects of the disease on the parents. The scores are then transformed on a scale of 0 to 100, higher scores indicating a better quality of life.

In the CP-4-006 study, the self-reported child version of the QoLISSY questionnaire was used for children and adolescents aged 7 years and above, while for younger children aged 3 to 7 years, parents completed the parent proxy questionnaire.

For the QoLISSY questionnaire, no statistically significant difference was found between treatment groups for improvement by ≥ 15 points in month 12 in the CP-4-006 study.

Side effects

In the CP-4-006 study, no statistically significant difference was observed between the treatment groups for the endpoints of serious adverse events (SAEs) and severe adverse events.

In the CP-4-006 study, one subject in the somatrogon arm discontinued treatment due to AEs. This results in no statistically significant difference between the treatment groups for the endpoint of therapy discontinuations due to AEs.

At the level of SOC (system organ class) and PT (preferred term), a statistically significant disadvantage of somatrogon over genotropin was observed for each of the endpoints general disorders and administration site conditions, eye disorders (SOC), pain at the injection site (PT). For the endpoint of examinations (SOC), a statistically significant advantage of somatrogon over genotropin was found.

For the AEs of special interest, a statistically significant disadvantage of somatrogon over genotropin was observed for each of the endpoints injection site reactions and immunogenicity.

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

Overall assessment

For the assessment of the additional benefit of somatrogon for children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone, the pharmaceutical company submitted the open-label, randomised, controlled phase III CP-4-006 pivotal study in a parallel-group design with data cut-off in month 12.

The CP-4-006 study produced results on mortality, morbidity, quality of life and side effects.

There were no deaths in the CP-4-006 study.

For the endpoint of the morbidity category body height (z score), no statistically significant difference was found between the treatment groups.

In the quality of life category, no statistically significant difference was found between the treatment groups for the endpoint QoLISSY.

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

In the overall assessment, a non-quantifiable additional benefit is identified since the scientific data basis does not allow quantification.

Significance of the evidence

There is a high risk of bias at study level for the CP-4-006 study presented due to the open-label study design.

Confirmation of the diagnosis of GHD was made in the CP-4-006 study by two different GH stimulation tests at a maximum GH concentration of ≤ 10 ng/ml measured by a local or central laboratory. 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. It therefore remains unclear whether all patients enrolled in the CP-4-006 study have GHD.

Somatrogon is indicated for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone. The use of somatrogon is limited to a bone age for girls of ≤ 14 years and for boys of ≤ 16 years. The CP-4-006 study enrolled paediatric patients aged 3 to < 11 years (for girls) and < 12 years (for boys). The bone age of the patients enrolled in the CP-4-006 study is not older than the chronological age and should be < 10 years for girls and < 11 years for boys. It remains unclear whether the results from the CP-4-006 study in month 12 are also applicable to patients with a bone age of ≥ 10 to ≤ 14 years (girls) or ≥ 11 to ≤ 16 years (boys).

In the overall assessment, this results in a hint for a non-quantifiable additional benefit concerning the significance of the evidence.

2.1.3 Summary of the assessment

The present assessment concerns the benefit assessment of the new medicinal product Ngenla with the active ingredient somatrogon.

Somatrogon was approved as an orphan drug for the "treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone".

The benefit assessment of somatrogon was based on the pivotal, open-label, randomised, controlled phase III CP-4-006 study in parallel-group design with data cut-off in month 12. The CP-4-006 study produced results on mortality, morbidity, quality of life and side effects.

There were no deaths in the CP-4-006 study.

For the endpoint of body height (z score) in the morbidity category and for the endpoint QoLISSY in the quality of life category, no statistically significant difference was found between the treatment groups.

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

Uncertainties remain due to the open-label study design and the cut-off value used in the CP-4-006 study to diagnose GHD. Furthermore, it remains unclear whether the results of the CP-4-006 study are also applicable to patients with a bone age of ≥ 10 to ≤ 14 years (girls) or ≥ 11 to ≤ 16 years (boys).

In the overall assessment, for children and adolescents from 3 years of age with growth disturbances due to insufficient secretion of growth hormone, a hint for a non-quantifiable additional benefit is identified since the scientific data does not allow quantification.

2.2 Number of patients or demarcation of patient groups eligible for treatment

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

The resolution is based on the information from the dossier of the pharmaceutical company.

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.

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 Ngenla (active ingredient: somatrogon) at the following publicly accessible link (last access: 14 July 2022):

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

Treatment with somatrogon 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 contents of the product information and the information listed in the LAUER-TAXE® (last revised: 15 August 2022).

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 is patient-individual 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				
Somatrogon	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: 67.0 kg).[2]

[2] Federal Statistical Office, Wiesbaden 2018: http://www.gbe-bund.de/

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					
Somatrogon	Patients ≥ 3 to under 4 years				
	0.66 mg/ kg bw = 10.7 mg	10.7 mg	10.8 mg [3]	52.1	52.1 x 10.8 mg
	Patients ≥ 17 to under 18 years				
	0.66 mg/ kg bw = 44.2 mg	44.2 mg	44.0 mg [4]	52.1	52.1 x 44.0 mg

Costs:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Section 130 and Section 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Costs of the medicinal products:

Designation of the therapy	Packaging size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed					
Somatrogon 24 mg	1 SFI	€ 628.83	€ 1.77	€ 34.19	€ 592.87
Somatrogon 60 mg	1 SFI	€ 1,554.32	€ 1.77	€ 85.48	€ 1,467.07

[3] The pre-filled pen to be used delivers the active ingredient in increments of 0.2 mg.
[4] The pre-filled pen to be used delivers the active ingredient in increments of 0.5 mg.

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
Abbreviations: SFI = solution for injection					

LAUER-TAXE® last revised: 15 August 2022

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, 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.

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 31 March 2022, the pharmaceutical company submitted a dossier for the benefit assessment of somatrogon 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 1 July 2022 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 written statements was 22 July 2022.

The oral hearing was held on 8 August 2022.

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 6 September 2022, and the proposed resolution was approved.

At its session on 15 September 2022, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal products	28 June 2022	Information of the benefit assessment of the G-BA
Working group Section 35a	3 August 2022	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal products	8 August 2022	Conduct of the oral hearing
Working group Section 35a	17 August 2022 31 August 2022	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	6 September 2022	Concluding discussion of the draft resolution
Plenum	15 September 2022	Adoption of the resolution on the amendment of Annex XII AM-RL

Berlin, 15 September 2022

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

Prof. Hecken