Gemeinsamer Bundesausschuss

Resolution

of the Federal Joint Committee 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

At its session on 7 March 2024, the Federal Joint Committee (G-BA) resolved to amend the Pharmaceuticals Directive (AM-RL) in the version dated 18 December 2008 / 22 January 2009 (Federal Gazette, BAnz. No. 49a of 31 March 2009), as last amended by the publication of the resolution of D Month YYYY (Federal Gazette, BAnz AT DD.MM.YYYY BX), as follows:

I. Annex XII shall be amended in alphabetical order to include the active ingredient Lonapegsomatropin as follows:

Lonapegsomatropin

Resolution of: 7 March 2024
Entry into force on: 7 March 2024
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 11 January 2022):

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 therapeutic indication according to marketing authorisation.

1. Extent of the additional benefit and significance of the evidence

Lonapegsomatropin is approved as a medicinal product for the treatment of rare diseases under Regulation (EC) No. 141/2000 of the European Parliament and the Council of 16 December 1999 on orphan drugs. In accordance with Section 35a, paragraph 1, sentence 11, 1st half of the sentence SGB V, the additional medical benefit is considered to be proven through the grant of the marketing authorisation.

The Federal Joint Committee (G-BA) determines the extent of the additional benefit for the number of patients and patient groups for which there is a therapeutically significant additional benefit in accordance with Chapter 5 Section 12, paragraph 1, number 1, sentence 2 of its Rules of Procedure (VerfO) in conjunction with Section 5, paragraph 8 AM-NutzenV, indicating the significance of the evidence. This quantification of the additional benefit is based on the criteria laid out in Chapter 5 Section 5, paragraph 7, numbers 1 to 4 of the Rules of Procedure (VerfO).

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

Extent of the additional benefit and significance of the evidence of lonapegsomatropin:

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

Study results according to endpoints:[1]

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

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No deaths occurred.
Morbidity	↔	Overall, no relevant differences for the benefit assessment
Health-related quality of life	∅	No data available.
Side effects	↔	Overall, no relevant differences for the benefit assessment
Explanations: ↑: statistically significant and relevant positive effect with low/unclear reliability of data ↓: statistically significant and relevant negative effect with low/unclear reliability of data ↑↑: statistically significant and relevant positive effect with high reliability of data ↓↓: statistically significant and relevant negative effect with high reliability of data ↔: no statistically significant or relevant difference ∅: No data available. n.a.: not assessable		

heiGHt and CT-301-CN studies: randomised, open-label, actively controlled phase III studies, lonapegsomatropin vs somatropin, 52 weeks

Mortality

Endpoint Study	Lonapegsomatropin		Somatropin		Lonapegsomatropin vs somatropin
	N[b)]	Patients with event n (%)	N[b)]	Patients with event n (%)	Effect estimator [95% CI] p value
Overall mortality[a)]					
heiGHt	No deaths occurred.				
CT-301-CN	No deaths occurred.				

[1] Data from the dossier assessment of the G-BA (published on 15. Dezember 2023), and from the amendment to the dossier assessment from 09.02.2024, unless otherwise indicated.

Morbidity

Endpoint Study	Lonapegsomatropin			somatropin			Lonapegsomatropin vs somatropin
	N[c)]	Baseline MV (SD) MV [95% CI][r)]	Change to month 12 LS-MV (SE) LS-MV [95% CI][r)]	N[c)]	Baseline MV (SD) MV [95% CI][r)]	Change to month 12 LS-MV (SE) LS-MV [95% CI][r)]	LS-MD [95% CI]; p value
Body height (SDS) - ANCOVA							
heiGHt	105[d)]	-2.89 (0.85)	1.10 (0.04)[e)]	56[d)]	-3.00 (0.90)	0.96 (0.05)[e)]	0.14 [0.03; 0.26]; 0.015[e)]
CT-301-CN[f)]	100[g)]	-2.12 (0.57)	0.96 (0.042)	53[g)]	-2.21 (0.66)	0.81 (0.051)	0.16 [0.049; 0.262] 0.0046
Meta-analysis[f)]	205	-2.37 [-2.46; -2.27]	1.03 [0.97; 1.09]	109	-2.49 [-2.64; -2.35]	0.88 [0.81; 0.96]	0.15 [0.07; 0.23]; 0.0002
Body height (SDS) - MMRM							
heiGHt	105[d)]	-2.89 (0.85)	1.05; (0.04)[h)]	56[d)]	-3.00 (0.90)	0.94; (0.06)[h)]	0.11 [-0.03; 0.26]; 0.12[h)]
CT-301-CN	-	-	-[i)]	-	-	-[i)]	-[i)]

Endpoint Study	Lonapegsomatropin		Somatropin		Lonapegsomatropin vs somatropin
	N	month 12 LS-MV (SE)[q),r)] [95% CI][r)]	N	month 12 LS-MV (SE)[q),r)] [95% CI][r)]	LS-MD [95% CI]; p value[r)]
Annualized growth rate [cm/year][o)] (presented additionally)					
Change to month 12					
heiGHt	105	11.17 (0.233)	56	10.31 (0.298)	0.86 [0.216; 1.502]; 0.0088
CT-301-CN	100	10.66 (0.218)	53	9.75 (0.261)	0.91 [0.367; 1.455]; 0.0010
Meta-analysis[p)]	205	10.892 [7.737; 14.047]	109	9.986 [7.151; 12.82]	0.889 [0.474; 1.304] n.d.

Health-related quality of life

No data on the endpoint category of quality of life are available.

Side effects

Endpoint Study	Lonapegsomatropin		Somatropin		Lonapegsomatropin vs Somatropin
	N[b)]	Patients with event n (%)	N[b)]	Patients with event n (%)	RR [95% CI][l),n)]; p value
Total adverse events (presented additionally)					
heiGHt	105	81 (77.1)	56	39 (69.64)	-
CT-301-CN	100	98 (98)	53	50 (94.3)	-
Meta-analysis	205	179 (87.3)[m)]	109	89 (81.7)[m)]	-
Severe adverse events					
heiGHt	105	1 (1.0)	56	0 (0)	1.59 [0.07; 38.26]; 0.47
CT-301-CN	100	2 (2.0)	53	0 (0)	1.62 [0.17; 15.16]; 0.30
Meta-analysis	205	3 (1.5)[j)]	109	0 (0)[j)]	n.d.
Serious adverse events (SAE)					
heiGHt	105	1 (1.0)	56	1 (1.8)	0.52 [0.03; 8.18]; 0.64
CT-301-CN	100	4 (4.0)	53	2 (3.8)	0.83 [0.17; 4.14]; 0.95
Meta-analysis	205	5 (2.4)[k)]	109	3 (2.8)[k)]	0.88 [0.22; 3.62]; 0.86[k)]
Therapy discontinuation due to adverse events					
heiGHt	105	0 (0)	56	0 (0)	n.d.
CT-301-CN	100	2 (2.0)	53	0 (0)	1.62 [0.17; 15.16]; 0.30
Meta-analysis	205	2 (1.0)[j)]	109	0 (0)[j)]	n.d.

Endpoint Study	Lonapegsomatropin		Somatropin		Lonapegsomatropin vs Somatropin
	N[b)]	Patients with event n (%)	N[b)]	Patients with event n (%)	RR [95% CI][l),n)]; p value
Severe adverse events according to MedDRA (with incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No severe AEs ≥ 5%					
SAEs according to MedDRA (with incidence ≥ 5% in one study arm and statistically significant difference between the treatment arms; SOC and PT)					
No SAEs ≥ 5%					
Adverse events of special interest (with statistically significant difference between the treatment arms)					
Condition of the injection site[t)]					
Abnormal reactions at the injection site (any severity grade)					
heiGHt	105	30 (28.6)	56	3 (5.4)	5.2799 [1.7005; 16.3935]; 0.0005
Redness (any severity grade)					
heiGHt	105	24 (22.9)	56	2 (3.6)	6.3224 [1.5652; 25.5389]; 0.0015

a) Fatalities were recorded using safety.
b) Safety population
c) ITT population.
d) Baseline values are available for 105 subjects in the lonapegsomatropin arm and 56 in the somatropin arm. For month 12, values are available for 104 subjects in the lonapegsomatropin arm and 55 in the somatropin arm.
e) Post hoc evaluation Model (ANCOVA) used in the heiGHt study for the change in standardised body height (SDS) not predefined.
f) Recalculations for the CT-301-CN study and for the meta-analysis according to the calculation formula for body height (SDS) from the heiGHt study
g) Baseline values are available for 100 subjects in the lonapegsomatropin arm and 53 in the somatropin arm. For month 12, values are available for 98 subjects in the lonapegsomatropin arm and 52 in the somatropin arm.
h) Model (ANCOVA) used in the CT-301-CN study for the change in standardised body height (SDS) predefined.
i) Model (MMRM) used for the change in standardised body height (SDS) predefined.
j) No evaluations using an MMRM were planned or reported for the study.
k) Own calculation of event frequency. Frequency and percentage data (purely descriptive) are available without weighting based on sample size. However, the effect estimators shown in the meta-analysis are weighted.
l) Calculated post hoc.
m) Adverse events: Calculated post hoc: The 95% CI for the RR was calculated using the Cochran-Mantel-Haenszel method.

Endpoint Study	Lonapegsomatropin		Somatropin		Lonapegsomatropin vs Somatropin
	N[b)]	Patients with event n (%)	N[b)]	Patients with event n (%)	RR [95% CI][l),n)]; p value

n) Adverse events: Own calculation of event frequency. Frequency and percentage data (purely descriptive) are available without weighting based on sample size. However, the effect estimators shown in the meta-analysis are weighted.
o) If there are no events in one of the treatment arms, the RR is calculated using a zero cell correction by adding a value of 0.5%. If the majority of cells had a value of zero, the RR was not calculated.
p) Primary endpoint of the heiGHt and CT-301-CN studies
q) Calculated post hoc.
r) LS-MV and LS-MD were determined using an ANCOVA. The LS-MV, CI and p values shown in the table are the overall estimates combined from all 100 models.
s) For the meta-analysis, only the 95% CI is given and not SE.
t) The scale for the respective condition of the injection site is divided into 4 levels and ranges from "no symptomatology" (0) to "severe symptomatology" (3).

Abbreviations:
ANCOVA: analysis of covariance; ITT: intention to treat; n.d.: no data available; CI: confidence interval; LS: Least Squares; MedDRA: Medical Dictionary for Regulatory Activities MAR: Missing At Random; MMRM: Mixed Model for Repeated Measurement; MV: mean value; MD: mean difference; RR: relative risk; SD: standard deviation; SDS: standard deviation score; SE: standard error; (S)AE: (serious) adverse event.

2. Number of patients or demarcation of patient groups eligible for treatment

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

approx. 5,710 – 6,550 patients

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: 15 February 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).

4. Treatment costs

Annual treatment costs:

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

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Lonapegsomatropin	€ 14,287.51 - € 59,328.35

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 1 February 2024)

Costs for additionally required SHI services: not applicable

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

In the context of the designation of medicinal products with new active ingredients pursuant to Section 35a, paragraph 3, sentence 4 SGB V, the following findings are made:

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.

The designation of combinations exclusively serves the implementation of the combination discount according to Section 130e SGB V between health insurance funds and pharmaceutical companies. 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.

III. The resolution will enter into force on the day of its publication on the website of the G-BA on 7 March 2024.

The justification to this resolution will be published on the website of the G-BA at www.g-ba.de.

Berlin, 7 March 2024

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

Prof. Hecken