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

of 15 September 2022

At its session on 15 September 2022, 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 Somatrogon as follows:**

Somatrogon

Resolution of: 15 September 2022
Entry into force on: 15 September 2022
Federal Gazette, BAnz AT DD. MM YYYY Bx

Therapeutic indication (according to the marketing authorisation of 14 February 2022):

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.

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

Somatrogon 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 from 3 years of age with growth disturbance due to insufficient secretion of growth hormone</u>

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

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

Study results according to endpoints:[1]

Children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone

Summary of results for relevant clinical endpoints

Endpoint category	Direction of effect/ risk of bias	Summary
Mortality	↔	No relevant differences for the benefit assessment.
Morbidity	↔	No relevant differences for the benefit assessment.
Health-related quality of life	↔	No relevant differences for the benefit assessment.
Side effects	↔	No relevant differences overall 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 ∅: There are no usable data for the benefit assessment. n.a.: not assessable		

CP-4-006 study: open-label RCT, somatrogon vs genotropin, 12 months

Mortality

CP-4-006 study Endpoint	Somatrogon		Genotropin		Somatrogon vs Genotropin
	N	Patients with event n (%)	N	Patients with event n (%)	Effect estimator [95% CI] p value
Overall mortality					
No deaths occurred.					

[1] Data from the dossier assessment of the G-BA (published on 1. July 2022), unless otherwise indicated.

Morbidity

CP-4-006 study Endpoint	Somatrogon N	Somatrogon Baseline MV (SD)	Somatrogon Month 12 MV (SD) LS mean [95% CI]	Genotropin N	Genotropin Baseline MV (SD)	Genotropin Month 12 MV (SD) LS mean [95% CI]	Somatrogon vs genotropin LS Mean Difference [95% CI]; p value
Body height (z score)							
Change to month 12	109[a)]	-2.9 (1.3)	-2.0 (1.1) 0.92 [0.82; 1.02]	115[a)]	-2.8 (1.3)	-1.9 (1.1) 0.87 (0.78; 0.97)	0.05 [-0.06; 0.16]; 0.388
Annualized growth velocity [cm/year][b)] (presented additionally)							
Change to month 12	109	n.d.	10.2 (2.4) 10.10 [9.58; 10.63]	115	n.d.	9.7 (2.5) 9.78 [9.29; 10.26]	0.33 [-0.24; 0.89]; 0.259

Quality of life

CP-4-006 study Endpoint	Somatrogon N	Somatrogon n/N (%)	Genotropin N	Genotropin n/N (%)	Somatrogon vs genotropin RR[c)] [95% CI]; p value
QoLISSY[d), e)]					
Improvement to month 12 by ≥ 15 points[f)]	54	17/49 (34.7)	64	14/59 (23.7)	1.43 [0.81; 2.50]; 0.218

Side effects

CP-4-006 study Endpoint	Somatrogon		Genotropin		Somatrogon vs Genotropin
	N	Patients with event n (%)	N	Patients with event n (%)	RR[c] [95% CI]; p value
Total adverse events (presented additionally)					
	109	95 (87.2)	115	97 (84.3)	-
Serious adverse events (SAE)					
	109	3 (2.8)	115	2 (1.7)	1.99 [0.45; 8.72] 0.229
Severe adverse events[f]					
	109	9 (8.3)	115	6 (5.2)	1.91 [0.79; 4.58] 0.213
Therapy discontinuation due to adverse events					
	109	1 (0.9)	115	0 (0)	6.00 [0.31; 116.61] 0.127
AE with an incidence of ≥ 10% in one of the study arms and a difference of ≥ 5% between the treatment groups **MedDRA system organ classes** Preferred terms					
General disorders and administration site conditions	**109**	**54 (49.5)**	**115**	**38 (33.0)**	**1.48 [1.10; 1.99] 0.004**
Pain at the injection site	109	43 (39.4)	115	29 (25.2)	1.37 [1.02; 1.85] 0.021
Infections and infestations	**109**	**59 (54.1)**	**115**	**56 (48.7)**	**1.17 [0.91; 1.50] 0.222**
Injury, poisoning and procedural complications	**109**	**14 (12.8)**	**115**	**9 (7.8)**	**1.22 [0.63; 2.35] 0.231**
Investigations	**109**	**8 (7.3)**	**115**	**22 (19.1)**	**0.48 [0.25; 0.91] 0.004**
Headache	109	18 (16.5)	115	25 (21.7)	1.07 [0.71; 1.62] 0.392
Eye disorders	**109**	**10 (9.2)**	**115**	**1 (0.9)**	**2.97 [0.98; 9.05] 0.010**
AEs of special interest (regardless of severity grade)					

CP-4-006 study Endpoint	Somatrogon		Genotropin		Somatrogon vs Genotropin
	N	Patients with event n (%)	N	Patients with event n (%)	RR[c] [95% CI]; p value
Reactions at the injection site[g]	109	47 (43.1)	115	29 (25.2)	1.43 [1.06; 1.93] 0.004
Immunogenicity[g]	109	20 (18.3)	115	9 (7.8)	1.78 [0.91; 3.51] 0.034
Impairment of glucose metabolism[g]	109	0 (0)	115	3 (2.6)	0.46 [0.09; 2.40] 0.162
Impairment of thyroid function[g]	109	10 (9.2)	115	11 (9.6)	1.21 [0.64; 2.30] 0.983
Cortisol changes[g]	109	0 (0)	115	1 (0.9)	0.33 [0.02; 7.45] 0.317
Pancreatitis[h]	109	12 (11.0)	115	14 (12.2)	1.15 [0.61; 2.18] 0.608
Epiphyseal disorders[h]	109	0 (0)	115	0 (0)	n.c.

a) Results for the baseline values are available for 109 subjects in the somatrogon arm and 115 in the genotropin arm; month 12 values are available for 108 subjects in the somatrogon arm and 113 in the genotropin arm (FAS).
b) Primary endpoint of the CP-4-006 study
c) Calculated post hoc.
d) The QoLISSY questionnaire was only used in the following countries where a validated translation is available: USA, Australia, New Zealand, Belarus, Russia, Ukraine, Great Britain and Spain. Results for the baseline values are available for the self-reported child version of the QoLISSY for study participants ≥ 7 years (N = 35 in the somatrogon arm, N = 35 in the genotropin arm) and the parent proxy questionnaire for study participants < 7 years (N = 19 in the somatrogon arm, N = 28 in the genotropin arm).
e) Scale from 0 to 100; higher values mean better quality of life.
f) Study-individual classification; severe AE: Severe limitation of activity, usually some assistance is required; medical intervention/ therapy required; hospitalisation possible.
g) Named as safety endpoints in the study protocol; however, the definition of which events are grouped into which AEs of special interest was only made in the study report and in module 4 of the benefit assessment dossier.
h) Required post hoc by the regulatory authorities.

Abbreviations:

FAS: Full Analysis Set; FCS: Fully Conditional Specification; n.d.: CI: Confidence Interval; LS: Least Squares; MedDRA: MAR: Missing At Random; Medical Dictionary for Regulatory Activities; MV: Mean Value; QoLISSY: Quality of Life in RR: Relative Risk; SD: Standard Deviation; Short Stature Youth; (S)AE: (Serious) Adverse Event.

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

Children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone

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 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).

4. Treatment costs

Annual treatment costs:

Children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone

Designation of the therapy	Annual treatment costs/ patient
Medicinal product to be assessed:	
Somatrogon	€ 13,899.84 - € 56,051.85

Costs after deduction of statutory rebates (LAUER-TAXE®) as last revised: 15 August 2022)

Costs for additionally required SHI services: not applicable

II. The resolution will enter into force on the day of its publication on the website of the G-BA on 15 September 2022.

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

Berlin, 15 September 2022

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

Prof. Hecken