EDA Assessment Report for Biological Medicinal Product

(Scientific Discussion)

Omnitrope

Date: November 2024

Unit: Technical Assessment Unit

Assessment report

Omnitrope

Administrative information:

Trade name of the medicinal product:	Omnitrope 15 mg/1.5ml
INN (or common name) of the active substance(s):	Somatropin, RH-GH 15 mg/1.5ml
Manufacturer of the finished product	Sandoz GmbH Schaftenau, Biochemiestrasse 10, 6336 Langkampfen, Austria.
Marketing Authorization holder	Sandoz GmbH, Biochemiestrasse 10, A-6250 Kundl, Austria.
Applied Indication(s):	-**Infants, children and adolescents** -Growth disturbance due to insufficient secretion of growth hormone (growth hormone deficiency, GHD). -Growth disturbance associated with Turner syndrome. -Growth disturbance associated with chronic renal insufficiency. -Growth disturbance (current height standard deviation score (SDS) < -2.5 and parental adjusted height SDS < -1) in short children/adolescents born small for gestational age (SGA), with a birth weight and/or length below -2 standard deviation (SD), who failed to show catch-up growth (height velocity (HV) SDS < 0 during the last year) by 4 years of age or later. -Prader-Willi syndrome (PWS), for improvement of growth and body composition. The diagnosis of PWS should be confirmed by appropriate genetic testing. **Adults**

	-Replacement therapy in adults with pronounced growth hormone deficiency. -*Adult onset:* Patients who have severe growth hormone deficiency associated with multiple hormone deficiencies as a result of known hypothalamic or pituitary pathology, and who have at least one known deficiency of a pituitary hormone not being prolactin. These patients should undergo an appropriate dynamic test in order to diagnose or exclude a growth hormone deficiency. -*Childhood onset:* Patients who were growth hormone deficient during childhood as a result of congenital, genetic, acquired, or idiopathic causes. Patients with childhood onset GHD should be re-evaluated for growth hormone secretory capacity after completion of longitudinal growth. In patients with a high likelihood for persistent GHD, i.e. a congenital cause or GHD secondary to a hypothalamic-pituitary disease or insult, an insulin-like growth factor-I (IGF-I) SDS < -2 off growth hormone treatment for at least 4 weeks should be considered sufficient evidence of profound GHD. **All other patients will require IGF-I assay and one growth hormone stimulation test.
Pharmaceutical form(s) and strength(s):	- Solution for S.C injection in Cartiadge -The strength is 10mg/ml(15mg/1.5ml)
Route of administration	-S.C injection
Approved pack	- Carton box containing 1,5 or 10 colorless glass (type I) cartridges, each of 1.5 ml solution, closed on one side with siliconized bromobutyl plunger and a blue ring, and on the other side with bromobutyl disc and aluminum cap. -The glass cartilage is irreversibly integrated in transparent container and assembled to

	plastic mechanism with a threated rod at one extremity + Insert Leaflet.

List of abbreviations:

GHD	Growth hormone deficiency
SGA	small gestational age
PWS	Prader-Willi syndrome
IGF-I	insulin-like growth factor-I
S.C	Subcutaneous
EMA	European medicines Agency
CTD	Common Technical Document
hCH	for human growth hormone
DNA	Deoxyribonucleic Acid
CRS	Cytokine Release Syndrome
HCF	High concentrated form
BDS	Bulk drug substance
GMP	Good manufacturing practice

Dossier initial submission and evaluation process:

- The product was submitted for registration via reliance level I.
- The dossier evaluation by the registration administration units was started on 12.4.2023 after providing all the required documents (EMA list of questions for Day 120 and Day 150 along with Full CTD for the product)

1. **General introduction about the product including brief description of the AI, its mode of action and indications**:

Somatropin Sandoz is a recombinant human growth hormone produced in *Escherichia coli* K-12 strain MG1655, which has been transformed with the natural cDNA sequence for human growth hormone (hGH). Somatropin Sandoz is produced by fermentation of recombinant *E.coli* K-12 under the control of the PVHb promoter. Somatropin Sandoz is expressed as an N-terminal fusion protein with the signal sequence of the *E. coli* outer membrane protein A

(OmpAss), directing the protein to the periplasm with concurrent processing of the signal sequence. Somatropin Sandoz is a non-glycosylated protein composed of 191 amino acids. The three-letter sequence of the polypeptide chain,the N-terminal and C-terminal amino acids are phenylalanine. The protein molecule contains 4 cysteines, which form 2 intramolecular disulphide bonds between positions Cys53-Cys165 and Cys182-Cys189.

- The drug substance solution used for the manufacturing of Omnitrope 15 mg/1.5 mL complies with the Ph. Eur. monograph (Somatropin Bulk Solution) and has been extensively characterized and compared to the Ph. Eur. standard (Somatropin CRS). The same Somatropin drug substance is used as for the previously developed drug products Omnitrope 3.3 mg/mL and Omnitrope 6.7 mg/mL solution for injection.

- Growth hormone is released by the pituitary gland (a gland at the base of the brain). It is important for growth during childhood and adolescence, and it also affects how the body handles proteins, fat and carbohydrates. The active substance in Omnitrope, somatropin, is identical to the human growth hormone, which it replaces. Somatropin is produced by a method known as 'recombinant DNA technology': the hormone is made by bacteria into which a gene (DNA) has been introduced that makes them able to produce somatropin.
- Omnitrope is also used as replacement therapy in adult patients with pronounced growth hormone deficiency. The deficiency can have started in adulthood or childhood, and needs to be confirmed by testing before treatment.

2. **Quality aspects:**

- **Manufacturer(s):**

Drug substance:

The Somatropin Sandoz drug substance (BDS and HCF) is manufactured according to current Good Manufacturing Practices (cGMP) by Sandoz GmbH Biochemiestrasse 10 A-6250 Kundl, Austria.

Drug product:

Manufacture, release, quality control and packaging (primary and secondary packaging) of Somatropin Sandoz 15.0 mg/1.5 ml Solution for Injection is performed by Sandoz GmbH Plant Schaftenau Biochemiestrasse 10 A-6336 Langkampfen Austria;

- **Stability**

- **Approved shelf life:**

Intermediates:

CAP.P	≤ 167
HIC.PC	≤ 24
HIC.P	≤ 23
RPC.P	≤ 48
AEX.P	≤ 24
DR.62	≤ 24
DR.62A	≤ 24

Active substance:
High Concentrated Form (HCF): 12 months
Finished product:
-18 months
-After first opening: 28 Days

- **Approved Storage Conditions:**

Intermediates:

CAP.P	**2 – 8 ℃**
HIC.PC	**16 – 20 ℃**
HIC.P	**2 – 8 ℃**
RPC.P	**2 – 8 ℃**
AEX.P	**2 – 8 ℃**
DR.62	**2 – 8 ℃**
DR.62A	**2 – 8 ℃**

Active substance:
High Concentrated Form (HCF): Store at -20±5°C
Finished product:
-Store & transport refrigerated between (2 -8°C), don't freeze and store in original package in order to protect from light.
-After first use the cartridge should remain in the pen and has to be kept in a refrigerator (2°C - 8°C) for a maximum of 28 days. Store and transport refrigerated (2°C - 8°C). Do not freeze. Store in the original pen in order to protect from light

3. Non-clinical and clinical aspects:

-The applicant submitted an adequate nonclinical according to the applied guidelines and is considered acceptable from the preclinical point for the proposed indication.

- In conclusion the overall benefit/risk of Omnitrope 10 mg/ ml (15mg/1.5 ml) is favorable in the treatment all indication mentioned above for children and adult.

For more information, please visit EMA published assessment report link:

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