SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Skytrofa 3 mg powder and solvent for solution for injection in cartridge

Skytrofa 3.6 mg powder and solvent for solution for injection in cartridge

Skytrofa 4.3 mg powder and solvent for solution for injection in cartridge

Skytrofa 5.2 mg powder and solvent for solution for injection in cartridge

Skytrofa 6.3 mg powder and solvent for solution for injection in cartridge

Skytrofa 7.6 mg powder and solvent for solution for injection in cartridge

Skytrofa 9.1 mg powder and solvent for solution for injection in cartridge

Skytrofa 11 mg powder and solvent for solution for injection in cartridge

Skytrofa 13.3 mg powder and solvent for solution for injection in cartridge

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Lonapegsomatropin Ascendis Pharma consists of somatropin transiently conjugated to a methoxypolyethylene glycol carrier (mPEG) via a proprietary TransCon Linker. The strength of Lonapegsomatropin Ascendis Pharma always indicates the quantity of the somatropin moiety.

Each dual-chamber cartridge contains 4.3 mg of somatropin* equivalent to 12.3 mg of lonapegsomatropin and 0.388 mL of solvent. After reconstitution the concentration based on somatropin** protein is 11 mg/mL.

* The strength indicates the quantity of the somatropin moiety without consideration of the mPEG-linker.

** Produced in *Escherichia coli* cells by recombinant DNA technology.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and solvent for solution for injection (injection).

White to off-white powder.

The solvent is a clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

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]).

4.2 Posology and method of administration

Method of administration

Each injection should be administered subcutaneously once-weekly in the abdomen, buttock or thigh. The site of administration should be varied to prevent lipoatrophy.

Lonapegsomatropin is intended to be administered after reconstitution of the powder for solution for injection with the enclosed solvent. Lonapegsomatropin should be administered by means of the Skytrofa Auto-Injector. The patient and caregiver should receive training to ensure understanding of the administration procedure by means of the device in order to be allowed to (self)-inject lonapegsomatropin.

The reconstituted solution should be colourless and clear to opalescent and free or practically free of visible particles (see section 6.6).

For instructions on reconstitution of the medicinal product before administration, see section 6.6 and the instructions included at the end of the package leaflet.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 (see section 4.4).

Somatropin must not be used when there is any evidence of activity of a tumour (see section 4.4). Intracranial tumours must be inactive and anti-tumour therapy must be completed prior to starting growth hormone therapy. Treatment should be discontinued if there is evidence of tumour growth.

Patients with acute critical illness suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions must not be treated with lonapegsomatropin (regarding patients undergoing substitution therapy, see section 4.4).

Lonapegsomatropin must not be used for growth promotion in children with closed epiphyses.

4.4 Special warnings and precautions for use

Traceability

In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

Acute critical illness

In critically ill adult patients suffering complications following open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure mortality was higher in patients treated with 5.3 mg or 8 mg somatropin daily (i.e. 37.1 – 56 mg/week) compared to patients receiving placebo, 42% vs. 19%. As there is no information available on the safety of growth hormone substitution therapy in acutely critically ill patients, the benefits of continued lonapegsomatropin treatment in this situation should be weighed against the potential risks involved. In all patients developing other or similar acute critical illness, the possible benefit of treatment with lonapegsomatropin must be weighed against the potential risk involved.

Neoplasm

In patients with previous malignant disease, special attention should be given to signs and symptoms of relapse.
Patients with pre-existing tumours or GHD secondary to an intracranial lesion should be examined routinely for progression or recurrence of the underlying disease process.
In childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with growth hormone after their first neoplasm. Intracranial tumours, in particular meningiomas, were the most common form of a second neoplasm reported in patients treated with radiation to the head for their first neoplasm.

Hypersensitivity

Anaphylactic reactions including angioedema have been reported with the use of lonapegsomatropin.
Inform patients and caregivers that such reactions can occur, particularly after first dose, and that prompt medical attention should be sought if a sudden serious hypersensitivity reaction occurs.
If a hypersensitivity reaction occurs, the use of lonapegsomatropin should be discontinued (see section 4.3).

Benign intracranial hypertension

In case of severe or recurrent ataxia, headache, visual problems, nausea and/or vomiting, a funduscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and, if appropriate, growth hormone treatment should be discontinued. At present there is insufficient evidence to give specific advice on the continuation of growth hormone treatment in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary. Funduscopic examination is recommended at the initiation and periodically during the course of treatment.

Insulin sensitivity

Growth hormone may reduce insulin sensitivity. For patients with diabetes mellitus, the insulin dose may require adjustment after lonapegsomatropin therapy is instituted. Patients with diabetes mellitus, glucose intolerance, or additional risk factors for diabetes mellitus should be monitored closely during lonapegsomatropin therapy (see section 4.5).

Hypoadrenalism

Introduction of growth hormone treatment may result in inhibition of 11β-Hydroxysteroid dehydrogenase type 1 (11βHSD-1) and reduced serum cortisol concentrations. Consequently, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoid

replacement therapy for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses, following initiation of lonapegsomatropin treatment (see section 4.5).

Thyroid function

Growth hormone increases the extrathyroidal conversion of T4 to T3 which may result in a reduction in serum T4 and an increase in serum T3 concentrations. Monitoring of thyroid function should therefore be conducted in all patients. In patients with hypopituitarism on standard replacement therapy, the potential effect of lonapegsomatropin treatment on thyroid function must be closely monitored (see section 4.5 and 4.8).

Slipped capital femoral epiphysis and osteonecrosis

In patients with endocrine disorders, including GHD, slipped epiphyses of the hip may occur more frequently than in the general population. Osteonecrosis has been reported in patients treated with other growth hormone products. Children with persistent hip/knee pain and/or limping during treatment with lonapegsomatropin should be examined clinically.

Scoliosis

Scoliosis may progress in any child during rapid growth. Because growth hormone treatment increases growth rate, signs and progression of scoliosis should be monitored during treatment. However, growth hormone treatment has not been shown to increase the incidence or severity of scoliosis (see section 4.8).

Pancreatitis

Although rare, pancreatitis should be considered in growth hormone treated children who develop unexplained abdominal pain.

Prader-Willi syndrome

Lonapegsomatropin has not been studied in patients with Prader-Willi syndrome. Lonapegsomatropin is not indicated for the long-term treatment of paediatric patients who have growth failure due to genetically confirmed Prader-Willi syndrome unless they also have a diagnosis of GHD. There have been reports of sudden death after initiating therapy with growth hormone in patients with Prader-Willi syndrome who had one or more of the following risk factors: severe obesity, history of upper airway obstruction or sleep apnoea, or unidentified respiratory infection.

Leukaemia

Leukaemia has been reported in a small number of GHD patients, some of whom have been treated with somatropin. However, there is no evidence that the leukaemia incidence is increased in growth hormone recipients without predisposing factors.

Use with oral oestrogen containing therapy

Oral oestrogen influences the IGF-1 response to growth hormone. If a female patient taking lonapegsomatropin begins oral oestrogen containing therapy, the dose of lonapegsomatropin may need to be increased to maintain the serum IGF-1 levels within the normal age appropriate range (see section 4.2). Conversely, if a female patient on lonapegsomatropin discontinues oral oestrogen containing therapy, the dose of lonapegsomatropin may need to be reduced to avoid excess of growth hormone and/or adverse reactions (see section 4.5).

Antibodies

Antibodies to lonapegsomatropin were observed in some patients. None of these antibodies were neutralising and there was no apparent clinical impact. However, testing for the presence of antibodies should be considered in patients who fail to respond to therapy.

4.5 Interaction with other medicinal products and other forms of interaction

Glucocorticoid treatment

Concomitant treatment with glucocorticoids inhibits the growth-promoting effects of lonapegsomatropin. Patients with adrenocorticotropic hormone (ACTH) deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth, and patients treated with glucocorticoids should have their growth monitored carefully to assess the potential impact of glucocorticoid treatment on growth.

Growth hormone decreases the conversion of cortisone to cortisol and may unmask previously undiscovered central hypoadrenalism or render low glucocorticoid replacement doses ineffective (see section 4.4).

Cytochrome P450-metabolised products

Drug-drug interaction studies have not been performed with lonapegsomatropin. Data from interaction studies with somatropin performed in growth hormone deficient children and adults, and healthy elderly men, suggest that somatropin administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes, especially CYP3A and CYP1A2. The clearance of compounds metabolised by CYP 3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and ciclosporin) and CYP1A2 (e.g. theophylline) may be increased and could result in lower exposure of these compounds. The clinical significance of this is unknown.

Insulin and/or other hypoglycaemic agents

In patients with diabetes mellitus requiring therapy with a medicinal product (e.g, anti-hyperglycaemic medicinal products), the dose of insulin and/or oral hypoglycaemic medicinal product may require adjustment when lonapegsomatropin therapy is initiated (see section 4.4).

Thyroid hormones

Because growth hormone increases the extrathyroidal conversion of T4 to T3, adjustment of thyroid hormone replacement therapy may be necessary (see section 4.4).

Oral oestrogen therapy

In female patients on oral oestrogen-containing therapy, a higher dose of growth hormone may be required to achieve the treatment goal (see section 4.2 and 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no or limited amount of data from the use of lonapegsomatropin in pregnant women; published studies with short-acting somatropin use in pregnant women over several decades have not identified any drug-associated risk of major birth defects, miscarriages, or adverse maternal or foetal outcomes.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). Lonapegsomatropin Ascendis Pharma is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breastfeeding

There are no data on the presence of lonapegsomatropin in human milk or effect on the breastfed newborns/infants. As lonapegsomatropin is not orally absorbed, it is unlikely to adversely affect the breastfed newborns/infants.

Lonapegsomatropin Ascendis Pharma can be used during breastfeeding on strict indication.

Fertility

There are no clinical data on the effect of lonapegsomatropin on fertility. Animal studies are insufficient with respect to fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Lonapegsomatropin has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The most frequently reported adverse reactions in clinical trials with lonapegsomatropin were headache (11.1%), arthralgia (4.6%), secondary hypothyroidism (2.6%), and injection site reactions (1.6%). In general, these reactions tended to be transient and severity was mild to moderate.

Tabulated list of adverse reactions

Table 3 below shows adverse reactions which occurred during lonapegsomatropin treatment. The adverse reactions are ranked under headings of MedDRA system organ class and frequency using the following terminology: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1,000 to <1/100), rare (≥1/10,000 to <1/1,000), very rare (<1/10,000), and frequency not known (cannot be estimated from the available data).

Table 3 Frequency of adverse reactions in clinical trials

System organ class	Very common	Common	Uncommon
Immune system disorders			Anaphylactic reaction[b]
Endocrine disorders		Secondary hypothyroidism	Secondary adrenocortical insufficiency
Nervous system disorders	Headache		
Musculoskeletal and connective tissue disorders		Arthralgia	Scoliosis Arthritis Growing pains
Reproductive system and breast disorders			Gynaecomastia
General disorders and administration site conditions		Injection site reactions[a]	

[a] Injection site reactions include hyperaemia, injection site atrophy, injection site pain, injection site urticaria, and localised oedema. The injection site reactions observed with lonapegsomatropin were generally mild and transient.

[b] Anaphylactic reactions reported with lonapegsomatropin included angioedema (see section 4.4).

Description of selected adverse reactions

Immunogenicity

Patients may develop antibodies to lonapegsomatropin. The proportion of patients testing positive for detectable binding antibodies at any time during treatment was low (6.3%) and no patients had neutralising antibodies. No apparent correlation of anti-lonapegsomatropin binding antibodies to adverse events or loss of efficacy was observed. In case of an otherwise unexplained lack of response to lonapegsomatropin treatment, testing for antibodies to lonapegsomatropin should be considered (see section 4.4).

Adverse reactions related to growth hormone pharmacological class

In addition to the above-mentioned adverse drug reactions, those presented below have been reported with other growth hormone-containing products. Frequencies of these adverse events cannot be estimated from the available data (unless otherwise indicated).

- Neoplasms benign, malignant and unspecified (including cysts and polyps): leukaemia (see section 4.4).
- Metabolism and nutrition disorders: diabetes mellitus type 2 (see section 4.4).
- Nervous system disorders: benign intracranial hypertension (see section 4.4), paraesthesia.
- Musculoskeletal and connective tissue disorders: myalgia.
- Reproductive system and breast disorders: gynaecomastia (frequency: uncommon).
- Skin and subcutaneous tissue disorders: skin rash, urticaria and pruritus.
- General disorders and administration site conditions: peripheral oedema, facial oedema.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Symptoms

Acute overdose could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Long-term overdose could result in signs and symptoms of gigantism.

Management

Treatment is symptomatic and supportive. There is no antidote for somatropin overdose.
It is recommended to monitor thyroid function following an overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatropin and somatropin agonists, ATC Code: H01AC09.

Mechanism of action

Lonapegsomatropin is a long-acting 'prodrug' of somatropin. Lonapegsomatropin consists of the parent drug, somatropin, that is transiently conjugated to a methoxypolyethylene glycol carrier (4 x 10 kDa mPEG) via a proprietary TransCon Linker. The carrier has a shielding effect that minimizes renal excretion and receptor-mediated clearance of lonapegsomatropin. After subcutaneous administration, lonapegsomatropin releases fully active somatropin via autocleavage of the TransCon Linker. Somatropin (191 amino acids) has the same mode of action and distribution as daily somatropin, but with a once-weekly subcutaneous injection.

Somatropin binds to a dimeric hGH receptor in the cell membrane of target cells resulting in intracellular signal transduction and a host of pharmacodynamic effects. Somatropin has direct tissue and metabolic effects, and indirect effects mediated by IGF-1, including stimulation of chondrocyte differentiation and proliferation, stimulation of hepatic glucose output, protein synthesis and lipolysis. Somatropin stimulates skeletal growth in paediatric patients with GHD as a result of effects on the growth plates (epiphyses) of bones.

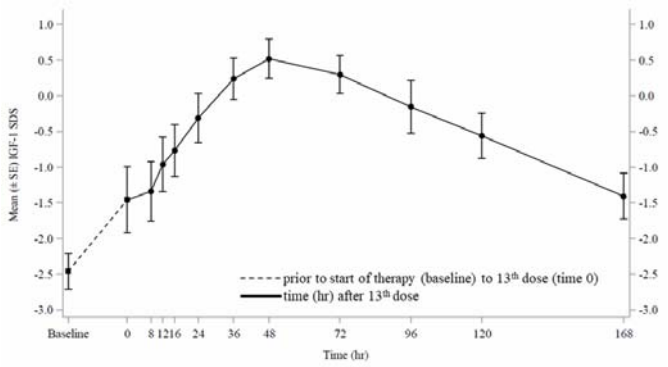
Pharmacodynamic effects

Somatropin released from lonapegsomatropin produces a dose linear IGF-1 response, with a change in dose of 0.02 mg somatropin/kg resulting in an approximate change in average weekly IGF-1 standard deviation score (SDS) of 0.17.

At steady-state, IGF-1 SDS levels peaked approximately 2 days post-dose, with the average weekly IGF-1 SDS coinciding with approximately 4.5 days post-dose

(Figure 1). IGF-1 SDS levels were in the normal range for GHD patients for the majority of the week, similar to daily somatropin.

Figure 1 Mean (±SE) IGF-1 SDS at steady-state in children with GHD after administration of once-weekly lonapegsomatropin 0.24 mg somatropin/kg/week



Clinical efficacy and safety

The efficacy and safety of once-weekly lonapegsomatropin were evaluated in phase 3 clinical trials that included 306 paediatric patients with GHD.

heiGHt trial:
In a 52-week multi-centre randomised, open-label, active-controlled, parallel-group phase 3 clinical trial, 161 treatment-naïve, prepubertal paediatric patients with GHD were randomised to once-weekly lonapegsomatropin (N=105) or daily somatropin (N=56), both at a total weekly dose of 0.24 mg somatropin/kg. The patients ranged in age from 3.2 to 13.1 years with a mean of 8.5 years. Most (N=132 (82%)) subjects were male. The patients had a mean baseline height SDS of -2.93. The primary efficacy endpoint was annualised height velocity (AHV) at week 52. Treatment with once-weekly lonapegsomatropin for 52 weeks resulted in a non-inferior AHV compared to daily somatropin (Table 4). Also, changes in the height standard deviation score (SDS) (change from baseline) tended to be larger for once-weekly lonapegsomatropin compared to daily somatropin (Table 4). Changes in AHV and height SDS tended to be larger for lonapegsomatropin compared to those of somatropin from week 26 through the end of the trial at week 52.

The mean (SD) ratio of bone age to chronological age advanced similarly in both arms from baseline to week 52: 0.69 (0.16) to 0.75 (0.15) with once-weekly lonapegsomatropin and 0.70 (0.14) to 0.76 (0.14) with daily somatropin.

Table 4 Growth and IGF-1 response at week 52 in paediatric treatment-naïve patients with GHD (Intention-to-treat analysis)

	Once-weekly lonapegsomatropin (N=105) (0.24 mg somatropin/kg/week)	**Daily somatropin (N=56) (0.24 mg somatropin/kg/week)**	**Estimate of treatment difference (lonapegsomatropin minus somatropin)**
AHV (cm/year)[a], LS mean (95% CI)	11.2 (10.7-11.6)	10.3 (9.7-10.9)	0.9[b] (0.2-1.5)
Height SDS, change from baseline[c], LS mean (95% CI)	1.10 (1.02-1.18)	0.96 (0.85-1.06)	0.14[d] (0.03-0.26)
IGF-1 SDS category[e], %			
< 0	23.1%	40.7%	Not analysed
0 to +2	69.2%	57.4%	
+2 to +3	7.7%	1.9%	
>+3	0	0	

[a] AHV: The estimates of LS mean and 95% CI are from an ANCOVA model that included baseline age, peak growth hormone levels (log transformed) at stimulation test, baseline height SDS – average SDS of parental height as covariates, and treatment and gender as factors. Missing data are imputed with multiple imputation method.

[b] p=0.0088 (2-sided) for superiority

[c] Height SDS, change from baseline: The estimates of LS mean and 95% CI are from an ANCOVA model that included baseline age, peak growth hormone levels (log transformed) at stimulation test and baseline height SDS as covariates, and treatment and gender as factors.

[d] p=0.0149 (2-sided)

[e] Average level at week 52

In an open-label extension trial, patients from the heiGHt trial who continued treatment with lonapegsomatropin had an increase in height SDS of 1.61 from baseline to week 104. Patients who switched from daily somatropin to lonapegsomatropin at week 52 had an increase in height SDS of 1.49 from baseline to week 104.

Supportive evidence

Evidence from additional clinical trials with lonapegsomatropin supports the long-term clinical efficacy of lonapegsomatropin treatment.

fliGHt trial:
In a 26-week single-arm open-label clinical trial evaluating lonapegsomatropin 0.24 mg somatropin/kg/week in 146 paediatric GHD patients aged 1 to 17 years old, of whom 143 had received prior daily somatropin treatment for mean (SD) 1.1 (0.7) years, the mean (SD) annualised height velocity was 9 (2.7) cm/year and the mean (SD) change from trial baseline in height SDS was 0.28 (0.25). Patient and caregiver preference were evaluated at week 13. 84% of patients and 90% of caregivers preferred once-weekly lonapegsomatropin over their prior daily somatropin.

Table 5 Average IGF-1 SDS levels at baseline and week 26 in paediatric treatment-experienced patients with GHD (intention-to-treat analysis)

Average IGF-1 SDS category	Baseline (N=143) n (%)	Week 26 (N=139) n (%)
< 0	37 (25.9)	13 (9.4)
0 to +2	74 (51.7)	71 (51.1)
+2 to +3	27 (18.9)	33 (23.7)
> +3	5 (3.5)	22 (15.8)

enliGHten trial:
In a long-term open-label extension trial, which enrolled patients from the heiGHt trial and fliGHt trial, patients (N=298) who continued treatment with lonapegsomatropin had a mean (SD) height SDS at extension trial baseline of -1.56 (0.88) and at week 208 (the last visit for which adequate data are available) -0.39 (0.90), corresponding to a mean (SD) change of +1.24 (0.65).

5.2 Pharmacokinetic properties

The pharmacokinetics following administration of lonapegsomatropin was assessed after single dose in a total of 73 healthy adults in 2 trials. In addition, PK in paediatrics with GHD was evaluated based on intense sampling at week 13 in 11 subjects and sparse sampling in 109 subjects across 2 trials. Demographic details are provided in Table 6 for the subjects included in the pharmacokinetic evaluation of lonapegsomatropin.

Table 6 Demography of subjects in pharmacokinetic evaluation of lonapegsomatropin

Category	Healthy adults	Children with GHD
N	73	109
Male / Female	55 / 19	87 / 22
American Indian or Alaska Native	0	0
Asian	10	1
Black or African American	13	2
Native Hawaiian or Other Pacific Islander	0	0
White	49	104 (11 with intense PK sampling)
Other/Multiple	1	2
Hispanic or Latino	23	5
Not Hispanic or Latino	50	104

Absorption

Following subcutaneous dose administration, lonapegsomatropin releases somatropin in a controlled manner that follows first-order kinetics.

In paediatric GHD patients, following subcutaneous dose administration of lonapegsomatropin 0.24 mg somatropin/kg/week, the observed mean (CV%) steady state peak serum concentration (C_{max}) of lonapegsomatropin

was 1230 (86.3) ng somatropin/mL at median T_{max} of 25 hours, and for released somatropin C_{max} was 15.2 (83.4) ng/mL with a median time to reach C_{max} of 12 hours. The mean (CV%) somatropin exposure over the one-week dose interval (area under the curve) was 500 (83.8) h*ng/mL. Accumulation of lonapegsomatropin or somatropin following repeat dose administration was not observed.

In paediatric GHD patients, injections were rotated between the abdomen, buttock, and thigh. No apparent association of administration site with somatropin exposure was observed.

The absolute bioavailability of lonapegsomatropin following subcutaneous dose administration has not been investigated.

Distribution

In paediatric GHD patients, the mean (CV%) steady state apparent volume of distribution of lonapegsomatropin after subcutaneous administration of 0.24 mg somatropin/kg/week was 0.13 (109) L/kg. Somatropin released from lonapegsomatropin is expected to have a similar volume of distribution as endogenous growth hormone.

Elimination

Metabolism

The metabolic fate of somatropin involves protein catabolism in both the liver and kidneys.

Excretion

In paediatric GHD patients, the mean (CV%) steady state apparent clearance of lonapegsomatropin after subcutaneous administration of 0.24 mg somatropin/kg/week was 3.2 (67) mL/h/kg with a mean (±SD) observed half-life of 30.7 (± 12.7) hours. The apparent half-life of somatropin released from lonapegsomatropin was approximately 25 hours.

Special populations

No sex-specific pharmacokinetic studies have been done with lonapegsomatropin. The available literature indicates that the pharmacokinetics of somatropin is similar in males and females.

Based on a population pharmacokinetic analysis, age, sex, race/ethnicity, and body weight do not have a clinically meaningful effect on the pharmacokinetics.

No studies in patients with renal or hepatic impairments have been conducted with lonapegsomatropin (see section 4.2). A reduction in somatropin clearance following administration of daily somatropin has been noted in patients with severe liver and kidney dysfunction. The clinical significance of this decrease is unknown. The pharmacokinetics of the mPEG carrier of lonapegsomatropin is expected to be dependent on renal function but has not been assessed in patients with renal impairment.

Lonapegsomatropin has not been studied in patients below 6 months of age (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenicity.

Reproductive toxicology studies performed in rats and histopathological evaluation of reproductive organs in monkeys administered subcutaneous lonapegsomatropin at doses up to 20-fold the clinical dose of 0.24 mg somatropin/kg/week did not induce adverse effects on male and female fertility or on reproductive organs. Due to antibody formation impairing exposure in rats, no firm conclusion can be made with respect to the relevance for human fertility.

No embryonic or foetal development toxicities occurred in rats administered subcutaneous lonapegsomatropin at doses up to 13-fold the clinical dose of 0.24 mg somatropin/kg/week. Due to intermittent exposure no firm conclusion can be made with respect to the embryo-foetal development study in rats.

An embryo-foetal development toxicity study in rabbits has shown foetal abnormalities and embryo-foetal mortality at 1.5-fold and 6-fold, the clinical dose of 0.24 mg somatropin/kg/week, respectively, and possibly caused by maternal toxicity. The clinical relevance of these findings is uncertain.

In a pre- and postnatal developmental study in rats there were no adverse effects on the pregnant/lactating female or on development of the conceptus and the offspring following exposure of the female from implantation through weaning to subcutaneous doses of a structurally related transiently pegylated somatropin prodrug up to 13-fold the clinical dose of 0.24 mg somatropin/kg/week.

<u>mPEG exposure</u>

At about 10 times the human exposure to the mPEG component of lonapegsomatropin, vacuolation occurs in choroid plexus (CP) epithelial cells of cynomolgus monkeys after one year of exposure. At about 34 times the human exposure to mPEG, a slight increase in the number of animals with

vacuoles was seen in CP epithelial cells of monkeys. The vacuolation was not associated with adverse morphological changes or clinical signs. Vacuolation of cells is considered an adaptive response. Therefore, this is not considered as a possible adverse effect in humans at the therapeutic dose.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Powder

Succinic acid
Trehalose dihydrate
Trometamol

Solvent

Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

Unopened

3 years when stored in a refrigerator (2°C - 8°C).

Alternatively, Lonapegsomatropin Ascendis Pharma may be stored at temperatures ≤30°C for up to 6 months. Within the 6 months, the medicinal product can be returned to refrigeration (2°C - 8°C).

Record the date on the carton when the medicinal product was first removed from the refrigerator. Discard the medicinal product when 6 months have passed.

After reconstitution

Chemical and physical in-use stability has been demonstrated for reconstituted product stored for 4 hours at temperatures ≤30°C.

From a microbiological point of view, the product should be used immediately after reconstitution. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and should not exceed 4 hours at temperatures ≤30°C.

6.4 Special precautions for storage

Store in refrigerator (2°C - 8°C). Do not freeze.

Store in the original package in order to protect from light.

For alternative storage conditions at temperatures ≤30°C, see section 6.3.

For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Glass cartridge (Type I glass) with two chambers separated by a rubber stopper (bromobutyl). The cartridge is closed by a rubber stopper (bromobutyl) in one end and by a rubber closure disc (bromobutyl) in the other end. The cartridge is mounted in a plastic needle adaptor.

Each pack contains 4 single-use dual-chamber cartridges packed in individual blisters and 6 disposable injection needles 0.25 mm x 4 mm (31G x 5/32”). Each dual-chamber cartridge has a specific label with assigned two-colour coding ribbons that is only used by the Auto-Injector to select the correct reconstitution settings. Strength colours are indicated on the carton and blister foil and should be used to differentiate the individual strengths.

Each dual-chamber cartridge contains 4.3 mg of somatropin as powder in the first chamber and 0.388 mL of solvent in the second chamber. The cartridge two-colour label (bottom/top) is yellow/pink. The strength colour on the carton and blister is dark grey.

6.6 Special precautions for disposal

Handling

If refrigerated, keep at room temperature for 15 minutes before use.

Each Skytrofa dual-chamber cartridge containing the powder and solvent for solution for injection is for single-use only and must only be used with the supplied injection needles and the Skytrofa Auto-Injector. The Skytrofa Auto-Injector is not included in this pack. The powder for solution for injection must be reconstituted with the enclosed solvent by a Skytrofa Auto-Injector after attaching the needle to the dual-chamber cartridge.

The reconstituted solution should be colourless and clear to opalescent and free or practically free of visible particles. The solution may occasionally contain air bubbles. If the solution contains particles, it must not be injected.

Following reconstitution, Skytrofa is administered subcutaneously (automatically dosed) by the Skytrofa Auto-Injector.

Skytrofa is dosed as a full single-dose (total use).

Read the instructions for use for preparing Skytrofa provided at the end of the package leaflet and the instructions for use provided with the Skytrofa Auto-Injector before use.

Disposal

The patient should be advised to discard the cartridge and injection needle after each injection. Any unused medicinal product or waste material should be disposed in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Ascendis Pharma Endocrinology Division A/S
Tuborg Boulevard 12
DK-2900 Hellerup
Denmark

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 47497/0003

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

17/10/2022

10 DATE OF REVISION OF THE TEXT

24/12/2025