**ANNEX I**

**SUMMARY OF PRODUCT CHARACTERISTICS**

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

## 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

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

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

Each dual-chamber cartridge contains 3 mg of somatropin* equivalent to 8.6 mg of lonapegsomatropin and 0.279 mL of solvent. After reconstitution the concentration based on somatropin** protein is 11 mg/mL.

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

Each dual-chamber cartridge contains 3.6 mg of somatropin* equivalent to 10.3 mg of lonapegsomatropin and 0.329 mL of solvent. After reconstitution the concentration based on somatropin** protein is 11 mg/mL.

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

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.

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

Each dual-chamber cartridge contains 5.2 mg of somatropin* equivalent to 14.8 mg of lonapegsomatropin and 0.464 mL of solvent. After reconstitution the concentration based on somatropin** protein is 11 mg/mL.

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

Each dual-chamber cartridge contains 6.3 mg of somatropin* equivalent to 18 mg of lonapegsomatropin and 0.285 mL of solvent. After reconstitution the concentration based on somatropin** protein is 22 mg/mL.

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

Each dual-chamber cartridge contains 7.6 mg of somatropin* equivalent to 21.7 mg of lonapegsomatropin and 0.338 mL of solvent. After reconstitution the concentration based on somatropin** protein is 22 mg/mL.

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

Each dual-chamber cartridge contains 9.1 mg of somatropin* equivalent to 25.9 mg of lonapegsomatropin and 0.4 mL of solvent. After reconstitution the concentration based on somatropin** protein is 22 mg/mL.

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

Each dual-chamber cartridge contains 11 mg of somatropin* equivalent to 31.4 mg of lonapegsomatropin and 0.479 mL of solvent. After reconstitution the concentration based on somatropin** protein is 22 mg/mL.

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

Each dual-chamber cartridge contains 13.3 mg of somatropin* equivalent to 37.9 mg of lonapegsomatropin and 0.574 mL of solvent. After reconstitution the concentration based on somatropin** protein is 22 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

Treatment should be initiated and monitored by physicians who are qualified and experienced in the diagnosis and management of paediatric patients with GHD.

The amount and concentration of lonapegsomatropin is always expressed in terms of mg somatropin referring to the content of the somatropin moiety and not including mPEG-linker in order to prevent medication errors when patients switch from daily somatropin therapy.

Posology

The posology and administration should be individualised for each patient.

*Starting dose*

The recommended starting dose of Skytrofa is 0.24 mg somatropin/kg body weight, given once weekly. The recommended starting dose strengths for such a dose by weight range can be found in Table 1.

**Table 1 Recommended dose for patients by weight, when prescribed doses of 0.24 mg somatropin/kg/week**

| Weight (kg) | Somatropin dose strength |
|---|---|
| 11.5 – 13.9 | 3 mg |
| 14 – 16.4 | 3.6 mg |
| 16.5 – 19.9 | 4.3 mg |
| 20 – 23.9 | 5.2 mg |
| 24 – 28.9 | 6.3 mg |
| 29 – 34.9 | 7.6 mg |
| 35 – 41.9 | 9.1 mg |
| 42 – 50.9 | 11 mg |
| 51 – 60.4 | 13.3 mg |
| 60.5 – 69.9 | 15.2 mg (using two dual-chamber cartridges of 7.6 mg each) |
| 70 – 84.9 | 18.2 mg (using two dual-chamber cartridges of 9.1 mg each) |
| 85 – 100 | 22 mg (using two dual-chamber cartridges of 11 mg each) |

If prescribing a dose other than 0.24 mg somatropin/kg/week, calculate the total weekly dose (in mg somatropin) and select the appropriate dose strength as follows:

- Total weekly dose (mg somatropin) = prescribed dose (mg somatropin/kg) x patient's body weight (kg)
- Round the total weekly dose (mg somatropin) to the closest dose strength while also considering treatment goals and clinical response.

*Starting dose for patients switching from daily somatropin medicinal products*

If changing therapy to once-weekly lonapegsomatropin from daily somatropin, there should be at least 8 hours between the final dose of once-daily somatropin and the first dose of lonapegsomatropin.

In children switching from daily somatropin, physicians may adjust the starting dose taking into consideration the current somatropin dose, individual clinical response, and clinical considerations specific to the patient.

For children switching from daily somatropin medicinal products at a weekly dose equal to or greater than 0.24 mg somatropin/kg body weight, the recommended starting dose of lonapegsomatropin is 0.24 mg somatropin/kg body weight (Table 1).

For children switching from daily somatropin medicinal products at a weekly dose less than 0.24 mg somatropin/kg body weight, use the previously prescribed weekly dose as the recommended starting dose of lonapegsomatropin (see equation above).

*Dose titration*

The dose of lonapegsomatropin should be individually adjusted for each patient based on clinical response, adverse reactions, and/or serum insulin-like growth factor-1 (IGF-1) concentrations outside the targeted range. Available somatropin dose strengths can be found in section 1.

Average IGF-1 standard deviation score (SDS) levels (drawn 4-5 days after dosing) can be used as guidance for dose titration (Table 2). It is necessary to wait a minimum of 2 weeks after initiation of lonapegsomatropin or after any dose change before assessing the resulting IGF-1 SDS levels. Dose adjustments should be targeted to achieve average IGF-1 SDS levels in the normal range, i.e. between -2 and +2 (preferably close to 0 SDS).

IGF-1 SDS levels may vary over time, and therefore routine monitoring of serum IGF-1 SDS levels throughout the course of treatment is recommended, especially during puberty.

**Table 2 Recommended change in somatropin dose strength for average IGF-1 SDS categories**

| Average IGF-1 SDS range (drawn on post-dose day 4-5) | Recommended change in somatropin dose strength |
|---|---|
| > +4 | Reduce by 3 dose strengths |
| +3 to +4 | Reduce by 2 dose strengths |
| +2 to +3 | Reduce by 1 dose strength |
| -2 to +2 | No change |
| < -2 | Increase by 1 dose strength |

*Treatment evaluation*

Evaluation of efficacy and safety should be considered at approximately 6- to 12-month intervals and may be assessed by evaluating auxological parameters, biochemistry (IGF-1, hormones, glucose, and lipid levels), and pubertal status. More frequent evaluations should be considered during puberty.

Treatment should be discontinued in patients with annualised height velocity < 2 cm/year, final height achievement, height velocity SDS < + 1 after the first year of treatment, or in case bone age is > 14 years (girls) or > 16 years (boys) which corresponds to the closure of the epiphyseal growth plates.

Once the epiphyses are fused, patients should be clinically re-evaluated for the need for growth hormone treatment.

*Oral oestrogen therapy*

Females on oral oestrogen-containing therapy may require a higher dose of growth hormone to achieve the treatment goal (see section 4.4).

*Missed dose*

If a dose is missed, it should be administered as soon as possible and no more than 2 days after the missed dose. If more than 2 days have passed, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day. In each case, patients can then resume their regular once-weekly dosing schedule.

*Changing the dosing day*

The day of weekly injection can be changed to a different day of the week. Lonapegsomatropin can be administered 2 days before or 2 days after the scheduled dosing day. It should be ensured that at least 5 days will pass between the last dose and the newly-established regular once-weekly dosing day.

*Special populations*

*Renal impairment*

No information in patients with renal impairment is available and dose recommendations cannot be given.

*Hepatic impairment*

No information in patients with hepatic impairment is available and dose recommendations cannot be given.

*Paediatric population*

The safety and efficacy of lonapegsomatropin in children under 3 years of age has not been established. Currently available data are described in section 5.1 but no recommendation on a posology can be made.

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). Skytrofa 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.

Skytrofa 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<br>Arthritis<br>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 the national reporting system listed in Appendix V.

### 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.

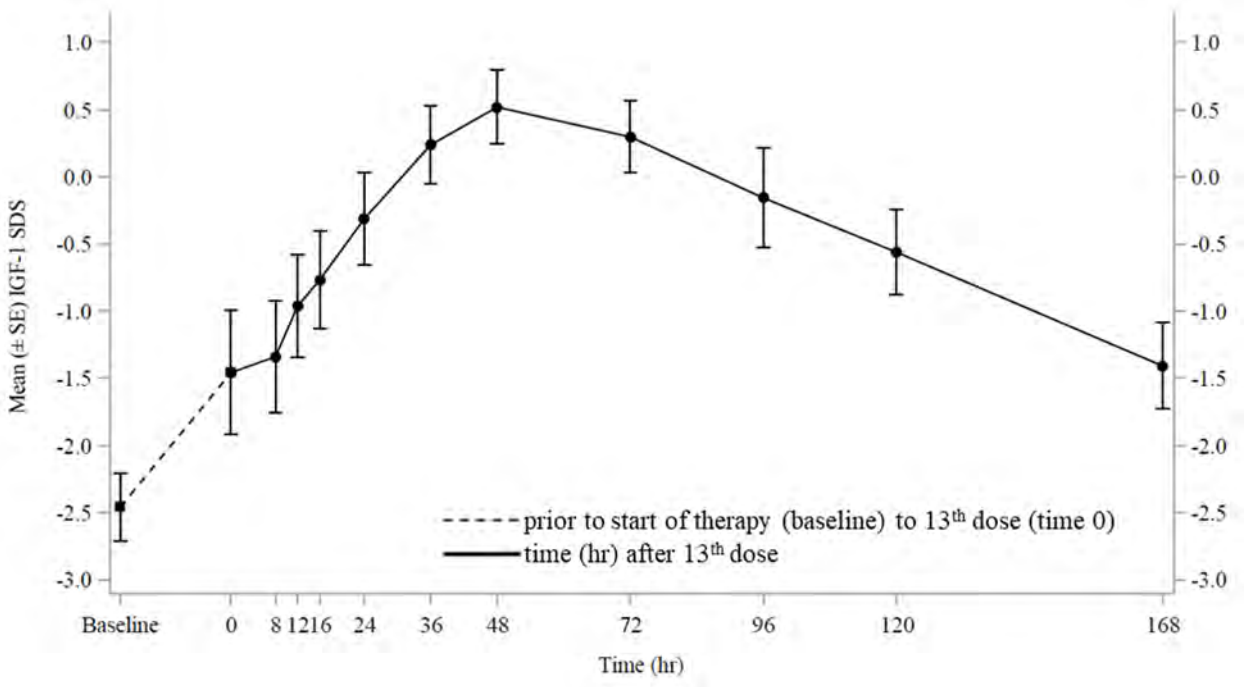
Somatropin stimulates skeletal growth in paediatric patients with GHD as a result of effects on the growth plates (epiphyses) of bones.

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.

mPEG exposure

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

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

Alternatively, Skytrofa 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.

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

Each dual-chamber cartridge contains 3 mg of somatropin as powder in the first chamber and 0.279 mL of solvent in the second chamber. The cartridge two-colour label (bottom/top) is yellow/green. The strength colour on the carton and blister is light apricot.

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

Each dual-chamber cartridge contains 3.6 mg of somatropin as powder in the first chamber and 0.329 mL of solvent in the second chamber. The cartridge two-colour label (bottom/top) is yellow/cyan. The strength colour on the carton and blister is cyan.

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

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.

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

Each dual-chamber cartridge contains 5.2 mg of somatropin as powder in the first chamber and 0.464 mL of solvent in the second chamber. The cartridge two-colour label (bottom/top) is green/pink. The strength colour on the carton and blister is yellow.

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

Each dual-chamber cartridge contains 6.3 mg of somatropin as powder in the first chamber and 0.285 mL of solvent in the second chamber. The cartridge two-colour label (bottom/top) is cyan/yellow. The strength colour on the carton and blister is orange.

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

Each dual-chamber cartridge contains 7.6 mg of somatropin as powder in the first chamber and 0.338 mL of solvent in the second chamber. The cartridge two-colour label (bottom/top) is cyan/pink. The strength colour on the carton and blister is dark purple.

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

Each dual-chamber cartridge contains 9.1 mg of somatropin as powder in the first chamber and 0.4 mL of solvent in the second chamber. The cartridge two-colour label (bottom/top) is pink/yellow. The strength colour on the carton and blister is golden brown.

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

Each dual-chamber cartridge contains 11 mg of somatropin as powder in the first chamber and 0.479 mL of solvent in the second chamber. The cartridge two-colour label (bottom/top) is pink/green. The strength colour on the carton and blister is dark blue.

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

Each dual-chamber cartridge contains 13.3 mg of somatropin as powder in the first chamber and 0.574 mL of solvent in the second chamber. The cartridge two-colour label (bottom/top) is pink/cyan. The strength colour on the carton and blister is dark red.

## 6.6 Special precautions for disposal and other handling

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)

EU/1/21/1607/001
EU/1/21/1607/002
EU/1/21/1607/003
EU/1/21/1607/004
EU/1/21/1607/005
EU/1/21/1607/006
EU/1/21/1607/007
EU/1/21/1607/008
EU/1/21/1607/009

## 9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 11 January 2022

## 10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

# ANNEX II

**A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE**

**B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE**

**C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION**

**D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

## A. MANUFACTURER(S) OF THE BIOLOGICAL ACTIVE SUBSTANCE(S) AND MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) of the biological active substance(s)

FUJIFILM Diosynth Biotechnologies UK Limited
Belasis Avenue
Billingham
TS23 1LH
United Kingdom

LONZA AG
Lonzastrasse
3930 Visp
Switzerland

Name and address of the manufacturer(s) responsible for batch release

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

## B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

## C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

## D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile

or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

**ANNEX III**

**LABELLING AND PACKAGE LEAFLET**

# A. LABELLING

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dual-chamber cartridge contains 3 mg of somatropin equivalent to 8.6 mg of lonapegsomatropin and 0.279 mL of solvent. After reconstitution the concentration based on somatropin protein is 11 mg/mL

## 3. LIST OF EXCIPIENTS

Excipients:
Powder: succinic acid, trehalose dihydrate, trometamol
Solvent: water for injections
See leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
4 single-use cartridges and 6 disposable injection needles

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use
Once-weekly injection
For use only with Skytrofa Auto-Injector

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use within 4 hours

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at temperatures up to 30°C for up to 6 months. Within the 6 months, this medicine can be returned to refrigeration (2°C to 8°C).

Date first removed from refrigerator: _____. Discard after 6 months

Store in the original package in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1607/001

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Skytrofa 3 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ascendis Pharma Endocrinology Division A/S

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

STOP HERE

Do not remove this part of the peel paper

Subcutaneous use

Read the package leaflet before use

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL FOR DUAL-CHAMBER CARTRIDGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Skytrofa 3 mg powder and solvent for solution for injection
lonapegsomatropin
SC

## 2. METHOD OF ADMINISTRATION

Subcutaneous use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dual-chamber cartridge contains 3.6 mg of somatropin equivalent to 10.3 mg of lonapegsomatropin and 0.329 mL of solvent. After reconstitution the concentration based on somatropin protein is 11 mg/mL

## 3. LIST OF EXCIPIENTS

Excipients:
Powder: succinic acid, trehalose dihydrate, trometamol
Solvent: water for injections
See leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
4 single-use cartridges and 6 disposable injection needles

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use
Once-weekly injection
For use only with Skytrofa Auto-Injector

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use within 4 hours

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at temperatures up to 30°C for up to 6 months. Within the 6 months, this medicine can be returned to refrigeration (2°C to 8°C)

Date first removed from refrigerator: _____. Discard after 6 months

Store in the original package in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1607/002

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Skytrofa 3.6 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ascendis Pharma Endocrinology Division A/S

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

STOP HERE

Do not remove this part of the peel paper

Subcutaneous use

Read the package leaflet before use

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL FOR DUAL-CHAMBER CARTRIDGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Skytrofa 3.6 mg powder and solvent for solution for injection
lonapegsomatropin
SC

## 2. METHOD OF ADMINISTRATION

Subcutaneous use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

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

## 3. LIST OF EXCIPIENTS

Excipients:
Powder: succinic acid, trehalose dihydrate, trometamol
Solvent: water for injections
See leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
4 single-use cartridges and 6 disposable injection needles

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use
Once-weekly injection
For use only with Skytrofa Auto-Injector

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use within 4 hours

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at temperatures up to 30°C for up to 6 months. Within the 6 months, this medicine can be returned to refrigeration (2°C to 8°C)

Date first removed from refrigerator: _____. Discard after 6 months

Store in the original package in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1607/003

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Skytrofa 4.3 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ascendis Pharma Endocrinology Division A/S

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

STOP HERE

Do not remove this part of the peel paper

Subcutaneous use

Read the package leaflet before use

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL FOR DUAL-CHAMBER CARTRIDGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Skytrofa 4.3 mg powder and solvent for solution for injection
lonapegsomatropin
SC

## 2. METHOD OF ADMINISTRATION

Subcutaneous use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dual-chamber cartridge contains 5.2 mg of somatropin equivalent to 14.8 mg of lonapegsomatropin and 0.464 mL of solvent. After reconstitution the concentration based on somatropin protein is 11 mg/mL

## 3. LIST OF EXCIPIENTS

Excipients:
Powder: succinic acid, trehalose dihydrate, trometamol
Solvent: water for injections
See leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
4 single-use cartridges and 6 disposable injection needles

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use
Once-weekly injection
For use only with Skytrofa Auto-Injector

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use within 4 hours

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at temperatures up to 30°C for up to 6 months. Within the 6 months, this medicine can be returned to refrigeration (2°C to 8°C)

Date first removed from refrigerator: _____. Discard after 6 months

Store in the original package in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1607/004

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Skytrofa 5.2 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ascendis Pharma Endocrinology Division A/S

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

STOP HERE

Do not remove this part of the peel paper

Subcutaneous use

Read the package leaflet before use

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL FOR DUAL-CHAMBER CARTRIDGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Skytrofa 5.2 mg powder and solvent for solution for injection
lonapegsomatropin
SC

## 2. METHOD OF ADMINISTRATION

Subcutaneous use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dual-chamber cartridge contains 6.3 mg of somatropin equivalent to 18 mg of lonapegsomatropin and 0.285 mL of solvent. After reconstitution the concentration based on somatropin protein is 22 mg/mL

## 3. LIST OF EXCIPIENTS

Excipients:
Powder: succinic acid, trehalose dihydrate, trometamol
Solvent: water for injections
See leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
4 single-use cartridges and 6 disposable injection needles

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use
Once-weekly injection
For use only with Skytrofa Auto-Injector

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use within 4 hours

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at temperatures up to 30°C for up to 6 months. Within the 6 months, this medicine can be returned to refrigeration (2°C to 8°C)

Date first removed from refrigerator: _____. Discard after 6 months

Store in the original package in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1607/005

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Skytrofa 6.3 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ascendis Pharma Endocrinology Division A/S

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

STOP HERE

Do not remove this part of the peel paper

Subcutaneous use

Read the package leaflet before use

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL FOR DUAL-CHAMBER CARTRIDGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Skytrofa 6.3 mg powder and solvent for solution for injection
lonapegsomatropin
SC

## 2. METHOD OF ADMINISTRATION

Subcutaneous use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dual-chamber cartridge contains 7.6 mg of somatropin equivalent to 21.7 mg of lonapegsomatropin and 0.338 mL of solvent. After reconstitution the concentration based on somatropin protein is 22 mg/mL

## 3. LIST OF EXCIPIENTS

Excipients:
Powder: succinic acid, trehalose dihydrate, trometamol
Solvent: water for injections
See leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
4 single-use cartridges and 6 disposable injection needles

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use
Once-weekly injection
For use only with Skytrofa Auto-Injector

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use within 4 hours

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at temperatures up to 30°C for up to 6 months. Within the 6 months, this medicine can be returned to refrigeration (2°C to 8°C)

Date first removed from refrigerator: _____. Discard after 6 months

Store in the original package in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1607/006

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Skytrofa 7.6 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ascendis Pharma Endocrinology Division A/S

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

STOP HERE

Do not remove this part of the peel paper

Subcutaneous use

Read the package leaflet before use

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL FOR DUAL-CHAMBER CARTRIDGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Skytrofa 7.6 mg powder and solvent for solution for injection
lonapegsomatropin
SC

## 2. METHOD OF ADMINISTRATION

Subcutaneous use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dual-chamber cartridge contains 9.1 mg of somatropin equivalent to 25.9 mg of lonapegsomatropin and 0.4 mL of solvent. After reconstitution the concentration based on somatropin protein is 22 mg/mL

## 3. LIST OF EXCIPIENTS

Excipients:
Powder: succinic acid, trehalose dihydrate, trometamol
Solvent: water for injections
See leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
4 single-use cartridges and 6 disposable injection needles

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use
Once-weekly injection
For use only with Skytrofa Auto-Injector

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use within 4 hours

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at temperatures up to 30°C for up to 6 months. Within the 6 months, this medicine can be returned to refrigeration (2°C to 8°C)

Date first removed from refrigerator: _____. Discard after 6 months

Store in the original package in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1607/007

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Skytrofa 9.1 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ascendis Pharma Endocrinology Division A/S

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

STOP HERE

Do not remove this part of the peel paper

Subcutaneous use

Read the package leaflet before use

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL FOR DUAL-CHAMBER CARTRIDGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Skytrofa 9.1 mg powder and solvent for solution for injection
Lonapegsomatropin
SC

## 2. METHOD OF ADMINISTRATION

Subcutaneous use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dual-chamber cartridge contains 11 mg of somatropin equivalent to 31.4 mg of lonapegsomatropin and 0.479 mL of solvent. After reconstitution the concentration based on somatropin protein is 22 mg/mL

## 3. LIST OF EXCIPIENTS

Excipients:
Powder: succinic acid, trehalose dihydrate, trometamol
Solvent: water for injections
See leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
4 single-use cartridges and 6 disposable injection needles

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use
Once-weekly injection
For use only with Skytrofa Auto-Injector

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use within 4 hours

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at temperatures up to 30°C for up to 6 months. Within the 6 months, this medicine can be returned to refrigeration (2°C to 8°C)

Date first removed from refrigerator: _____. Discard after 6 months

Store in the original package in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1607/008

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Skytrofa 11 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ascendis Pharma Endocrinology Division A/S

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

STOP HERE

Do not remove this part of the peel paper

Subcutaneous use

Read the package leaflet before use

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL FOR DUAL-CHAMBER CARTRIDGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Skytrofa 11 mg powder and solvent for solution for injection
Lonapegsomatropin
SC

## 2. METHOD OF ADMINISTRATION

Subcutaneous use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

**PARTICULARS TO APPEAR ON THE OUTER PACKAGING**

**OUTER CARTON**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each dual-chamber cartridge contains 13.3 mg of somatropin equivalent to 37.9 mg of lonapegsomatropin and 0.574 mL of solvent. After reconstitution the concentration based on somatropin protein is 22 mg/mL

## 3. LIST OF EXCIPIENTS

Excipients:
Powder: succinic acid, trehalose dihydrate, trometamol
Solvent: water for injections
See leaflet for further information

## 4. PHARMACEUTICAL FORM AND CONTENTS

Powder and solvent for solution for injection
4 single-use cartridges and 6 disposable injection needles

## 5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use
Subcutaneous use
Once-weekly injection
For use only with Skytrofa Auto-Injector

## 6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children

## 7. OTHER SPECIAL WARNING(S), IF NECESSARY

## 8. EXPIRY DATE

EXP

After reconstitution, use within 4 hours

## 9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator. Do not freeze
Can be stored at temperatures up to 30°C for up to 6 months. Within the 6 months, this medicine can be returned to refrigeration (2°C to 8°C)

Date first removed from refrigerator: _____. Discard after 6 months

Store in the original package in order to protect from light

## 10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

## 11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

## 12. MARKETING AUTHORISATION NUMBER(S)

EU/1/21/1607/009

## 13. BATCH NUMBER

Lot

## 14. GENERAL CLASSIFICATION FOR SUPPLY

## 15. INSTRUCTIONS ON USE

## 16. INFORMATION IN BRAILLE

Skytrofa 13.3 mg

## 17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

## 18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

**MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS**

**BLISTER FOIL**

## 1. NAME OF THE MEDICINAL PRODUCT

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

## 2. NAME OF THE MARKETING AUTHORISATION HOLDER

Ascendis Pharma Endocrinology Division A/S

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. OTHER

STOP HERE

Do not remove this part of the peel paper

Subcutaneous use

Read the package leaflet before use

**MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS**

**LABEL FOR DUAL-CHAMBER CARTRIDGE**

## 1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Skytrofa 13.3 mg powder and solvent for solution for injection
Lonapegsomatropin
SC

## 2. METHOD OF ADMINISTRATION

Subcutaneous use

## 3. EXPIRY DATE

EXP

## 4. BATCH NUMBER

Lot

## 5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

## 6. OTHER

**B. PACKAGE LEAFLET**

**Package leaflet: Information for the user**

**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**
lonapegsomatropin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

**Read all of this leaflet carefully before you or your child start using this medicine because it contains important information for you or your child.**
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

**What is in this leaflet**


## 1. What Skytrofa is and what it is used for

Skytrofa is a medicine that contains the active substance lonapegsomatropin. This is a substance that the body can convert into somatropin, also called human growth hormone (hGH). Somatropin is needed for bones and muscles to grow and helps your body to develop the right amount of fat and muscle tissues.

Skytrofa is used to treat children and adolescents, aged 3 up to 18 years, who have failed to grow because their body produces no growth hormone or not enough. Doctors call this growth hormone deficiency (GHD). After injection, Skytrofa is slowly converted into somatropin, supplying the missing growth hormone.

## 2. What you or your child need to know before you or your child use Skytrofa

**Do not use Skytrofa**
- If you **are allergic** to lonapegsomatropin or any of the other ingredients of this medicine (listed in section 6)
- If you **have** a **tumour (cancer)** which is growing. You must have finished your anti-tumour treatment, and tumours must be inactive before you start your treatment with Skytrofa
- If you **have recently had** an open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure

- If you have been told by your doctor that the parts of your bones that grow and increase height (growth plates or epiphyses) have closed and stopped growing

Tell your doctor before starting the treatment if any of these apply to you.

**Warnings and precautions**

Talk to your doctor, pharmacist, or nurse before using Skytrofa. It is especially important to talk about anything mentioned below:

- If you previously had an **intracranial tumour**, a doctor will examine you regularly during your treatment for recurrence of the tumour or any other cancer.
- If you develop **a strong headache, disturbed vision, vomiting or inability to coordinate voluntary muscle movements (ataxia)**, especially in the first few weeks of treatment, **tell your doctor straight away**. These may be signs of raised pressure in the skull (intracranial pressure). See section 4, possible side effects.
- If you have **diabetes mellitus, high blood sugar** (glucose intolerance), or additional risk factors for diabetes, your blood sugar may need to be checked regularly and the dose of your diabetes medicine may need to be adjusted.
- If you are being treated for **adrenal insufficiency** with corticosteroids, talk to your doctor, as your steroid dose may need regular adjustment.
- If you are being treated with **thyroid hormones** or you need to start thyroid hormone replacement, your doctor will test your thyroid function regularly and the dose may need to be adjusted.
- If you have persistent hip or knee pain when walking, or if you start to limp during your growth hormone treatment, tell your doctor. These could be symptoms of a condition that affects the thighbone (femur) where it inserts into the hip (slipped capital femoral epiphysis) and that occurs with greater frequency in children on growth hormone therapy. These symptoms may also be caused by loss of bone tissue due to insufficient blood supply (osteonecrosis), which has been reported in patients treated with other growth hormone products. Talk to your doctor about persistent pain in any joint.
- If you notice a sideways **curve in your spine** (scoliosis), you will need to be checked often by your doctor.
- If you get a **stomach ache** (pain in your tummy) that gets worse, **tell your doctor**. Your doctor may test for pancreatitis, which is when an organ called the pancreas becomes inflamed. See section 4, possible side effects.
- If you have signs and symptoms of a **sudden serious allergic reaction** (e.g. breathing difficulty, swelling of your face, mouth, or tongue, fast heartbeat, hives, rash, fever), you should promptly seek medical attention.
- If you have **Prader-Willi syndrome**, you should not be treated with Skytrofa unless you also have GHD. Skytrofa has not been studied in individuals with Prader-Willi syndrome and therefore its effectiveness as a treatment for this condition is unknown.
- A small number of patients given growth hormone replacement have developed **a type of cancer of the blood and bone marrow** (leukaemia). However, it has not been proven that growth hormone treatment caused the cancer.
- If you have immediate complications following open heart surgery, abdominal surgery, a bad accident (trauma), or an **acute critical illness like** acute respiratory failure.
- If you are a female taking **oral contraception or hormonal replacement therapy with oestrogen**, your dose of Skytrofa may need to be higher. If you or your child stop using oral oestrogen, your dose of Skytrofa may need to be reduced.

**Other medicines and Skytrofa**
Tell your doctor, pharmacist, or nurse if you are using, have recently used or might use any other medicines.

In particular, tell your doctor if you are taking or have recently taken any of the following medicines:

- Insulin or any other medicines to treat diabetes mellitus
- Thyroid hormone treatments such as levothyroxine
- Tablets containing oestrogen, including tablets for oestrogen replacement therapy or for contraception
- Steroids or synthetic adrenal hormones (corticosteroids or glucocorticoids)
- Medicines to treat epilepsy or fits (seizures) - antiseizure medicines (anticonvulsants) such as carbamazepine
- Ciclosporin (immunosuppressive medicine) - a medicine to suppress your immune system
- Theophylline, a medicine used to treat asthma and other chronic lung diseases.

Your doctor may need to adjust the dose of these medicines or the dose of Skytrofa.

**Pregnancy, breastfeeding and fertility**

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor before taking this medicine.

**Pregnancy**
If you are able to get pregnant, you should not use Skytrofa unless you are also using reliable contraception. There are no data from the use of Skytrofa in pregnant women. Skytrofa is not to be used during pregnancy. This is because it is not known if it could harm your unborn child. If you are pregnant, think you may be pregnant or are planning to have a baby, talk to your doctor. If you become pregnant during treatment, **tell your doctor immediately**.

**Breastfeeding**
It is not known whether Skytrofa can pass into breast milk. However, as lonapegsomatropin is not absorbed by mouth, it is unlikely to adversely affect the breastfed infant. If you are breast-feeding or intend to breast-feed, ask your doctor for advice before using Skytrofa. Skytrofa can be used during breastfeeding on strict indication.

**Driving and using machines**
Skytrofa does not affect the ability to drive or to use machines.

## 3. How to use Skytrofa

This medicine will only be prescribed by a doctor who has experience with growth hormone treatment and who has confirmed your diagnosis.

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure. Your doctor will show you how to use Skytrofa.

Skytrofa is given as an injection under the skin (subcutaneous injection). This means that it is injected with a short needle into fatty tissue under the skin of the abdomen, buttock or thigh. It is important to change the place where you have your injection every week to avoid damaging your skin. Your doctor or nurse will tell you the right dose and show you how to give the injection when you start treatment.

**Recommended dose**
Your doctor will work out your dose of Skytrofa from your body weight in kilograms. Because lonapegsomatropin is converted into somatropin in the body, doses of Skytrofa are described in terms of the amount of somatropin it produces. The recommended dose of Skytrofa is 0.24 mg somatropin per kilogram of body weight, given once a week.

If changing from daily somatropin therapy to once-weekly Skytrofa, your doctor will tell you to wait at least 8 hours between the final dose of once-daily somatropin and the first dose of Skytrofa. The recommended dose may be reduced according to previous daily dose of somatropin.

**When to use Skytrofa**
You need to inject Skytrofa once a week, on the same day each week, at any time during the day.

If necessary, you can change the day of your weekly injection. Skytrofa can be administered 2 days before or 2 days after the scheduled dosing day. There should be at least 5 days since your last injection, on the old day and the first dose on the new day. After selecting a new dosing day, continue giving yourself the injection on that day each week. Ask your doctor if you are not sure how to do this.

**Preparation and administration**
Read "Instructions for use" at the end of this leaflet before you start using this medicine.

Skytrofa comes in a two-chamber cartridge containing both medicine (powder) and a solvent (liquid). It is to be used with the needles supplied. To give injections, you also need a Skytrofa Auto-Injector. The Skytrofa Auto-Injector is supplied separately.
The powder and solvent will be mixed together into a solution for injection by the Skytrofa Auto-Injector. After mixing, the solution is ready for use and the medicine can be injected under the skin using the Skytrofa Auto-Injector.

Read the instructions for use provided with the Skytrofa Auto-Injector.

**If you or your child use more than you should**
If you have injected more Skytrofa than you should have, contact your doctor for advice. If you inject too much Skytrofa, your blood sugar level may fall too low and later rise too high. Long-term overdose could cause irregular growth.

**If you or your child forget to use Skytrofa**
If you miss your weekly dose and you are 1 or 2 days late: inject today, then on your usual day next week. If you are 3 days late or more: skip the missed dose and then resume injections on your next usual dosing day. Leave at least 5 clear days between injections.

**If you or your child stop using Skytrofa**
Do not stop using Skytrofa without talking to your doctor. If you stop taking Skytrofa prematurely, your growth rate may decline, and your final height may be less than if you had completed the full course of treatment.
If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

## 4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

**Very common side effects** (may affect more than 1 in 10 people)
- Headache

**Common side effects** (may affect up to 1 in 10 people)
- Low levels of the hormone thyroxine seen in blood tests (secondary hypothyroidism)
- Joint pain (arthralgia)
- Injection site reactions. The skin around the injection area can get uneven or lumpy, but this should not happen if you inject in a different place each time.

**Uncommon side effects** (may affect up to 1 in 100 people)
- Sudden serious allergic reactions, including angioedema (rapid swelling of the mucous membranes or the skin that may occur in the face, mouth, tongue, abdomen, or arms and legs)
- A decrease in the levels of the hormone cortisol seen in blood tests
- Stiffness of the joints (arthritis)
- An increased sideways curve of the spine (scoliosis)
- Growing pains

- Breast enlargement affecting males

**Not known** (frequency cannot be estimated from the available data)
Below side effects have been seen with other growth hormone-containing medicine.
- Leukaemia
- Type 2 diabetes mellitus
- Increased pressure of the fluid surrounding the brain (which causes symptoms such as strong headache, visual disturbances and vomiting)
- Numbness/tingling
- Muscle pain
- Swelling of the lower legs and feet and/or arms and hands
- Swelling of the face
- Rash
- Itching
- Hives

If any of the side effects gets severe, **tell your doctor or pharmacist**.

**Reporting of side effects**
If you get any side effects, talk to your doctor, pharmacist, or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

## 5. How to store Skytrofa

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton after EXP.

Store in a refrigerator (2°C - 8°C). Do not freeze. Store in the original package in order to protect from light.

Skytrofa may be taken out of the refrigerator for a maximum period of 6 months and stored at temperatures up to 30°C. During these 6 months this medicine can be returned to refrigeration (2°C - 8°C). Record on the carton the date Skytrofa is first removed from the refrigerator. Discard this medicine 6 months after the date this medicine was first stored outside the refrigerator.

The powder is white to off-white, and the solvent is a clear colourless solution.

The mixed solution is colourless and clear. The solution may occasionally contain air bubbles, these are okay. Do not use this medicine if you notice visible particles in the mixed solution. Inject immediately after the powder and solvent has been mixed together by using the Skytrofa Auto-Injector. If you cannot use the mixed solution immediately, it should be used within 4 hours.

When you have finished with a cartridge with needle, you must dispose of it carefully in a suitable container.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicine you no longer use. These measures will help protect the environment.

## 6. Contents of the pack and other information

### What Skytrofa contains

The active substance is lonapegsomatropin.

Cartridges come in 9 different strengths:

Skytrofa 3 mg powder and solvent for solution for injection (injection) in cartridge
Each two-chamber cartridge contains 3 mg of somatropin (equivalent to 8.6 mg of lonapegsomatropin [powder]) and 0.279 mL of solvent (liquid). After mixing the somatropin concentration is 11 mg/mL.

Skytrofa 3.6 mg powder and solvent for solution for injection (injection) in cartridge
Each two-chamber cartridge contains 3.6 mg of somatropin (equivalent to 10.3 mg of lonapegsomatropin [powder]) and 0.329 mL of solvent (liquid). After mixing the somatropin concentration is 11 mg/mL.

Skytrofa 4.3 mg powder and solvent for solution for injection (injection) in cartridge
Each two-chamber cartridge contains 4.3 mg of somatropin (equivalent to 12.3 mg of lonapegsomatropin [powder]) and 0.388 mL of solvent (liquid). After mixing the somatropin concentration is 11 mg/mL.

Skytrofa 5.2 mg powder and solvent for solution for injection (injection) in cartridge
Each two-chamber cartridge contains 5.2 mg of somatropin (equivalent to 14.8 mg of lonapegsomatropin [powder]) and 0.464 mL of solvent (liquid). After mixing the somatropin concentration is 11 mg/mL.

Skytrofa 6.3 mg powder and solvent for solution for injection (injection) in cartridge
Each two-chamber cartridge contains 6.3 mg of somatropin (equivalent to 18 mg of lonapegsomatropin [powder]) and 0.285 mL of solvent (liquid). After mixing the somatropin concentration is 22 mg/mL.

Skytrofa 7.6 mg powder and solvent for solution for injection (injection) in cartridge
Each two-chamber cartridge contains 7.6 mg of somatropin (equivalent to 21.7 mg of lonapegsomatropin [powder]) and 0.338 mL of solvent (liquid). After mixing the somatropin concentration is 22 mg/mL.

Skytrofa 9.1 mg powder and solvent for solution for injection (injection) in cartridge
Each two-chamber cartridge contains 9.1 mg of somatropin (equivalent to 25.9 mg of lonapegsomatropin [powder]) and 0.4 mL of solvent (liquid). After mixing the somatropin concentration is 22 mg/mL.

Skytrofa 11 mg powder and solvent for solution for injection (injection) in cartridge
Each two-chamber cartridge contains 11 mg of somatropin (equivalent to 31.4 mg of lonapegsomatropin [powder]) and 0.479 mL of solvent (liquid). After mixing the somatropin concentration is 22 mg/mL.

Skytrofa 13.3 mg powder and solvent for solution for injection (injection) in cartridge
Each two-chamber cartridge contains 13.3 mg of somatropin (equivalent to 37.9 mg of lonapegsomatropin [powder]) and 0.574 mL of solvent (liquid). After mixing the somatropin concentration is 22 mg/mL.

The other ingredients in this medicine (for all strengths) are:

Powder: succinic acid, trehalose dihydrate, trometamol

Solvent: water for injections

**What Skytrofa looks like and contents of the pack**

Skytrofa contains medicine as a powder together with a solvent to make a solution for injection, in a two-chamber cartridge, containing powder in one chamber and the solvent in the other.

The powder is white to off-white, and the solvent is a clear colourless solution. When the powder and solvent has been mixed together into a solution for injection, the solution is colourless and clear.

Each pack of Skytrofa contains 4 single-use two-chamber cartridges packed in individual blisters and 6 disposable injection needles (two spare needles). Each cartridge has a specific label with assigned two-colour coding ribbons only for use by the Skytrofa Auto-Injector to select the correct mixing settings. Strength colours are indicated on the carton and blister foil and should be used to differentiate the individual strengths.

The strength colours on the carton and blister indicate the strength of your Skytrofa medicine:

| **Carton/blister strength colours** | **Strength** | **Cartridge two-colour label** (bottom/top) |
|---|---|---|
| Light Apricot | 3 mg | Yellow/green |
| Cyan | 3.6 mg | Yellow/cyan |
| Dark grey | 4.3 mg | Yellow/pink |
| Yellow | 5.2 mg | Green/pink |
| Orange | 6.3 mg | Cyan/yellow |
| Dark purple | 7.6 mg | Cyan/pink |
| Golden brown | 9.1 mg | Pink/yellow |
| Dark blue | 11 mg | Pink/green |
| Dark red | 13.3 mg | Pink/cyan |

Skytrofa is designed for use with the injection needles supplied and the Skytrofa Auto-Injector. The Skytrofa Auto-Injector is not included in this pack and is supplied separately. The instructions for use for the Skytrofa Auto-Injector comes with your Skytrofa Auto-Injector box.

**Marketing Authorisation Holder**

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

**Manufacturer**
Ascendis Pharma A/S
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**This leaflet was last revised in**

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu

**Instructions for use**

This guide is designed to help you prepare, mix, and inject your Skytrofa medicine.

**These instructions are divided into 5 stages**

| |
|---|
| **Getting to know the parts of your or your child's medicine** |
| **Preparing your or your child's medicine** |
| **Mixing your or your child's medicine** |
| **Injecting your or your child's medicine** |
| **After injecting your or your child's medicine** |

**If you or your child need help at any time, contact your doctor, pharmacist or nurse.**

**What you need to know before getting started**

- Always read the package leaflet before use.
- Always wash and dry your hands.
- A new cartridge should be used for every injection.
- A new needle must be used for every injection. **Do not** re-use needle.
- **Do not** use this medicine beyond the expiry date printed after 'EXP' on the outer carton and on the cartridge pack or 6 months after the date it was first removed from refrigeration (whichever is earlier).
- **Do not** use this medicine if you notice that it contains visible particles.
- The cartridge and needle are for single-use and designed for use only with the Skytrofa Auto-Injector [hereafter referenced as the auto-injector].

| |
|---|
| **Getting to know the parts of your or your child's Skytrofa medicine** |

Skytrofa is a powder and solvent for solution for injection in a cartridge. Each package contains 4 single-use cartridges and 6 disposable injection needles. Your cartridge contains medicine powder and solvent to mix the powder with.

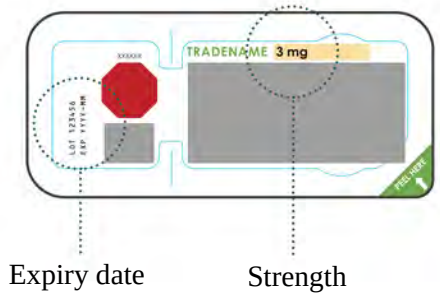
**Two-chamber cartridge**


To give injections, you also need the Skytrofa Auto-Injector. This is not included in the Skytrofa package but comes in a separate box. Read also the instructions for use provided with the Skytrofa Auto-Injector.

**Preparing your or your child's medicine**

If you keep your medicine in a refrigerator, take it out 15 minutes before use.

## 1. Check and assemble cartridge and needle

| | |
|---|---|
| • Take out the cartridge pack.<br>• Check the expiry date and dose strength on the cartridge pack.<br>• **Do not** use if the expiry date printed after 'EXP' has passed. |  |
| • Open the cartridge pack as far as the red STOP sign. This will ensure that the orange plug remains in the cartridge pack. In order to secure the cartridge stopper position during transportation an orange plug is affixed to the cartridge in the blister.<br>• Lift the cartridge out of its pack. |  |
| • If there still is an orange plug on your cartridge, remove the orange plug by pulling it straight off and throw it away. |  |
| • Take out a new needle. If the protective paper is not fully sealed or if it is broken, **do not** use.<br>• Remove the protective paper. |  |
| • Screw the needle securely onto the cartridge by turning clockwise until it fits tightly.<br>• **Do not** remove the plastic needle cover. |  |

## 2. Turn on the auto-injector

| | |
|---|---|
| • Press and release the green button to turn on the auto-injector.<br>• You will hear **2** loud beeps , the battery icon lights up and green top will start flashing. |  |

## 3. Insert cartridge

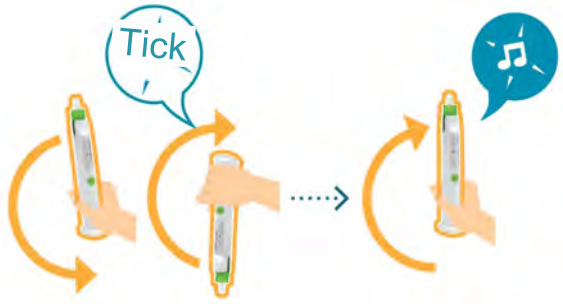
| | |
|---|---|
| • Insert cartridge into flashing green top. |  |
| • Click cartridge into place. The green top will stop flashing, the green mixing icon will light up and the battery icon will switch off. |  |
| • After clicking the cartridge into place, remove finger from cartridge. |  |

**Mixing your or your child's medicine**

## 4. Wait while mixing

| | |
|---|---|
| • Wait 4 to 8 minutes for the auto-injector to mix your medicine.<br>• Watch the progress bar gradually light up.<br>• Wait until you hear **2** loud beeps, and the entire progress bar starts flashing. |  |

## 5. Turn the auto-injector up and down

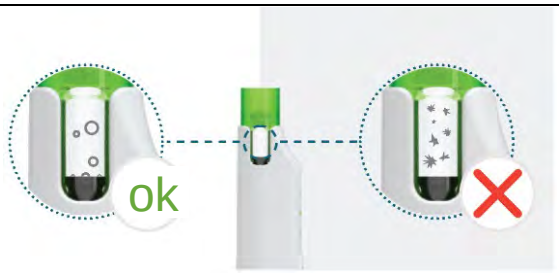
| | |
|---|---|
| • Turn the auto-injector up and down. A tick sound confirms you are turning correctly.<br>• Turn 5 to 10 times until you hear **2** loud beeps and the progress bar, except the top element, lights up. |  |

## 6. Finish mixing

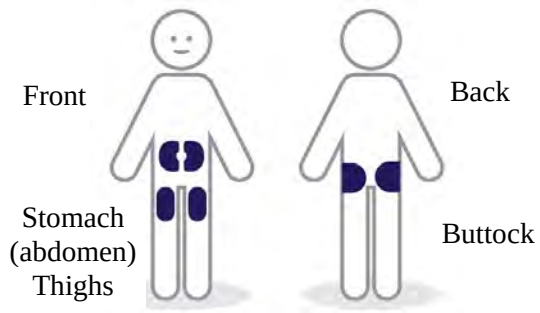
| | |
|---|---|
| • Keep the auto-injector upright until you hear **2** loud beeps and the entire progress bar lights up. |  |
| • Pull off needle cover.<br>• **Do not** twist.<br>• **Keep** needle cover for later.<br><br>(Green eye icon will light up) |  |

**Injecting your or your child's medicine**

## 7. Check mixed solution

| | |
|---|---|
| • Solution is OK if it is colourless and clear (some air bubbles are OK).<br>• **Do not** use solution if it has visible particles. If visible particles press the green button for 3 seconds and remove cartridge. |  |

## 8. Prepare for injection

| | |
|---|---|
| • Choose injection site: stomach, thighs, or buttocks. Change injection site every week. |  |
| • Wash and dry your hands. |  |
| • Clean injection site with alcohol wipe.<br>• **Do not** inject through clothes. |  |

## 9. Inject medicine

| | |
|---|---|
| • Press and hold green top against injection site for **10** to **15** seconds until you hear **2** loud beeps. (Green top will flash twice and the green check mark icon ✓ will light up). |  |
| • Remove the auto-injector from skin and wait until you hear **2** loud beeps. (Green top will start flashing). |  |

**After injecting your or your child's medicine**

## 10. Remove cartridge

| | |
|---|---|
| • Press needle cover into flashing green top. |  |
| • Press needle cover down to release cartridge. |  |

| | |
|---|---|
| • Remove used cartridge. |  |

**11. Dispose cartridge and needle**

| | |
|---|---|
| • Check that the cartridge is empty. Do not use the auto-injector if there is medicine left in the cartridge after injection.<br>• Safely dispose of used cartridge and needle as instructed by your pharmacist.<br>• **Do not** throw it out with the ordinary household waste. |  |
| **Does your weekly dose require 2 cartridges?**<br>• Then take the second injection by repeating step 1-11 with a new cartridge and needle. | |

**12. Store the auto-injector**

| | |
|---|---|
| • Put on the protective cover and store at room temperature ready for use next time. |  |