▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

SKYTROFA® (lonapegsomatropin)

POWDER AND SOLVENT FOR SOLUTION FOR INJECTION

1 NAME OF THE MEDICINE

Lonapegsomatropin

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 List of excipients.

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.

4.2 DOSE 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.

Dosage

The dosage 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 (see Table 1). Doses greater

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 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 (see 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.

The recommended starting dose is 0.24 mg/kg body weight/week based on clinical trial protocols. Higher starting doses have not been studied in clinically relevant trial settings.

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 dosage 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 for use included in the medicine carton.

4.3 CONTRAINDICATIONS

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

Lonapegsomatropin 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.

Use in the elderly

No information in the elderly is available.

Paediatric use

The safety and efficacy of Skytrofa in children below 3 years of age have not been established and dose recommendation cannot be given (see section 4.2).

Effects on laboratory tests

Serum levels of phosphate, alkaline phosphatase, and parathyroid hormone may increase after somatropin treatment. If a patient is found to have abnormal laboratory tests, monitor as appropriate.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

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

Effects on fertility

There are no clinical data on the effect of lonapegsomatropin on fertility. Lonapegsomatropin did not affect male or female fertility in rats at subcutaneous doses up to 20-fold the clinical dose of 0.24 mg/kg/week. Anti-drug antibodies developed in treated rats, reducing exposure to lonapegsomatropin, and limiting the predictive value of the study. No microscopic changes in male or female reproductive organs to indicate potential impairment of fertility were observed in monkeys treated with lonapegsomatropin at subcutaneous doses up to 4.8 mg/kg/week (in terms of the somatropin content), yielding systemic exposure more than 50-times higher than in patients at 0.24 mg/kg/week.

Use in pregnancy

Category B2

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 fetal outcomes.

No adverse effects on embryofetal development were observed in pregnant rats administered lonapegsomatropin at subcutaneous doses up to 13-fold the clinical dose of 0.24 mg/kg/week. Weekly dosing in rats yielded intermittent exposure during critical periods of organogenesis, limiting the predictive value of the study. In a pre- and postnatal developmental study performed with a structurally related transiently pegylated somatropin prodrug in rats there were no adverse effects on the development of the conceptus or the offspring with maternal weekly administration from implantation through weaning at subcutaneous doses up to 13-fold the clinical dose of 0.24 mg somatropin/kg/week. A study in rabbits revealed malformations with lonapegsomatropin at all tested dose levels (≥0.35 mg/kg every second day) and embryofetal lethality at 1.4 mg/kg every second day. Adverse effects on embryofetal development observed in the rabbit are most likely to be secondary to maternal toxicity.

Skytrofa should not be used during pregnancy unless clearly needed.

Use in lactation

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.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

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

Tabulated list of adverse reactions

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

Table 3 Frequency of adverse reactions in clinical trials

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

[a] Injection site reactions include hyperaemia, injection site atrophy, injection site pain, injection site urticaria, and localised oedema. The injection site reactions observed with lonapegsomatropin were generally mild and transient.
[b] Anaphylactic reactions reported with lonapegsomatropin included angioedema (see section 4.4).

Description of selected adverse reactions

Immunogenicity

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

Adverse reactions related to growth hormone pharmacological class

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

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

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems and drugsafety-STA@stbiopharma.com.

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.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

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

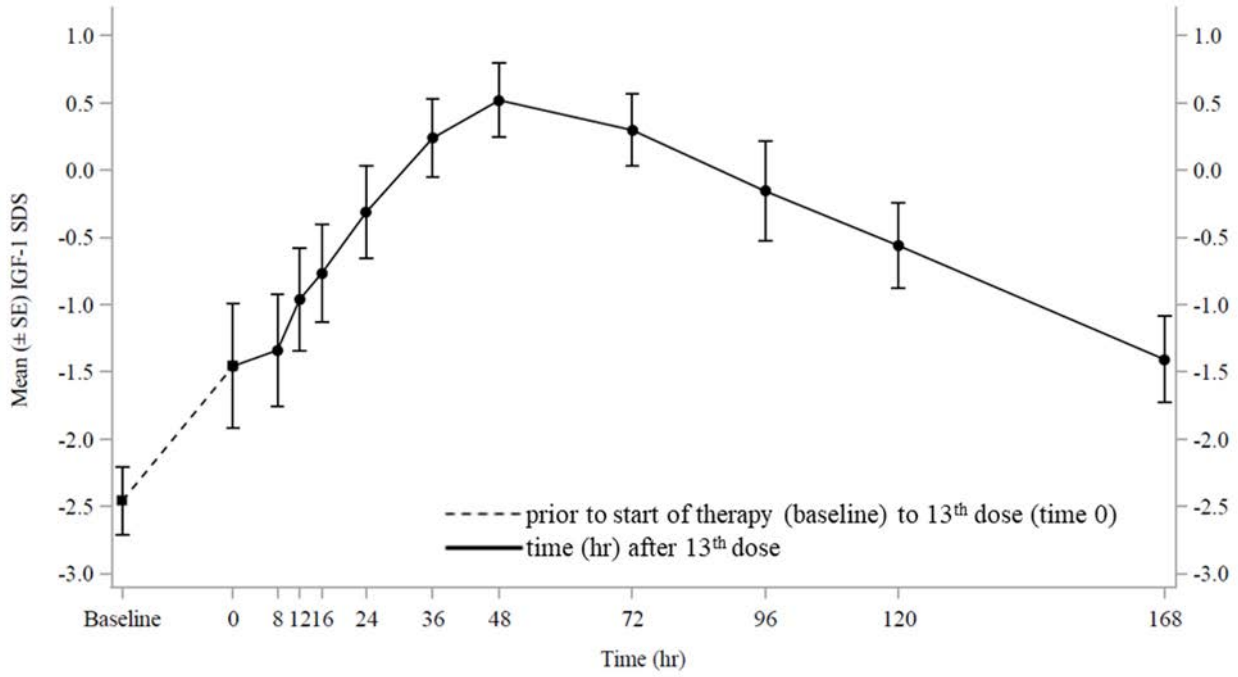
Somatropin binds to a dimeric hGH receptor in the cell membrane of target cells resulting in intracellular signal transduction and a host of pharmacodynamic effects. Somatropin has direct tissue and metabolic effects, and indirect effects mediated by IGF-1, including stimulation of chondrocyte differentiation 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 trials

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 once-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 once-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

enliGHten trial:

In an open-label extension trial, patients in the 52-week randomised trial who were previously treated with lonapegsomatropin continued lonapegsomatropin treatment; those who were previously treated with somatropin switched to lonapegsomatropin (Table 4).

Patients who continued treatment with lonapegsomatropin had LS mean 1.61 (95% CI 1.49 to 1.72) increase in height SDS after 104 weeks of total treatment (N=101) and LS mean 2.56 (95% CI 2.36 to 2.77) increase in height SDS after 260 weeks of total treatment (N=72).

Patients who switched from somatropin to lonapegsomatropin had LS mean 1.49 (95% CI 1.34 to 1.63) increase in height SDS after 104 weeks of total treatment (N=54) and LS mean 2.61 (95% CI 2.34 to 2.89) increase in height SDS after 260 weeks of total treatment (N=33) (Table 5).

Table 5 Growth response after 104 and 260 weeks of growth hormone treatment in paediatric treatment-naïve patients with GHD

Randomised trial treatment through week 52	**Once-weekly lonapegsomatropin (0.24 mg somatropin/kg/week)**	**Daily somatropin (0.24 mg somatropin/kg/week)**
Open-label extension trial treatment	**Once-weekly lonapegsomatropin (0.24 mg somatropin/kg/week)**	
Week 104[a]	N=101	N=54
Height SDS change from baseline	1.61	1.49

LS mean (95% CI)[b]	(1.49-1.72)	(1.34-1.63)
Week 260[a]	N=72	N=33
Height SDS change from baseline LS mean (95% CI)[b]	2.56 (2.36-2.77)	2.61 (2.34-2.89)

[a] N is the number of subjects with non-missing baseline and specific post-baseline results. Week 104 includes 52 weeks treatment in the randomised trial plus 52 weeks in the extension trial. Week 260 includes 52 weeks treatment in the randomised trial plus 208 weeks in the extension trial.

[b] The height SDS change from baseline at each visit is modelled using ANCOVA, adjusting for randomised trial treatment group, baseline age, peak GH levels (log transformed) at diagnosis, and baseline height SDS as covariates and gender as a factor. Baseline measurement is before the start of growth hormone treatment in the randomised trial.

Supportive evidence

Evidence from an additional clinical trial 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 6 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)

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 7 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.

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.

Pharmacokinetics in special patient 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

Genotoxicity

Lonapegsomatropin was not mutagenic in the Ames test, and not clastogenic in the human chromosomal aberration assay or in the rat bone marrow micronucleus test.

Carcinogenicity

No carcinogenicity study has been conducted with lonapegsomatropin.

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

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened

Store at 2 to 8 °C. Do not freeze.
Store in the original package in order to protect from light.

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 to 8 °C).

Record the date on the carton when the medicinal product was first removed from the refrigerator.

Product is for single use in one patient only. Discard any residue.

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 should not exceed 4 hours at temperatures ≤30 °C.

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

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

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 in the medicine carton and the instructions for use provided with the Skytrofa Auto-Injector before use.

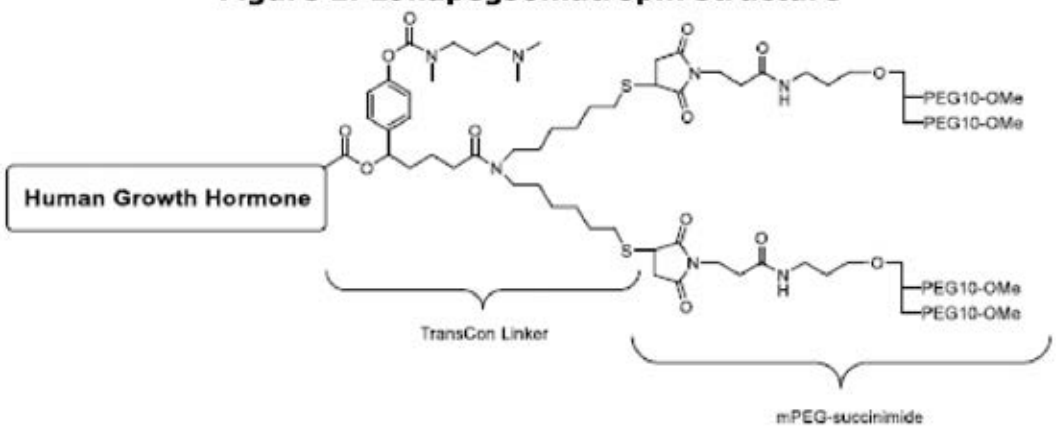
Disposal

The patient should be advised to discard the cartridge and injection needle after each injection.

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Figure 1. Lonapegsomatropin structure



Molecular Formula: $C_{1051}H_{1628}N_{269}O_{317}S_9$ +4 x $[C_2H_4O]_n$ where n is approximately 230

Molecular Weight: The average molecular weight is approximately 63 kDa

CAS number 1934255-39-6

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 - Prescription Only Medicine

8 SPONSOR

Specialised Therapeutics Pharma Pty Ltd
Level 2, 17 Cotham Road
Kew
Victoria 3101

Australia

Phone: +61 3 9859 1493
Website: www.stbiopharma.com

9 DATE OF FIRST APPROVAL

DD/Month/YYYY

10 DATE OF REVISION

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information