▼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

Sogroya® 5 mg (somapacitan 3.3 mg/mL) solution for injection
Sogroya® 10 mg (somapacitan 6.7 mg/mL) solution for injection
Sogroya® 15 mg (somapacitan 10 mg/mL) solution for injection

1. NAME OF THE MEDICINE

somapacitan

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Somapacitan is a long-acting recombinant human growth hormone derivative produced by recombinant DNA technology in *Escherichia coli* followed by attachment of an albumin binding moiety. It consists of 191 amino acids similar to endogenous human growth hormone, with a single substitution in the amino acid backbone (L101C) to which the albumin binding moiety has been attached. The albumin binding moiety (side chain) consists of a fatty acid moiety and a hydrophilic spacer attached to position 101 of the protein.

One Sogroya® 5 mg/1.5 mL pre-filled pen contains 5 mg of somapacitan in 1.5 mL solution. One mL of solution contains 3.3 mg of somapacitan.

One Sogroya® 10 mg/1.5 mL pre-filled pen contains 10 mg of somapacitan in 1.5 mL solution. One mL of solution contains 6.7 mg of somapacitan.

One Sogroya® 15 mg/1.5 mL pre-filled pen contains 15 mg of somapacitan in 1.5 mL solution. One mL of solution contains 10 mg of somapacitan.

For the full list of excipients, see Section 6.1 List of excipients.

3. PHARMACEUTICAL FORM

Solution for injection.

Clear to slightly opalescent, colourless to slightly yellow liquid, essentially free from visible particles.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Sogroya is indicated for

- the replacement of endogenous growth hormone (GH) in paediatric patients aged 2 years and above with growth failure due to growth hormone deficiency (GHD).

- the replacement of endogenous growth hormone (GH) in adults with growth hormone deficiency (AGHD).

4.2. Dose and method of administration

Somapacitan should be initiated and monitored by physicians who are appropriately qualified and experienced in the diagnosis and management of patients with the condition for which somapacitan is indicated (e.g. endocrinologists).

Dosage

Table 1: Dose recommendation

Paediatric GHD	**Recommended dose**
Treatment-naïve patients and patients switching from other growth hormone products.	0.16 mg/kg/week
Adult GHD	**Recommended starting dose**
Naïve patients	
Adults (18 to less than 60 years)	1.5 mg/week
Women on oral estrogen therapy (irrespective of age)	2 mg/week
Elderly (60 years or older)	1 mg/week
Patients switching from daily GH medicinal products	
Adults (18 to less than 60 years)	2 mg/week
Women on oral estrogen therapy (irrespective of age)	4 mg/week
Elderly (60 years or older)	1.5 mg/week

Paediatric GHD

Individualise and adjust the dosage based on response.

When GHD persists after growth completion, growth hormone treatment should be continued to achieve full somatic adult development including lean body mass and bone mineral accrual (for guidance on dosing see recommended dose for adults Table 1).

Adult GHD

Dose titration

The somapacitan dose must be individually adjusted for each patient. It is recommended to increase the dose gradually with 2-4 week intervals in steps from 0.5 mg to 1.5 mg based on the patient's clinical response and experience of adverse reactions up to a dose of 8 mg somapacitan per week.

Serum insulin like growth factor-I (IGF-I) levels (drawn 3-4 days after dosing) can be used as guidance for the dose titration. The aim should be to target the IGF-I value in the age-adjusted upper half of the normal range. IGF-I levels in the target range are usually achieved within 8 weeks of dose titration. Longer dose titration may be necessary in some AGHD patients (see below and section 5.1 Pharmacodynamic properties).

Treatment evaluation

Using IGF-I as a biomarker for dose titration, the aim is to reach IGF-I levels within the age-adjusted upper half of the normal range within 12 months of titration. If this target range cannot be achieved within this period, or the patient does not obtain the desired clinical response, other treatment options should be considered. During somapacitan maintenance treatment, evaluation of efficacy and safety should be considered at approximately 6- to 12-month intervals and may be assessed by evaluating biochemistry (IGF-I-, glucose-, and lipid levels), body composition, and body mass index.

Maintenance dose

Maintenance dose varies from person to person and between male and female patients. The average somapacitan maintenance dose observed in the phase 3 clinical trials was 2.4 mg/week.

Missed dose

Patients who miss a dose are advised to inject once weekly somapacitan upon discovery as soon as possible, within 3 days after the missed dose, and then resume their usual once weekly dosing schedule. If more than 3 days have passed, the dose should be skipped, and the next dose should be administered on the regularly scheduled day. If two or more doses have been missed, the dose should be resumed on the regularly scheduled day.

Flexibility in dosing time

The day of weekly injection can be changed as long as the time between two doses is at least 4 days (96 hours). After selecting a new dosing day, the once weekly dosing should be continued.

On occasions when administration at the scheduled dosing day is not possible, once weekly somapacitan can be taken up to 2 days before or 3 days after the scheduled weekly dosing day as long as the time between two doses is at least 4 days (96 hours). Once weekly dosing for the next dose could be resumed at the regularly scheduled dosing day.

Switching from other growth hormone products

Switching a patient from another type or brand of growth hormone should be done by a physician who has experience in diagnosis and management of patients with the condition for which somapacitan is indicated.

Patients switching from a weekly human growth hormone to once weekly somapacitan are recommended to continue their once weekly dosing schedule.

Patients switching from daily human growth hormone to once weekly somapacitan should choose the preferred day for the weekly dose and stop the final dose of daily treatment the day before (or at least 8 hours before) taking the first dose of once weekly somapacitan. Patients should follow the instructions for the dose presented in section 4.2 Dose and method of administration.

Method of administration

Somapacitan is to be administered once weekly at any time of the day.

Somapacitan is to be injected subcutaneously in the abdomen, thighs, buttocks or upper arms.

The injection site should be rotated every week to prevent local lipoatrophy.

The Sogroya® 5 mg/1.5 mL (3.3 mg/mL) pen delivers doses from 0.025 mg to 2 mg in increments of 0.025 mg (0.0075 mL).

The Sogroya® 10 mg/1.5 mL (6.67 mg/ml) pen delivers doses from 0.05 mg to 4 mg in increments of 0.05 mg (0.0075 mL).

The Sogroya® 15 mg/1.5 mL (10 mg/ml) pen delivers doses from 0.10 mg to 8 mg in increments of 0.1 mg (0.01 mL).For instructions on handling the medicinal product before administration, see section 6.4 Special precautions for storage.

Dosage Adjustments

Elderly (60 years of age or older)

Generally, lower doses of somapacitan may be necessary in older patients. For further information, see section 5.2 Pharmacokinetic properties.

Gender

Adults: Men show an increasing IGF-I sensitivity over time. This means that there is a risk that men are overtreated.

Women, especially those on oral estrogen, may require higher doses and a longer titration period than men, see sections 5.1 Pharmacodynamic properties and 5.2 Pharmacokinetic properties. In women using oral estrogen, changing the route of estrogen administration (e.g. transdermal, vaginal) should be considered (see section 4.4 Special warnings and precautions for use).

Renal impairment

Adults: No adjustment of the starting dose is required for patients with renal impairment. Patients with renal impairment may need lower doses of somapacitan but since the dose of somapacitan is individually adjusted according to the need of each patient, no further dose adjustment is required (see section 5.2 Pharmacokinetic properties).

Paediatric: Somapacitan has not been studied in paediatric patients with renal impairment.

Hepatic impairment

Adults: No adjustment of the starting dose is required for patients with hepatic impairment. Patients with moderate hepatic impairment may need higher doses of somapacitan but since the dose of somapacitan is individually adjusted according to the need of each patient, no further dose adjustment is required. No information regarding the use of somapacitan in patients with severe hepatic impairment is available. Caution should be exercised if treating these patients with somapacitan (see section 5.2 Pharmacokinetic properties).

Paediatric: Somapacitan has not been studied in paediatric patients with hepatic impairment.

4.3. Contraindications

Somapacitan should not be used in patients with a known hypersensitivity to any of the ingredients.

Somapacitan must not be used when there is any evidence of activity of a tumour. Intracranial tumours must be inactive and anti-tumour therapy must be completed prior to starting somapacitan therapy. Treatment with somapacitan should be discontinued if there is evidence of tumour growth.

Somapacitan should not be used for longitudinal growth promotion in children with closed epiphyses.

Adults: Patients with acute critical illness suffering from complications following open heart surgery, abdominal surgery, multiple accidental trauma, acute respiratory failure or similar conditions should not be treated with somapacitan (for patients undergoing substitution therapy, see section 4.4 Special warnings and precautions for use).

4.4. Special warnings and precautions for use

Adrenocortical insufficiency

Introduction of growth hormone treatment may result in inhibition of 11βHSD-1 and reduced serum cortisol concentrations. In patients treated with growth hormone, previously undiagnosed central (secondary) hypoadrenalism may be unmasked and glucocorticoid replacement may be required. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of growth hormone treatment. Patients with known hypoadrenalism should be monitored for reduced serum cortisol levels and/or the need for increased doses of glucocorticoid (see section 4.5 Interactions with other medicines and other forms of interactions).

Glucose metabolism impairment

Treatment with growth hormone may decrease insulin sensitivity, particularly at higher doses in susceptible patients, and consequently hyperglycaemia may occur in subjects with inadequate insulin secretory capacity. As a result, previously undiagnosed impaired glucose tolerance and overt diabetes mellitus may be unmasked during growth hormone treatment. Therefore, glucose levels should be monitored periodically in all patients treated with growth hormone, especially in those with risk factors for diabetes mellitus, such as obesity, or a family history of diabetes mellitus. Patients with pre-existing type 1 or type 2 diabetes mellitus or impaired glucose tolerance should be monitored closely during growth hormone therapy. The doses of antihyperglycaemic medicinal products may require adjustment when growth hormone therapy is instituted in these patients.

Neoplasms

There is no evidence for increased risk of new primary cancers in adults treated with growth hormone.

In patients in complete remission from malignant disease or pituitary tumours, growth hormone therapy has not been associated with an increased relapse rate.

Patients who have achieved complete remission of malignant disease or pituitary tumours should be followed closely for relapse after commencement of growth hormone therapy. Growth hormone treatment should be interrupted in case of any development or reoccurrence of malignant disease.

An overall slight increase in second neoplasms has been observed in childhood cancer survivors treated with growth hormone, with the most frequent being intracranial tumours. The dominant risk factor for secondary neoplasms seems to be prior exposure to radiation.

Benign intracranial hypertension

In the event of severe or recurrent headache, visual symptoms, nausea, and/or vomiting, a fundoscopy for papilloedema is recommended. If papilloedema is confirmed, a diagnosis of benign intracranial hypertension should be considered and if appropriate the growth hormone treatment should be discontinued. At present there is insufficient evidence to guide clinical decision making in patients with resolved intracranial hypertension. If growth hormone treatment is restarted, careful monitoring for symptoms of intracranial hypertension is necessary.

Thyroid function

Growth hormone increases the extrathyroidal conversion of T4 to T3 and may as such unmask incipient hypothyroidism. As hypothyroidism interferes with the response to growth hormone therapy, patients should have their thyroid function tested regularly and should receive replacement therapy with thyroid hormone when indicated (see sections 4.5 Interactions with other medicines and other forms of interactions and 4.8. Adverse effects).

Adults: Use with oral estrogen

Oral estrogen influences the IGF-I response to growth hormone including somapacitan.

Women taking any form of oral estrogen (hormone therapy or contraception) should consider changing the route of estrogen administration (e.g. transdermal-, vaginal hormone products) or use another form of contraception. If a woman on oral estrogen is starting somapacitan therapy, higher starting doses and a longer titration period may be required (see section 4.2 Dose and method of administration).

If a woman taking somapacitan begins oral estrogen therapy, the dose of somapacitan may need to be increased to maintain the serum IGF-I levels within the normal age-appropriate range. Conversely, if a woman on somapacitan discontinues oral estrogen therapy, the dose of somapacitan may need to be reduced to avoid excess of somapacitan and/or undesirable effects (see sections 4.2 Dose and method of administration and 4.5 Interactions with other medicines and other forms of interactions).

Skin and subcutaneous tissue disorders

When somapacitan is administered at the same site over a long period of time, local changes in the subcutaneous tissue such as lipohypertrophy, lipoatrophy, and acquired lipodystrophy

might occur. The injection site should be rotated to reduce the risk, see sections 4.2 Dose and method of administration and 4.8 Adverse effects.

Antibodies

Although no neutralising antibodies were observed after treatment with somapacitan, antibodies could be expected as observed with other therapeutic proteins. Testing for presence of anti-somapacitan antibodies should be carried out in patients who fail to respond to therapy.

Long term treatment

Growth hormone deficiency in adults is a lifelong disease and needs to be treated accordingly, however, experience in patients older than 60 years and in patients with more than five years of treatment in adult growth hormone deficiency is still limited.

Drug abuse and dependence

There is no clinical experience with somapacitan on drug abuse and dependence.

Acute critical illness

The effect of growth hormone on recovery was studied in two placebo-controlled trials involving 522 critically ill adult patients suffering from complications following open heart surgery, abdominal surgery, multiple accidental trauma or acute respiratory failure. Mortality was higher in patients treated with 5.3 or 8 mg growth hormone daily compared to patients receiving placebo, 42% vs 19%. Based on this information, these types of patients should not be treated with somapacitan. As there is no information available on the safety of growth hormone substitution therapy in acutely critically ill patients, the benefits of continued treatment in this situation should be weighed against the potential risks involved.

Slipped capital femoral epiphysis

In fast growing children and patients with endocrine disorders, including GHD, slipped epiphysis of the hip may occur more frequently than in the general population. Children with persistent hip/knee pain and/or limping during treatment with somapacitan should be examined clinically.

Osteonecrosis of femoral head

Osteonecrosis of femoral head has been reported in patients receiving other growth hormone products.

Use in the elderly

Generally, lower doses of somapacitan may be necessary in older patients. For further information, see section 5.2 Pharmacokinetic properties.

Effects on laboratory tests

Serum levels of alkaline phosphatase may increase after somapacitan therapy.

4.5. Interactions with other medicines and other forms of interactions

Cytochrome P450 metabolised drugs

Data from an interaction study performed in growth hormone deficient adults suggests that growth hormone administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes. The clearance of compounds metabolised by cytochrome P450 (e.g. sex steroids, corticosteroids, anticonvulsants and ciclosporine) may be especially increased resulting in lower plasma levels of these compounds. The clinical significance of this is unknown.

Glucocorticoids

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 Special warnings and precautions for use.

Oral estrogens

In adult women on oral estrogen therapy, a higher dose of somapacitan may be required to achieve the treatment goal, see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use.

Antihyperglycaemic products

Antihyperglycaemic treatment including insulin may require dose adjustment in case of somapacitan co-administration since somapacitan may decrease insulin sensitivity, see sections 4.4 Special warnings and precautions for use and 4.8 Adverse effects.

Other

The metabolic effects of somapacitan can also be influenced by concomitant therapy with other hormones, e.g. testosterone and thyroid hormones, see section 4.4 Special warnings and precautions for use.

4.6. Fertility, pregnancy and lactation

Effects on fertility

There is no clinical experience with somapacitan use and its potential effect on fertility is therefore unknown.

No adverse effects were observed on male and female fertility in rats at a subcutaneous dose of 4 mg/week, resulting in exposure around 30 times greater than the expected maximum clinical exposure at 8 mg/week in adults. However, irregular female oestrus cycle was seen at all doses treated starting at 1 mg/twice weekly (~3-4-fold the expected exposure at the maximum clinical dose of 8 mg/week). Somapacitan (at exposures 30 times the MRHD based on AUC), had no effect on mating performance, fertility, litter size mean numbers of implantations, resorptions and live embryos in rats.

Use in pregnancy – Pregnancy Category B1

There are no data from the use of somapacitan in pregnant women.

No evidence of fetal harm was identified when pregnant rats and rabbits were administered subcutaneous somapacitan during organogenesis at doses leading to exposures well above expected exposure at the maximum clinical dose of 8 mg/week (at least 18-fold). At high doses leading to exposure at least 250-fold above the expected maximum clinical exposure at 8 mg/week, short/bent/thickened long bones were found in pups from female rats receiving somapacitan. Such findings in rats are known to resolve after birth and should be regarded as minor malformations, not permanent abnormalities.

Fetal growth was reduced when pregnant rabbits were dosed with somapacitan subcutaneously at exposures at least 130-fold above the expected exposure at the maximum clinical dose of 8 mg/week.

Somapacitan is not recommended during pregnancy and in women of childbearing potential not using contraception.

Use in lactation

It is unknown whether somapacitan/metabolites are excreted in human milk.

In lactating rats, somapacitan related material was secreted into milk but to a lower level than observed in plasma (up to 50% of level in plasma).

A risk to the breastfed newborns/infants cannot be excluded.

A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from somapacitan therapy, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

4.7. Effects on ability to drive and use machines

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

4.8. Adverse effects (Undesirable effects)

Paediatric GHD

Summary of safety profile

In paediatric patients, the ADRs are (in decreasing order): Headache (12%), Pain in extremity (9%), Hypothyroidism (5%), Injection site reactions (5%), Peripheral oedema (3%), Arthralgia (2%), Hyperglycaemia (2%), Fatigue (2%), and Adrenocortical insufficiency (1.5%).

In general, the ADRs are non-serious, of mild severity and generally transient.

Tabulated list of adverse reactions

The ADRs listed below are based on the safety data from one ongoing pivotal phase 3 trial (52 weeks) in paediatric patients with GHD and adverse reactions considered as class effect

from somapacitan treatment. The frequencies of the ADRs have been calculated based on the frequencies in the pivotal phase 3 trial.

The ADRs are listed by MedDRA system organ class and frequency category defined as: 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).

Table 2: Adverse reactions from phase 3 clinical trials (GHD)

MedDRA system organ class	Very common	Common
Endocrine disorders		Hypothyroidism Adrenocortical insufficiency
Metabolism and nutrition disorders		Hyperglycaemia
Nervous system disorders	Headache	
Musculo-skeletal and connective tissue disorders		Arthralgia
General disorders and administration site conditions		Peripheral oedema Injection site reactions Fatigue

Table 3: Most frequent adverse events (≥5%) by system organ class and preferred term - safety analysis

MedDRA System organ class Preferred term	Somapacitan N (%)	Somatropin N (%)
Subjects Exposed	132	68
Infections and infestations		
Nasopharyngitis	15 (11.4)	7 (10.3)
Bronchitis	4 (3.0)	5 (7.4)
Nervous system disorders		
Headache	16 (12.1)	6 (8.8)
Musculoskeletal and connective tissue disorders		
Pain in extremity	12 (9.1)	2 (2.9)
General disorders and administration site conditions		
Pyrexia	10 (7.6)	7 (10.3)
Gastrointestinal disorders		
Vomiting	6 (4.5)	4 (5.9)

Adverse reactions from post-marketing sources

N/A

Description of selected ADRs

Headache

Headache was very commonly observed (12%). Almost all of the cases were of mild severity, and the majority of the cases recovered.

Peripheral oedema

Peripheral oedema was commonly observed (3%). All cases were of mild severity, and all cases recovered.

Hypothyroidism

Hypothyroidism was commonly observed (5%). Almost all of the cases were of mild severity, and the hypothyroidism did not recover spontaneously. Refer to section 4.4 Special warnings and precautions for use.

Injection site reactions

Injection site reactions were commonly observed (5%). All cases were of mild severity, and the majority of cases recovered after short durations. The injection site reactions were injection site bruising (1.5%), injection site pain (1.5%), injection site haematoma (1.5%) and injection site swelling (0.8%).

Adult GHD

Summary of safety profile

The adverse reactions and adverse events listed below are based on the compiled safety data from three completed phase 3 trials in patients with AGHD.

In the phase 3 trials, 333 patients were exposed to somapacitan for a total of 377.8 patient years.

In adults, ADRs are headache (12%), arthralgia (7%), fatigue (6%), peripheral oedema (4%), adrenocortical insufficiency (3%), asthenia (3%), paresthesia (2%), hypothyroidism (1.8%), injection site reaction (1%), hyperglycaemia (1%), carpal tunnel syndrome (0.9%) and lipohypertrophy (0.4%).

In general, the ADRs are non-serious and of mild, or moderate severity.

Tabulated list of adverse reactions

The adverse reactions below are presented by MedDRA system organ class and frequency category defined as: 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).

Table 4: Adverse reactions from phase 3 clinical trials

MedDRA system organ class	Very common	Common	Uncommon
Endocrine disorders		Adrenocortical insufficiency Hypothyroidism	

MedDRA system organ class	Very common	Common	Uncommon
General disorders and administration site conditions		Peripheral oedema Injection site reactions Fatigue Asthenia	
Metabolism and nutrition disorders		Hyperglycaemia	
Musculo-skeletal and connective tissue disorders		Arthralgia Myalgia Muscle stiffness	Joint stiffness
Nervous system disorders	Headache	Paraesthesia	Carpal tunnel syndrome
Skin and subcutaneous tissue disorders		Rash Urticaria	Lipohypertrophy Pruritus

Tabulated list of adverse events

Table 5 Most frequent adverse events (⩾5%) by system organ class and preferred term - safety analysis (pooled phase 3 trial data)

MedDRA System organ class Preferred term	Somapacitan N (%)	Somatropin N (%)	Placebo N (%)
Subjects Exposed	333 (100)	166 (100)	61 (100)
Infections and infestations			
Nasopharyngitis	84 (25.2)	38 (22.9)	9 (14.8)
Upper respiratory tract infection	22 (6.6)	13 (7.8)	7 (11.5)
Gastroenteritis	17 (5.1)	3 (1.8)	2 (3.3)
Influenza	18 (5.4)	3 (1.8)	2 (3.3)
Nervous system disorders			
Headache	43 (12.9)	22 (13.3)	10 (16.4)
Dizziness	14 (4.2)	9 (5.4)	1 (1.6)
Musculoskeletal and connective tissue disorders			
Arthralgia	23 (6.9)	17 (10.2)	1 (1.6)
Back pain	21 (6.3)	6 (3.6)	2 (3.3)
General disorders and administration site conditions			
Fatigue	19 (5.7)	13 (7.8)	2 (3.3)
Gastrointestinal disorders			
Diarrhoea	21 (6.3)	8 (4.8)	5 (8.2)
Skin and subcutaneous tissue disorders			
Rash	6 (1.8)	10 (6.0)	2 (3.3)

Description of selected adverse reactions

Headache

Headache was very commonly observed (12%). Almost half of the cases were of mild severity and almost all cases were transient and recovered.

Fatigue and asthenia

Fatigue and asthenia (weakness) was commonly observed (6% and 3%, respectively). The majority of cases were of mild severity and the majority recovered.

Peripheral oedema

Peripheral oedema was commonly observed (4%). Growth hormone deficient patients are characterised by extracellular volume deficit. When treatment with growth hormone products is initiated, this deficit is corrected. Fluid retention with peripheral oedema may occur. The symptoms are usually transient, dose dependent and may require transient dose reduction.

Adrenocortical insufficiency

Adrenocortical insufficiency was commonly observed (3%), see section 4.4 Special warnings and precautions for use.

Hyperglycaemia

Hyperglycaemia was commonly observed (1%). All cases were of mild severity, and all were transient and recovered.

Lipohypertrophy

Lipohypertrophy at the injection site was uncommonly observed (0.4%). In the single case observed, the adverse event was of mild severity, non-serious, transient and recovered after change of the injection site.

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.

4.9. Overdose

Treatment with growth hormone can lead to an acute overdose with low blood glucose levels initially, followed by high blood glucose levels. These decreased glucose levels have been detected biochemically, but without clinical signs of hypoglycaemia.

Long-term overdosage could result in signs and symptoms consistent with the known undesirable effects of human growth hormone excess.

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: H01AC07

Mechanism of action

The mechanism of action of somapacitan is either directly via the GH-receptor and/or indirectly via IGF-I produced in tissues throughout the body, but predominantly by the liver.

When growth hormone deficiency is treated with somapacitan, a normalisation of body composition (i.e., decreased body fat mass, increased lean body mass) and of metabolic action is achieved.

Published data show that somapacitan distributes to the hypertrophic zone and primary spongiosa in the epiphysis of proximal tibia of GH‑deficient hypophysectomised rats. Distribution of somapacitan to peripheral tissues is comparable to GH.

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

Pharmacodynamic effects

IGF-I

IGF-I is a generally accepted biomarker for efficacy in GHD.

A dose-dependent IGF-I response is induced following somapacitan administration. A steady state pattern in IGF-I responses is reached after 1-2 weekly doses.

The IGF-I levels fluctuate during the week. The IGF-I response is maximal after 2 to 4 days. Compared with daily GH treatment, the IGF-I profile of somapacitan differs, see Figure 1.

In paediatric GHD patients somapacitan produces a dose linear IGF-I response, with a change of 0.02 mg/kg on average resulting in a change in IGF-I standard deviation score (SDS) of 0.32.

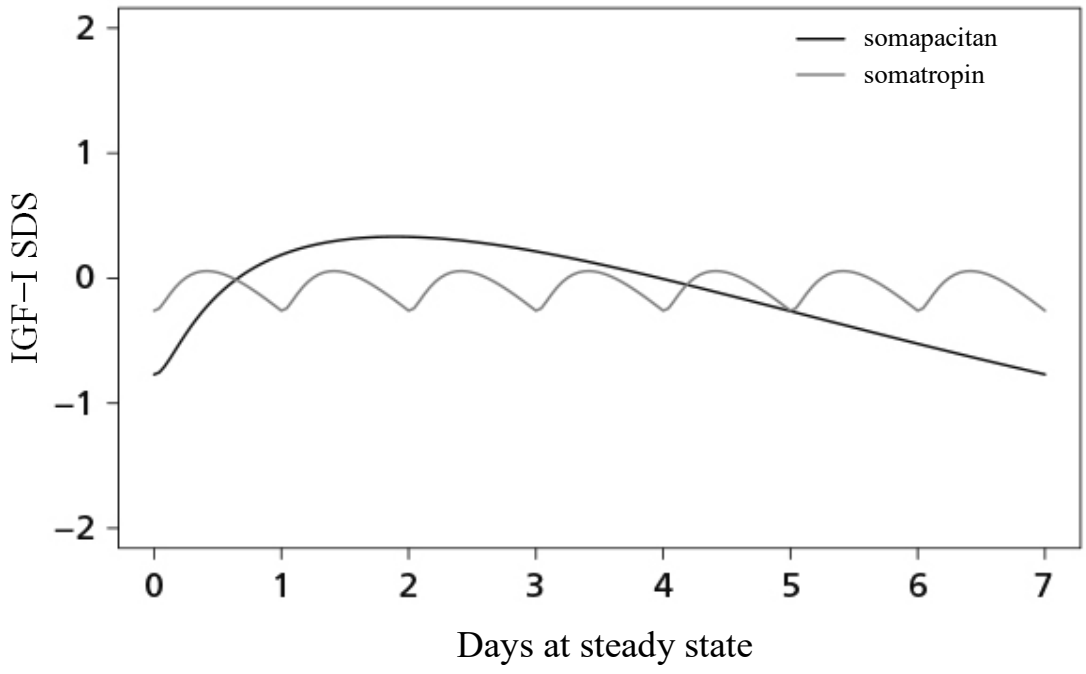


Figure 1: Model-derived IGF-I profiles during steady state of somapacitan (weekly) and somatropin (daily) (based on data from AGHD)

Clinical trials

Paediatric GHD

REAL 4 (phase 3)

The efficacy and safety of once weekly somapacitan (5 mg/1.5 mL, 10 mg/1.5 mL and 15 mg/1.5 mL) were evaluated in a 52 week randomised, multi-centre, open-label, active-controlled, parallel-group phase 3 trial (REAL 4) in 200 treatment-naïve, pre-pubertal paediatric patients with GHD. Patients were randomised to 0.16 mg/kg/week once weekly somapacitan (N=132) or 0.034 mg/kg/day daily somatropin (N=68).

At baseline, the 200 patients had a mean age of 6.4 years (range: 2.5 to 11). 25.5% patients were female and 74.5% were male. 37% of patients were Asian, 0.5% were Black or African American, 57% were Caucasian, and 5.5% were categorised as "other" or not reported.

Treatment with once weekly somapacitan for 52 weeks resulted in an annualised height velocity of 11.2 cm/year. Patients treated with daily somatropin achieved an annualised height velocity of 11.7 cm/year after 52 weeks of treatment (Table 6).

Table 6: Growth results at Week 52 in paediatric patients with GHD

	Once weekly somapacitan (N=132)	**Daily somatropin (N=68)**	**Estimate of treatment difference (95% CI) (somapacitan minus somatropin)**
Annualised Height Velocity (cm/year)	11.2	11.7	-0.5 [-1.1; 0.2]

Height SDS (change from baseline) was 1.25 in the once weekly somapacitan arm and 1.30 in the daily somatropin arm at Week 52 (Table 7). The IGF-I SDS change from baseline at week 52 was highly similar in the two arms with values of 2.36 for once weekly somapacitan and 2.33 for daily somatropin. Mean IGF-I SDS was also similar between once weekly somapacitan and daily somatropin at week 52.

Table 7: Height SDS and IGF-I SDS in paediatric patients with GHD – 52 weeks treatment

	Once Weekly somapacitan (N=132)	**Daily somatropin (N=68)**	**Estimate of treatment difference (95% CI) (somapacitan minus somatropin)**
Height SDS, baseline[a]	-2.99	-3.47	
Height SDS, change from baseline	1.25	1.30	0.05 [-0.18; 0.08]
IGF-I SDS, baseline[a]	-2.03	-2.33	
IGF-I SDS, week 52[a]	0.28	0.10	
IGF-I SDS level change from baseline	2.36	2.33	0.03 [-0.30; 0.36]

[a] Observed mean

The vast majority of paediatric patients (97%) in the trial achieved an average IGF-I SDS level within normal range (-2 to +2) after 52 weeks of treatment with once weekly somapacitan (Table 8). Low number of patients had average IGF-I SDS above +2 (2.3%) and no patients had average IGF-I SDS above +3.

Table 8: Average IGF-I SDS values after 52 weeks in paediatric patients with GHD with once weekly somapacitan

IGF-I SDS category	Week 52 Average (N=132)
<-2	0.8%
-2 to 0	21.2%
0 to +2	75.8%
+2 to +3	2.3%
>+3	0

REAL 3 (phase 2)

A total of 59 GH treatment-naïve GH-deficient paediatric patients completed a 26-week main period and a 26-week extension in a 4-arm parallel group trial with once weekly somapacitan at dose levels of 0.04, 0.08 and 0.16 mg/kg/week and active control arm of 0.034 mg/kg/day daily somatropin. The patients continued in a 104-week open-label safety extension parallel arms with somapacitan 0.16 mg/kg/week and daily somatropin 0.034 mg/kg/day. All patients were afterwards transferred to once weekly somapacitan 0.16 mg/kg/week in a 208-week long-term safety extension.

Treatment with once weekly somapacitan 0.16 mg/kg/week led to continuous treatment benefits up to at least 4 years. Height SDS was -1.06 (change from baseline: +2.85) in 38 patients.

Height outcome obtained at week 208 in patients switching from 0.034 mg/kg/day daily somatropin to 0.16 mg/kg/week once weekly somapacitan at week 156 indicated that treatment benefits with daily GH treatment are maintained after switching to once weekly somapacitan.

Mean IGF-I SDS remained within the normal range for all groups.

IGF-I SDS sampling after injection:

Blood samples may be taken on any day of the week following injections of somapacitan. Sampling 2 days after the injection closely approximates the expected maximum IGF-I value, whereas the average IGF-I concentration over the weekly dosing interval is most closely approximated with a sample taken 4 days after injection.

Based on clinical trial data in paediatric GHD patients, a guidance for calculating average IGF-I SDS based on blood sampling after injection is provided in Table 9.

Table 9: Formula for calculating approximate average IGF-I SDS over the weekly dosing interval in paediatric subjects based on blood sampling after injection

Interval Days (hours) after dose	**Measured IGF-I SDS adjustment to approximate average IGF-I SDS**
1 day after dose (25-48 hours)	IGF-I SDS – 0.8
2 days after dose (49-72 hours)	IGF-I SDS – 1.0
3 days after dose (73-96 hours)	IGF-I SDS – 0.5
4 days after dose (97-120 hours)	No adjustment*
5 days after dose (121-144 hours)	IGF-I SDS + 0.7
6 days after dose (145-168 hours)	IGF-I SDS + 1.1

* No adjustment based on the result of IGF-I SDS + 0.1, which is considered of negligible clinical relevance

Clinical safety:

The safety profile of somapacitan was similar to the well-known safety profile of somatropin, see section 4.8 Adverse Effects (Undesirable effects). No new safety issues were identified. No local tolerability issues were identified.

Immunogenicity:

A low number of patients tested positive for detectable somapacitan binding antibodies at any time during treatment. None of these antibodies were neutralising and there was no apparent clinical impact.

Patient Reported Outcomes

REAL 4

Paediatric patients treated with once weekly somapacitan reported a lower treatment burden as measured using the GHD-CTB at week 52 compared to patients treated with daily somatropin.

Caregivers of paediatric patients treated with once weekly somapacitan reported lower treatment burden as measured using the GHD-PTB at week 52 compared to patients treated with daily somatropin.

Table 10: Results of GHD-CTB and GHD-PTB in REAL 4 at 52 weeks

	Result at Week 52 (somapacitan)	Result at Week 52 (somatropin)	ETD* (somapacitan – somatropin) [95% CI]
GHD-CTB			
Physical	11.6	14.5	-2.9 [-6.8; 1.0]
Emotional well-being	15.5	19.1	-3.5 [-9.5; 2.4]
Interference	5.2	6.4	-1.3 [-3.9; 1.3]
Overall score	10.7	13.1	-2.4 [-5.7; 0.9]
GHD-PTB			
Emotional well-being	12.4	17.7	-5.3 [-10.0; -0.7]
Interference	4.9	11.6	-6.7 [-11.6; -1.9]
Overall score	8.7	14.7	-6.0 [-10.0; -2.1]

* Lower scores indicate improvement
ETD (estimated treatment difference)
[1] GHD-CTB (Growth Hormone Deficiency – Child Treatment Burden)
[2] GHD-PTB (Growth Hormone Deficiency – Parent Treatment Burden)

REAL 3

82% of caregivers of paediatric patients who switched from daily somatropin preferred once weekly somapacitan using the PPQ (Patient Preference Questionnaire).

89% of those who preferred once weekly somapacitan, indicated that they would be more adherent to therapy than daily somatropin.

Adult GHD

In a 34-week placebo-controlled (double-blind) and active-controlled (open) trial (REAL 1), 301 treatment-naïve adult patients with GHD were randomised (2:1:2) and exposed to once-weekly somapacitan or to placebo or to daily somatropin for a 34-week treatment period (main phase of the trial).

The patient population had a mean age of 45.1 years (range 23-77 years; 41 patients were 65 years or above), 51.7% were females, and 69.7% had adult onset GHD.

A total of 272 AGHD patients who completed the 34-week main phase continued in a 53-week open-label extension period. Subjects on placebo were switched to somapacitan and patients on somatropin were re-randomised (1:1) to either somapacitan or somatropin.

Observed clinical effects for the main endpoints in the main treatment phase (Table 11) and extension treatment phase (Table 12) are presented below.

Table 11: Change from baseline to week 34 in body composition parameters (REAL 1)

Change from baseline at 34 weeks[a]	**somapacitan**	**somatropin**	**placebo**	**Difference somapacitan - placebo [95% CI] p-value**	**Difference somapacitan-somatropin [95% CI]**
Number of subjects (N)	120	119	61		
Truncal fat % (Primary endpoint)	-1.06	-2.23	0.47	-1.53 [-2.68; -0.38] 0.0090[b]	1.17 [0.23;2.11]
Visceral adipose tissue (cm^2)	-10	-9	3	-14 [-21; -7]	-1 [-7; 4]
Appendicular skeletal muscle mass (g)	558	462	-121	679 [340; 1,019]	96 [-182; 374]
Lean body mass (g)	1,394	1,345	250	1144 [459; 1,829]	49 [-513;610]
IGF-I SDS level	2.40	2.37	-0.01	2.40 [2.09; 2.72]	0.02 [-0.23;0.28]

Abbreviations: N = Number of subjects in full analysis set, CI = Confidence interval, DM=Diabetes mellitus. IGF-I SDS: Insulin-like growth factor-I standard deviation score.

[a] Body composition parameters are based on dual-energy X-ray absorptiometry (DXA) scanning.

[b] The primary analysis was a comparison of changes from baseline for somapacitan and placebo in truncal fat %. Changes in truncal fat % from baseline to the 34 week's measurements were analysed using an analysis of covariance model with treatment, GHD onset type, sex, region, DM and sex by region by DM interaction as factors and baseline as a covariate incorporating a multiple imputation technique where missing week 34 values were imputed based on data from the placebo group.

Post-hoc subgroup analysis of changes from baseline in truncal fat percentage (%) compared to placebo at week 34 showed an estimated treatment difference (somapacitan-placebo) of -2.49% [-4.19; -0.79] in men, -0.80% [-2.99; 1.39] in women not on oral estrogen, -1.44% [-3.97; 1.09] in women on oral estrogen.

Table 12: Change from baseline to week 87 in body composition parameters (REAL 1)

Change from baseline at 87 weeks[a]	somapacitan/ somapacitan	somatropin/ somatropin	placebo/ somapacitan	somatropin/ somapacitan	Difference somapacitan/ somapacitan vs somatropin/ somatropin [95% CI]
Number of subjects (N)	114	52	54	51	
Truncal fat %	-1.52	-2.67	-2.28	-1.35	1.15 [-0.10; 2.40]
Visceral adipose tissue (cm^2)	-6.64	-6.85	-10.21	-8.77	0.22 [-10; 10]
Appendicular skeletal muscle mass (g)	546.11	449.09	411.05	575.80	97.02 [-362; 556]
Lean body mass (g)	1,739.05	1,305.73	1,660.56	1,707.82	433.32 [-404; 1271]

[a] Body composition parameters are based on DXA scanning.

Observed and simulated IGF-I SDS levels in the clinical study

In the main phase of the clinical study IGF-I SDS values of 0 and above were overall achieved in 53% of somapacitan-treated AGHD study patients after an 8-week dose titration period. This proportion was however lower in particular subgroups such as women on oral estrogen (32%) and patients with childhood-onset (39%) (Table 13). *Post-hoc* simulation analyses indicated that the proportions of AGHD patients achieving IGF-I SDS levels above 0 are expected to be higher in case somapacitan dose titration beyond 8 weeks would be allowed. In this simulation analysis, it was assumed that somapacitan dose titration was well-tolerated in all patients until the IGF-I SDS target range or a somapacitan dose of 8 mg per week would be achieved.

Table 13: Proportions of somapacitan-treated AGHD patients with IGF-I SDS levels above 0

Subgroups	Men	Women not on oral estrogen	Women on oral estrogen	Childhood-onset AGHD	Adult-onset AGHD	All
Observed[a]	71%	46%	32%	39%	60%	53%
Post-hoc simulations	100%	96%	70%	84%	92%	90%

[a] The trial was designed to titrate towards a IGF-I SDS level above -0.5

5.2. Pharmacokinetic properties

Somapacitan has pharmacokinetic properties compatible with once weekly administration. The reversible binding to endogenous albumin delays elimination of somapacitan and thereby prolongs the *in vivo* half-life and duration of action.

The pharmacokinetics of somapacitan following subcutaneous administration have been investigated at dose levels from 0.02 to 0.16 mg/kg/week in paediatric population, at dose levels from 0.01 to 0.32 mg/kg in healthy adults, and in doses up to 0.12 mg/kg in adults with GHD.

Overall, somapacitan displays non-linear pharmacokinetics, but in the clinically relevant dose range of somapacitan in adults with GHD, somapacitan pharmacokinetics are approximately linear.

Absorption

In adult and paediatric patients with GHD median t_{max} ranged from 4 to 24 hours at doses from 0.02 mg/kg/week to 0.16 mg/kg/week.

Steady state exposure was achieved following 1-2 weekly administration.

Absolute bioavailability of somapacitan in humans has not been investigated.

Distribution

Somapacitan is extensively bound (>99%) to plasma proteins and is expected to be distributed like albumin. Based on population PK analyses, the estimated volume of distribution (V/F) was 1.7 L in paediatric GHD patients and 14.6 L in adults.

Metabolism

Somapacitan is extensively metabolised by proteolytic degradation and cleavage of the linker sequence between the peptide and albumin binder.

In adults with GHD, somapacitan was extensively metabolised before excretion and no intact somapacitan was found neither in urine, which was the main excretion route (81%), nor in faeces where 13% of somapacitan related material was found, indicating full biotransformation before excretion.

Elimination

Following a single dose of 0.16 mg/kg/week the terminal half-life was 34 h in paediatric GHD patients.

The terminal half-life was estimated with geometric means ranging from approximately 2 to 3 days at steady state in AGHD patients (doses: 0.02 to 0.12 mg/kg).

Somapacitan will be present in circulation for approximately 2 weeks after the last dose.

Little to no accumulation (mean accumulation ratio: 1-2) of somapacitan following multiple dosing has been observed.

Special populations

It is recommended that the dose is adjusted based on the clinical response and the patient's experience of adverse events. No additional dosing considerations of somapacitan is needed based on race (Japanese, Asian non-Japanese vs White), body weight, renal or hepatic impairment. For starting dose and dose adjustment information, refer to section 4.2 Dose and method of administration.

Paediatric GHD patients

Based on pharmacokinetic modelling gender, race and body weight do not have a clinically meaningful effect on the pharmacokinetics following weight-based dosing.

Adult GHD patients

Age

Subjects older than 60 years have higher exposure (29%) than younger subjects at the same somapacitan dose. A lower starting dose for subjects above 60 years is described in section 4.2 Dose and method of administration.

Gender

Female subjects and in particular female subjects on oral estrogen, have lower exposure (53% for females on oral estrogen and 30% for females not on oral estrogen) than male subjects at the same somapacitan dose. A higher starting dose for females on oral estrogen is described in section 4.2 Dose and method of administration.

Race

There was no difference in somapacitan exposure and IGF-I response between Japanese and White subjects. Despite a higher exposure in Asian Non-Japanese compared to White at the same somapacitan dose, White, Japanese and Asian Non-Japanese subjects needed the same doses to reach similar IGF-I levels. Therefore, there is no dose adjustment recommendation based on race.

Ethnicity

Ethnicity (Hispanic or Latino 4.5% (15 subjects received somapacitan)) was not investigated due to small sample size in the development programme.

Body weight

Despite a higher exposure in subjects with low body weight as compared to subjects with high body weight at the same somapacitan dose, subjects needed the same doses to reach similar IGF-I levels across the body weight range 35 kg to 150 kg. Therefore, there is no dose adjustment recommendation based on body weight.

Renal impairment

A somapacitan dose of 0.08 mg/kg at steady state resulted in higher exposures in subjects with renal impairment, most pronounced in subjects with severe renal impairment and in subjects requiring haemodialysis, where $AUC_{0\text{-}168h}$ ratios to normal renal function were 1.75 and 1.63, respectively. In general, somapacitan exposure tended to increase with decreasing GFR.

Higher IGF-I $AUC_{0\text{-}168h}$ levels were observed in subjects with moderate and severe renal impairment and subjects requiring haemodialysis, with ratios to normal renal function of 1.35, 1.40 and 1.24 respectively.

Due to the modest increase observed in IGF-I combined with the low recommended starting doses and the individual dose titration of somapacitan, there is no dose adjustment recommendation in patients with renal impairment.

Hepatic impairment

A somapacitan dose of 0.08 mg/kg at steady state resulted in higher exposure in subjects with moderate hepatic impairment with ratios to normal hepatic function of 4.69 for $AUC_{0\text{-}168h}$ and 3.52 for C_{max}.

Lower somapacitan stimulated IGF-I levels were observed in subjects with mild and moderate hepatic impairment compared to subjects with normal hepatic function (ratio to normal was 0.85 for mild and 0.75 for moderate).

Due to the modest decrease observed in IGF-I combined with the individual dose titration of somapacitan, there is no dose adjustment recommendation in patients with hepatic impairment.

5.3. Preclinical safety data

Genotoxicity

Somapacitan was not mutagenic or clastogenic in a standard battery of genotoxicity tests (bacterial mutagenicity (Ames), human lymphocyte chromosome aberration, rat bone marrow micronucleus).

Carcinogenicity

No carcinogenicity studies have been performed with somapacitan. Somapacitan raises serum levels of IGF-1. Associations between elevated serum IGF-1 concentrations and risks of certain cancers have been reported in epidemiological studies. Causality has not been demonstrated. The clinical significance of these associations, especially for subjects treated with somapacitan who do not have growth hormone deficiency and who are treated for prolonged periods, is not known.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Histidine
Mannitol
Poloxamer
Phenol
Hydrochloric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
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.

After first opening

Store in a refrigerator (2°C - 8°C). Discard pen 6 weeks after first use.

Do not freeze. Keep away from the freezing element.

Keep Sogroya in the outer carton with the pen cap on to protect from light.

Before and during use

If refrigeration is not possible (e.g. during travelling), Sogroya may be kept temporarily at temperatures up to 30°C for up to a total of 72 hours (3 days). Return Sogroya to the refrigerator again after storage at this temperature. If stored out of refrigeration and then returned to refrigeration, the total combined time out of refrigeration should not exceed 3 days, monitor this carefully. The Sogroya pen should be discarded if it has been kept up to 30°C for more than 72 hours (3 days) or for any period of time kept above 30°C.

Table 14: Tabulated storage conditions for Sogroya

	Before first use (unopened)		**After first use (opened)**	
Sogroya	Refrigerate 2°C to 8°C	Room temperature up to 30°C	Refrigerate 2°C to 8°C	Room temperature up to 30°
	Until expiry date	Maximum 72 hours (3 days)*	Up to 6 weeks	Maximum 72 hours (3 days)*

* To allow for portability, the total time allowed at room temperature (up to 30°C) is 72 hours (3 days) regardless of whether product is not yet used (unopened) or after first use (opened). Must be discarded if kept above 30°C.

6.4. Special precautions for storage

Store in a refrigerator (2°C - 8°C). Do not freeze. Keep away from the freezing element.

Keep Sogroya in the outer carton with the pen cap on to protect from light.

A needle must always be attached before use. Needles must not be re-used. The injection needle should be removed after each injection and the pen should be stored without a needle attached. This may prevent blocked needles, contamination, infection, leakage of solution and inaccurate dosing.

In the event of blocked needles, patients must follow the instructions described in the instructions for use accompanying the consumer medicine information.

Needles are not included. Sogroya pre-filled pen has been tested with 31G x 6 mm and 32G x 5 mm disposable needles. The pen is designed to be used with NovoFine® disposable needles up to a length of 8 mm and as thin as 32 G.

For storage conditions after first opening of the medicinal product, see section 6.3 Shelf-life.

6.5. Nature and contents of container

1.5 mL solution in a glass cartridge (Type I colourless glass) with a plunger made of chlorobutyl rubber and a stopper made of bromobutyl/isoprene rubber sealed with an aluminium cap.

The cartridge is contained in a multidose disposable colour–coded pen made of polypropylene, polyacetal, polycarbonate and acrylonitrile butadiene styrene and in addition two metal springs.

The cartridge is permanently sealed in a pen-injector.

The dose button and cap on the pen-injector is colour–coded according to strength:

5 mg/1.5 mL is coloured teal.

10 mg/1.5 mL is coloured yellow.

15 mg/1.5 mL is coloured rubine red.

Pack sizes of 1 pre-filled pen and multipack of 5 (5 packs of 1) pre-filled pen.

Not all strengths or pack sizes may be marketed.

6.6. Special precautions for disposal

The pen is for use by one person only.

Sogroya should not be used if the solution does not appear clear to slightly opalescent, colourless to slightly yellow and free from visible particles.

Sogroya must not be used if it has been frozen.

The cartridge must not be taken out of the pre-filled pen and refilled.

The patient should be advised to remove the injection needle after each injection, dispose of the needle in accordance with local requirements, and store the pen without a needle attached.

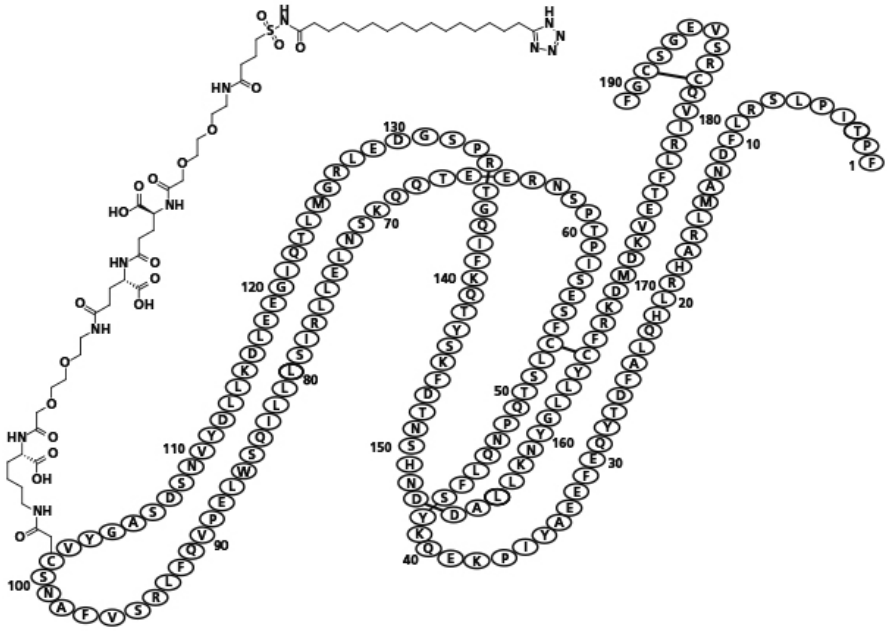
In Australia, any unused medicine or waste material should be disposed of in accordance with local requirements.

6.7. Physicochemical properties

Chemical structure

Structural formula:

[101-{S-[(8S,22S,27S)-8,22,27-tricarboxy-2,10,19,24,29,38,42,42,44-nonaoxo-59-(1H-tetrazol-5-yl)-12,15,31,34-tetraoxa-42λ6-thia3,9,18,23,28,37,43-heptaazanonapentacontan-1-yl]-L cysteine}] human somatropin



Molecular formula: $C_{1038}H_{1609}N_{273}O_{319}S_9$

Molar mass: 23305.10 g/mol

CAS number

1338578-34-9

7. MEDICINE SCHEDULE (POISONS STANDARD)

S4

8. SPONSOR

Novo Nordisk Pharmaceuticals Pty Limited
Level 10, 118 Mount Street,
North Sydney, NSW 2060,
Australia.

www.novonordisk.com.au

9. DATE OF FIRST APPROVAL

21 February 2022

10. DATE OF REVISION

06 November 2026

Summary table of changes

Section Changed	Summary of new information
4.2	Addition of injection site lipoatrophy
4.4	Update subsection title and description of injection site atrophy