▼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/safety/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION - NGENLA® (SOMATROGON) SOLUTION FOR INJECTION

1. NAME OF THE MEDICINE

Somatrogon.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each pre-filled pen contains 24 mg or 60 mg somatrogon.

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

3. PHARMACEUTICAL FORM

A clear and colourless to slightly light-yellow solution for injection available as:

- Single-patient-use disposable pre-filled pen containing 24 mg/ 1.2 mL that delivers a dose in 0.2 mg increments.
- Single-patient-use disposable pre-filled pen containing 60 mg/ 1.2 mL that delivers a dose in 0.5 mg increments.

The pre-filled pen is capable of setting and delivering a dose, which is variable, and is determined based on patient body weight.

NGENLA has a pH of approximately 6.6.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

NGENLA is indicated for the long-term treatment of paediatric patients with growth disturbance due to insufficient secretion of growth hormone (GH).

4.2 Dose and method of administration

The recommended dose is 0.66 mg/kg body weight administered once weekly by subcutaneous (SC) injection. For patients switching from daily growth hormone products, weekly therapy with NGENLA may be initiated at a dose of 0.66 mg/kg/week on the day following their last daily injection.

Regular monitoring of Insulin-like Growth Factor-1 (IGF-1) concentrations is recommended during treatment with NGENLA. When monitoring for IGF-1, samples should always be drawn 4 days after the prior dose.

NGENLA dosage may be adjusted as necessary, based on growth velocity, body weight and serum insulin-like growth factor 1 (IGF-1) concentration. In patients whose blood IGF-1 concentrations exceed the mean reference value for their age and sex by more than 2 SDS, the dose of NGENLA should be reduced by 15%. More than one dose reduction may be required in some patients.

Monitor growth rate closely during the first year of NGENLA treatment. If a patient's growth rate fails to increase in the first year, assess for treatment adherence and other causes of growth failure (e.g., hypothyroidism, undernutrition, advanced bone age) and consider discontinuation of NGENLA treatment.

Treatment should be discontinued when there is evidence of closure of the epiphyseal growth plates.

There is no clinical trial experience with doses of NGENLA above a dose of 0.66 mg/kg/week.

NGENLA must not be given by any other route of administration including intravenous (IV) or intramuscular (IM) injection.

NGENLA can be given in the abdomen, thighs, buttocks, or upper arms. The injection site should be rotated weekly to help prevent lipoatrophy (see section 4.8). If more than one injection is required to deliver a complete dose, each injection should be administered at a different injection site.

Administer NGENLA once weekly, on the same day each week, at any time of the day. The day of weekly administration can be changed if necessary, as long as the time between the two doses is at least 3 days (>72 hours). After selecting a new dosing day, the once weekly dosing should be continued.

If a dose is missed, administer NGENLA as soon as possible within 3 days after the missed dose. If more than 3 days have passed, skip the missed dose and administer the next dose on the regularly scheduled day. In each case, patients can then resume their regular once weekly dosing schedule.

Refer to the Instructions for Use leaflet for complete administration instructions.

4.3 Contraindications

Based on experience with daily growth hormone products, NGENLA is contraindicated in patients with active tumours and/or malignancy.

Based on experience with pharmacologic amounts of daily growth hormone products, NGENLA is contraindicated in patients with acute critical illness due to complications following open heart or abdominal surgery, multiple accidental trauma, or acute respiratory failure (see section 4.4).

NGENLA is contraindicated in patients with known hypersensitivity to somatrogon (see section 4.4) or any of its excipients (see section 6.1).

4.4 Special warnings and precautions for use

NGENLA should be administered by physicians who are experienced in the diagnosis and management of patients with growth hormone deficiency.

Acute critical illness

There is no clinical experience with NGENLA in patients with acute critical illness.

Treatment with pharmacologic amounts of daily growth hormone products has been associated with increased mortality in patients with acute critical illness due to complications following open heart surgery, abdominal surgery or multiple accidental trauma, or those with acute respiratory failure (see section 4.3).

Based on experience with daily growth hormone products, if patients who are receiving NGENLA therapy become acutely critically ill, the potential benefit of continued treatment should be weighed against the potential risk (see section 4.3).

Hypersensitivity reactions

Serious systemic hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with daily growth hormone products. If a serious hypersensitivity reaction occurs, immediately discontinue use of NGENLA; treat promptly per standard of care and monitor until signs and symptoms resolve. Do not use in patients with previous hypersensitivity to NGENLA (see section 4.3)

Hypoadrenalism

Based on published data, patients receiving daily growth hormone therapy who have or are at risk for pituitary hormone deficiency(s) may be at risk for reduced serum cortisol levels and/or unmasking of central (secondary) hypoadrenalism. In addition, patients treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance or stress doses following initiation of NGENLA treatment (see section 4.5). Monitor patients for reduced serum cortisol levels and/or need for glucocorticoid dose increases in those with known hypoadrenalism (see section 4.5).

Neoplasm

In childhood cancer survivors, an increased risk of a second neoplasm has been reported in patients treated with somatropin after their first neoplasm. Intracranial tumours, in particular meningiomas, in patients treated with radiation to the head for their first neoplasm, were the most common of these second neoplasms.

Benign intracranial hypertension

Intracranial hypertension (IH) with papilledema, visual changes, headache, nausea, and/or vomiting has been reported in a small number of patients treated with daily growth hormone products. Symptoms usually occurred within the first 8 weeks after the initiation of daily

growth hormone therapy. In all reported cases, IH-associated signs and symptoms rapidly resolved after cessation of therapy or a reduction of the daily growth hormone dose. NGENLA should be temporarily discontinued in patients with clinical or fundoscopic evidence of IH. If treatment with NGENLA is restarted, monitoring for signs and symptoms of IH is recommended.

No evidence of benign intracranial hypertension was reported in clinical trials with NGENLA.

Glucose metabolism impairment

Treatment with daily growth hormone products may induce a state of insulin resistance and hyperglycemia. Additional monitoring should be considered in patients treated with NGENLA who have glucose intolerance, or additional risk factors for diabetes. In patients treated with NGENLA who have diabetes mellitus, anti-diabetic therapy might require adjustment (see section 4.5).

No clinically meaningful changes in glucose metabolism, including insulin sensitivity, were observed in clinical trials with NGENLA.

Scoliosis

Because NGENLA increases growth rate, signs of development or progression of scoliosis should be monitored during treatment.

Closed epiphyses

In children with closed epiphyses, NGENLA is not recommended to be used for growth promotion.

Thyroid function impairment

Based on experience with daily growth hormone products, undiagnosed/untreated hypothyroidism may prevent an optimal response to NGENLA therapy. During NGENLA therapy, thyroid function should be monitored as indicated based on clinical evaluation.

Prader-Willi syndrome

NGENLA has not been studied in patients with Prader-Willi syndrome. NGENLA 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 growth hormone deficiency (GHD). There have been reports of sudden death after initiating therapy with growth hormone in paediatric 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.

Epiphyseal disorders

Post-marketing cases of epiphysiolysis associated with NGENLA use have been reported (see section 4.8). Epiphyseal disorders, including slipped capital femoral epiphysis may occur more frequently in patients with endocrine disorders or in patients undergoing rapid growth. Any paediatric patient with the onset of a limp or complaints of hip or knee pain during treatment should be carefully evaluated.

No epiphyseal disorders were reported with the administration of NGENLA in clinical trials.

Myositis

Myositis is a very rare adverse event that may be related to the preservative metacresol. In the case of myalgia or disproportionate pain at injection site, myositis should be considered and if confirmed, other growth hormone products without metacresol should be used.

Immunogenicity

Consistent with the potentially immunogenic properties of protein and peptide pharmaceuticals, patients treated with NGENLA may develop antibodies to somatrogon.

The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to somatrogon in the study described below with the incidence of antibodies in other studies or to other products may be misleading.

In the definitive safety and efficacy study, among 109 subjects treated with somatrogon, 84 (77%) tested positive for anti-drug antibodies (ADAs). There were no serious adverse drug reactions, or serious immune-related toxicities reported in patients with or without ADAs. In addition, efficacy was similar in patients with or without ADAs. In addition, annual height velocity, change in height SDS, height SDS, and IGF-1 response were similar in patients with or without treatment-emergent ADAs.

Use in hepatic impairment

NGENLA has not been studied in patients with hepatic impairment.

Use in renal impairment

NGENLA has not been studied in patients with renal impairment.

Use in the elderly

No data available.

Paediatric use

Currently available data are described in sections 4.8, 5.1 and 5.2. The recommended dose is 0.66 mg/kg body weight administered once weekly by subcutaneous (SC) injection (see section 4.2).

The efficacy and safety of NGENLA in paediatric patients 3 to 11 years of age with growth failure due to growth hormone deficiency have been established in clinical trials. The efficacy and safety of NGENLA have not been established in patients under 3 years of age. Data on the efficacy and safety of NGENLA in patients 12 to under 18 years of age are limited. Paediatric patients with growth failure due to acquired growth hormone deficiency caused by a malignancy were not studied in clinical trials.

Effects on laboratory tests

No data available.

4.5 Interactions with other medicines and other forms of interactions

Drugs metabolised by CYP3A4

In vitro data showing weak induction of CYP3A4 in cultured human hepatocytes by somatrogon suggest that treatment with NGENLA has the potential to increase clearance and reduce plasma level of concomitantly administered medications that are substrates for CYP3A4 (e.g., sex steroids, corticosteroids, anticonvulsants and ciclosporin). *In vivo* interaction studies have not been performed.

Glucocorticoids

In patients receiving concomitant NGENLA and glucocorticoid treatments, glucocorticoid dosing should be carefully monitored to avoid both hypoadrenalism and an inhibitory effect on growth.

The microsomal enzyme 11β-hydroxysteroid dehydrogenase type 1(11βHSD-1) is required for conversion of cortisone to its active metabolite, cortisol, in hepatic and adipose tissue.

Treatment with daily growth hormone products inhibits 11βHSD-1, reducing serum cortisol concentrations, which may unmask previously undiagnosed central (secondary) hypoadrenalism or render low glucocorticoid replacement doses ineffective (see section 4.4).

Patients treated with cortisone acetate and prednisone may be affected more than others because conversion of these drugs to their biologically active metabolites is dependent on the activity of 11βHSD-1.

Insulin and/or oral/injectable hypoglycaemic agents

In patients with diabetes mellitus requiring drug therapy, the dose of insulin and/or oral/injectable agent may require adjustment when NGENLA therapy is initiated (see section 4.4).

Oral oestrogen

Oral oestrogen may reduce the serum IGF-1 response to NGENLA. Female patients receiving oral oestrogen-containing therapy may require higher NGENLA dosage. If a female patient taking NGENLA begins or discontinues oral oestrogen-containing therapy, IGF-1 value should be monitored to determine if the dose of growth hormone should be adjusted to maintain the serum IGF-1 levels within the normal range.

4.6 Fertility, pregnancy and lactation

Effects on fertility

The risk of infertility in males and females of reproductive potential has not been studied in humans.

Male and female fertility indices were unaffected in rats treated with somatrogon at subcutaneous doses up to 30 mg/kg once every 2 days, yielding approximately 50 times the exposure in patients at the recommended human dose. Effects on ovulation (increased oestrous cycle length and the number of corpora lutea) were observed in treated female rats, but did not affect the incidence of pregnancy or the number of viable embryos per dam.

Use in pregnancy – Pregnancy Category B1

There are no studies in pregnant women. No adverse effects on embryofetal development were observed with somatrogon in rats at subcutaneous doses up to 30 mg/kg once every 2 days (yielding approximately 50 times the exposure in patients at the maximum recommended human dose, based on serum AUC). While birth weight was unaffected, postnatal body weight was increased in rats with maternal treatment at ≥10 mg/kg once every 2 days during gestation and lactation. At 30 mg/kg once every 2 days, oestrous cycle length was increased in the offspring of treated rats, but with no impact on the fertility index.

Because animal reproduction studies are not always predictive of human response, NGENLA should be used during pregnancy only if clearly needed.

Somatrogon has been shown not to interfere with blood or urine pregnancy tests.

Use in lactation

Lactation studies have not been conducted with somatrogon. It is not known whether somatrogon is excreted in human milk. Due to the potential risk to the infant, NGENLA should be used during breastfeeding only if clearly needed.

4.7 Effects on ability to drive and use machines

No effects on the ability to drive and use machines have been observed.

4.8 Adverse effects (undesirable effects)

The most frequently occurring adverse reactions after treatment with NGENLA are injection site reactions (ISRs) (25.1%), headache (10.7%), and pyrexia (10.2%).

Safety data are derived from the phase 2, multi-centre safety and dose finding study, and the pivotal phase 3, multi-centre non-inferiority study in paediatric GHD patients (see section 5.1) and post-marketing data. The data reflect exposure of 265 patients to NGENLA administered once weekly (0.66 mg/kg/week) in clinical studies.

Adverse drug reactions (ADRs) for NGENLA are presented in Table 1 within the system organ class (SOC) and CIOMS frequency using the following convention: 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), not known (cannot be estimated from the available data).

Table 1. Adverse Drug Reactions (ADRs) by SOC and CIOMS frequency category listed in order of decreasing medical seriousness or clinical importance within each frequency category and SOC

	Very Common ≥1/10	Common ≥1/100, <1/10	Uncommon ≥1/1000, <1/100	Rare ≥1/10,000, <1/1000	Very Rare <1/10,000	Frequency Not Known (Cannot be estimated from the available data)
Blood and lymphatic system disorders		Anaemia, Eosinophilia				
Endocrine disorders		Hypothyroidism	Adrenal insufficiency			
Nervous system disorders	Headache					
Eye disorders		Conjunctivitis allergic				
Skin and subcutaneous tissue disorders			Rash generalised			Lipoatrophy*
Musculoskeletal and connective tissue disorders		Arthralgia, Pain in extremity				Epiphysiolysis (including slipped capital femoral epiphysis)*
General disorders and administration site conditions	Injection site reactions[a], Pyrexia					

* ADR identified post-marketing.

[a] The term Injection site reactions was selected as the cluster term for the following PTs: Injection site bruising, Injection site deformation, Injection site erythema, Injection site haemorrhage, Injection site hypertrophy, Injection site induration, Injection site inflammation, Injection site pain, Injection site pruritus, Injection site swelling, Injection site urticaria and Injection site warmth.

The most frequently reported all-causality adverse events that occurred in ≥5% of subjects in any treatment group were injection site pain, nasopharyngitis, headache, pyrexia, cough, injection site erythema, vomiting, bronchitis, arthralgia, blood creatinine phosphokinase increased, anaemia, pharyngitis, hypothyroidism, otitis media, ear pain, oropharyngeal pain, rhinitis, arthropod bite, injection site pruritus, abdominal pain upper, and tonsillitis.

Long-term exposure

In an open label extension (OLE) of a safety and dose-finding study (see section 5.1), 37 patients received treatment with somatrogon for at least 5 years. No additional safety findings were reported.

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/safety/reporting-problems.

4.9 Overdose

Single doses of NGENLA higher than 0.66 mg/kg/wk have not been studied.

Based on experience with daily growth hormone products, short-term overdosage could lead initially to hypoglycaemia and subsequently to hyperglycaemia. Long-term overdosage could result in signs and symptoms of gigantism and/or acromegaly consistent with the effects of growth hormone excess.

There is no experience of overdose with NGENLA. Treatment of overdose with NGENLA should consist of general supportive measures.

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

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Mechanism of action

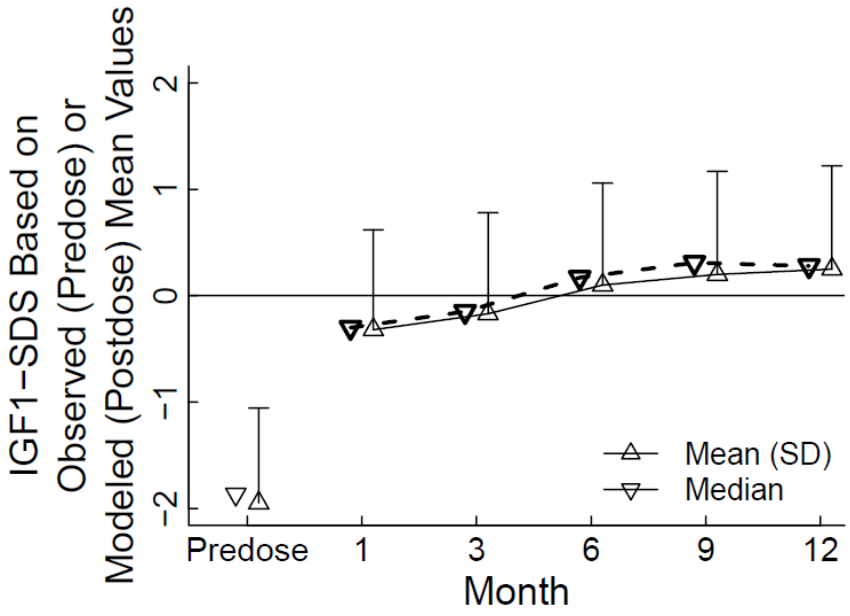
Somatrogon is a glycoprotein produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. It is comprised of the amino acid sequence of human growth hormone (hGH) with one copy of the of C-terminal peptide (CTP) from the beta chain of human chorionic gonadotropin (hCG) at the N-terminus and two copies of CTP (in tandem) at the C-terminus. The glycosylation and CTP domains account for the half-life of somatrogon, which allows for weekly dosing.

Somatrogon binds to the GH receptor and initiates a signal transduction cascade culminating in changes in growth and metabolism. Consistent with GH signalling, somatrogon binding leads to activation of the STAT5b signalling pathway and increases the serum concentration of IGF-1. IGF-1 was found to increase in a dose-dependent manner during treatment with somatrogon partially mediating the clinical effect. As a result, GH and IGF-1 stimulate metabolic changes, linear growth, and enhance growth velocity in paediatric patients with GHD.

Pharmacodynamics

Somatrogon increases IGF-1. Pharmacodynamic evaluations were performed approximately 96 hours after dose administration in order to assess the mean IGF-1 SDS over the dosing interval (see Figure 1).

Figure 1. Modelled IGF-1 SDS profiles in paediatric patients with GHD during 12 months of treatment with somatrogon



Clinical trials

The safety and efficacy of NGENLA for the treatment of paediatric patients with GHD were evaluated in two multi-centre randomised, open label controlled clinical studies. Both studies included a 12-month main study period that compared once weekly NGENLA to Genotropin administered once daily followed by a single arm open-label extension (OLE) period during which all patients were administered NGENLA once weekly. The primary efficacy endpoint for both studies was annualised height velocity (HV) following 12 months of treatment. Other endpoints reflective of catch-up growth such as change in height SDS from baseline and height SDS were also evaluated in both studies.

In an initial safety and dose-finding study, 53 paediatric patients with GHD were randomised and treated with one of 3 doses of once weekly NGENLA [0.25 mg/kg/wk (n=13), 0.48 mg/kg/wk (n=15), 0.66 mg/kg/wk (n=14)] or Genotropin administered once daily [0.034 mg/kg/day (n=11)]. The annual HV in patients treated with 0.66 mg/kg/wk of NGENLA was comparable to Genotropin administered once daily after 12 months of treatment (11.4 cm/yr [95% CI: 9.2, 13.7]); (12.5 cm/yr [95% CI: 11.0, 13.9]), respectively. During the OLE, 37 patients received 0.66 mg/kg/wk of NGENLA for at least 5 years. A progressive gain in height SDS from baseline was observed at 5 years (cumulative change in height SDS mean (SD)=3.11 (1.18), median=2.86).

The 0.66 mg/kg/wk dose of NGENLA was further evaluated in a definitive safety and efficacy study in 224 pre-pubertal paediatric patients with GHD. Patients were randomised and treated with once weekly NGENLA (n=109) or Genotropin administered once daily (n=115) at a dose of 0.034 mg/kg/day. The mean age across the treatment groups was 7.7 years (min 3.01, max 11.96), 40.2% of patients were >3 years to ⩽7 years, 59.8% were >7 years. 71.9% of patients were male and 28.1% were female. In this study 74.6% of patients were White, 20.1% were Asian; 0.9% were Black. Baseline disease characteristics were balanced across both treatment groups. Approximately 68% of patients had peak plasma growth hormone (GH) levels of ≤7 ng/mL, and the mean height was below -2 standard deviation score (SDS). The pubertal

stage at baseline was Tanner I. Once weekly NGENLA resulted in a non-inferior HV at 12 months compared to Genotropin administered once daily. Catch-up growth as reflected by change in height SDS from baseline was numerically higher for NGENLA (see Table 2). Once weekly NGENLA also produced an increase in IGF-1 SDS values, from a mean of -1.95 at baseline to a mean of 0.65 at 12 months.

Table 2. Efficacy of NGENLA compared to Genotropin in paediatric patients with GHD at Month 12

Treatment Parameter	Treatment Group		LSM Difference (95% CI)
	NGENLA (n=109)	Genotropin (n=115)	
	LSM Estimate	LSM Estimate	
Height Velocity (cm/yr)	10.10	9.78	0.33 (-0.24, 0.89)
Height Standard Deviation Score	-1.94	-1.99	0.05 (-0.06, 0.16)
Change in Height Standard Deviation Score from baseline	0.92	0.87	0.05 (-0.06, 0.16)

Abbreviations: CI=confidence interval; GHD=growth hormone deficiency; LSM=least square mean; n=number of patients randomised and treated.

There have been no clinical trials with NGENLA in children with Turner Syndrome, Prader Willi Syndrome or SGA.

5.2 Pharmacokinetic properties

Somatrogon pharmacokinetics (pK) was assessed using a population pK approach for NGENLA in 42 paediatric patients (age range 3-15.5 years) with GHD.

Absorption

Following SC injection, serum concentrations increased slowly, peaking 6 to 18 hours after dosing.

In paediatric patients with GHD, somatrogon exposure increases in a dose-proportional manner for doses of 0.25 mg/kg/wk, 0.48 mg/kg/wk and 0.66 mg/kg/wk. There is no accumulation of somatrogon after once-weekly administration. In paediatric patients with GHD, the mean population pK estimated steady-state peak concentrations following 0.66 mg/kg/wk was 690 ng/mL.

Distribution

In paediatric patients with GHD, the mean population pK estimated apparent central volume of distribution was 0.812 L/kg and the apparent peripheral volume of distribution was 0.169 L/kg.

Metabolism

The metabolic fate of somatrogon is believed to be classical protein catabolism, with subsequent reclamation of the amino acids and return to the systemic circulation.

Elimination

In paediatric patients with GHD, the mean population pK estimated apparent clearance was 0.0336 L/h/kg. With a mean population pK estimated effective half-life of 28.3 hours, somatrogon will be present in the circulation for about 6 days after the last dose.

Excretion

Excretion was not evaluated in clinical studies.

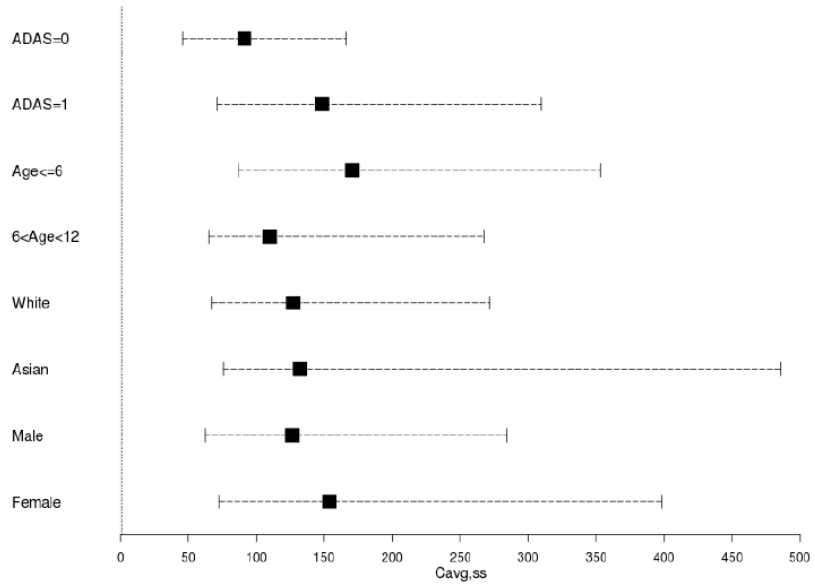
Special Populations

Age, race, gender, body weight

Based on population pK analyses, age, sex, race, and ethnicity do not have a clinically meaningful effect on the pharmacokinetics of somatrogon in paediatric patients with GHD.

The exposure of somatrogon decreases with an increase in body weight. However the somatrogon dosing regimen of 0.66 mg/kg/wk provides adequate systemic exposure over the body weight range of 10 to 54 kg evaluated in the clinical studies. The effects of individual intrinsic factors on the pharmacokinetics of somatrogon are shown in Figure 2.

Figure 2. Impact of individual intrinsic factor on somatrogon exposure



Abbreviations: ADAS=ADA status, 0=negative, 1=positive

Patients with renal impairment

NGENLA has not been studied in patients with renal impairment.

Patients with hepatic impairment

NGENLA has not been studied in patients with hepatic impairment.

5.3 Preclinical safety data

Genotoxicity

Genotoxicity studies have not been performed. As a large protein molecule, somatrogon is not expected to interact with DNA or other chromosomal material.

Carcinogenicity

Carcinogenicity studies have not been performed. Somatrogon 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 somatrogon 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

Citric acid monohydrate

Histidine

Metacresol

Poloxamer

Sodium citrate dihydrate

Sodium chloride

Water for injections

6.2 Incompatibilities

In the absence of compatibilities 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.

Chemical and physical in-use stability has been demonstrated for 28 days from the date of first use of the pre-filled pen, when the pre-filled pen has been stored at 2°C to 8°C in between each use.

6.4 Special precautions for storage

Before first use store NGENLA at 2°C to 8°C (refrigerate, do not freeze). Store in the original carton and away from direct sunlight. Do not freeze NGENLA or expose NGENLA to heat. Do

not use NGENLA if it has been frozen. Unused pre-filled pens may be used until the expiration date printed on the carton, only if the pen has been kept in the refrigerator.

After first use of NGENLA, the pen can be stored for up to 28 days of use in a refrigerator (2°C to 8°C). Store away from direct sunlight. Always remove and safely discard the needle after each injection and store the NGENLA pre-filled pen without an injection needle attached. Always use a new needle for each injection. Replace the cap on the pre-filled pen when it is not in use. Store the pre-filled pen at 2°C to 8°C in between each use. Do not expose the NGENLA to temperatures above 32°C, or leave it at room temperature for more than two hours with each use. The pre-filled pen should not be used more than 28 days after first use and should not be used beyond the expiration date. The same pre-filled pen should not be used more than 5 times.

The NGENLA pen should be discarded if it has been more than 28 days after first use or it has been used 5 times, or if it has been exposed to temperatures above 32°C, or left out of the refrigerator for more than two hours with each use.

6.5 Nature and contents of container

Cartridge with 1.2 mL preserved solution for injection contained in a single-patient-use disposable pre-filled pen: 1s

The medicinal product, the primary container (cartridge, bilayer disc seal, plunger stopper) and the pre-filled pen are not made with natural rubber latex.

NGENLA pre-filled pen is available in the following packages:

	24 mg Pre-filled Pen	**60 mg Pre-filled Pen**
Somatrogon solution concentration	20 mg/mL	50 mg/mL
Volume	1.2 mL	1.2 mL
Colour	Lilac pen cap, injection button, and label	Blue pen cap, injection button, and label
Dose increments	0.2 mg/ 0.01 mL	0.5 mg/ 0.01 mL
Maximum single-dose	12 mg (0.6 mL)	30 mg (0.6 mL)

Sterile needles are required for administration but are not included. Consult the Instruction for Use leaflet for needles that can be used.

6.6 Special precautions for disposal

Each NGENLA pre-filled pen is for use by a single patient. A NGENLA pre-filled pen must never be shared between patients, even if the needle is changed.

Do not inject the medicine if it is cloudy or dark yellow. Do not shake, shaking can damage the medicine.

Dose Preparation

The pen may be used straight from the refrigerator. For a more comfortable injection, allow the pre-filled pen containing the sterile solution of somatrogon to reach room temperature (20°C to 25°C) for up to 30 minutes. Inspect the solution in the pen for flakes, particles and colouration. Do not shake. If flakes, particulates or discolouration are observed, do not use the pen.

Administration

Prepare the designated injection site as instructed in the Instructions for Use leaflet. It is recommended to rotate the injection site at each administration. Rotate the site of injection weekly. Always use a new sterile needle for each injection. If there is medicine left in the pen after the injection has been administered, return the pen to the refrigerator for storage (see section 6.4).

Disposal

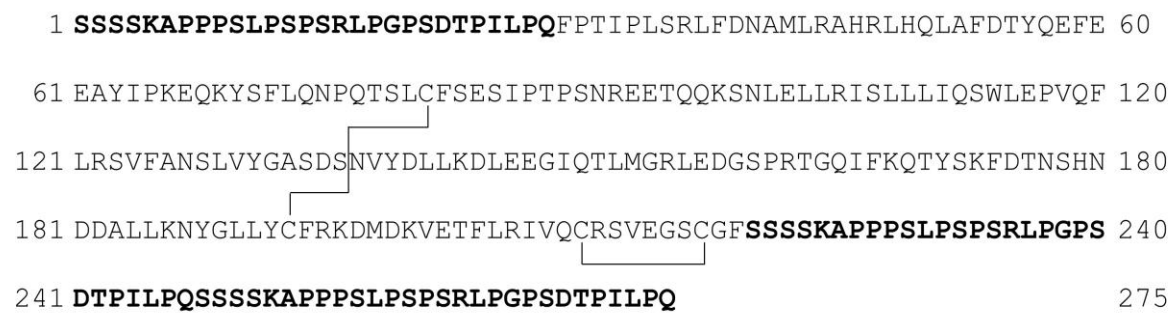
Any unused medicine or waste material should be disposed of in accordance with local requirements. If your NGENLA pen is empty, or it has been more than 28 days after first use, or it has been used 5 times, or if it has been exposed to temperatures above 32°C, or left out of the refrigerator for more than two hours with each use, throw it away even if it contains unused medicine.

6.7 Physicochemical properties

Chemical Structure

Somatrogon is a glycoprotein produced in Chinese Hamster Ovary (CHO) cells by recombinant DNA technology. It is comprised of the amino acid sequence of human growth hormone (hGH) with one copy of the C-terminal peptide (CTP) from the beta chain of human chorionic gonadotropin (hCG) at the N-terminus and two copies of CTP (in tandem) at the C-terminus. Each CTP includes multiple O-linked glycosylation sites. The glycosylation and CTP domains account for the half-life of somatrogon which allows for weekly dosing. The O-glycan occupancy ranges from 9 to 20 moieties per intact somatrogon molecule. The predominant somatrogon glycoforms include the molecule with 15 monosialylated, core-1 O-glycans or 16 monosialylated, core-1 O-glycans. Additionally, each CTP region contains hydroxyproline residues, which range from 0-5 hydroxy additions per intact somatrogon molecule. The complete, confirmed amino acid sequence of somatrogon is shown in Figure 3.

Figure 3. Somatrogon Primary Structure (Amino Acid Sequence)



Somatrogon amino acid sequence; residues are numbered sequentially starting with the N terminus. The confirmed disulfide bonds are illustrated with connecting lines. The functional, intact molecule is composed of recombinant hGH and one copy of CTP from the beta chain of hCG at the N-terminus (bold amino acids [1-28]) and two copies of CTP (in tandem) at the C-terminus (bold amino acids [220-247], and [248-275]).

CAS Number

1663481-09-1

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 - Prescription Only Medicine.

8. SPONSOR

Pfizer Australia Pty Ltd
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Toll Free Number: 1800 675 229
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9. DATE OF FIRST APPROVAL

30 November 2021

10. DATE OF REVISION

19 January 2026

® Registered trademark

Summary Table of Changes

Section Changed	Summary of new information
4.2	Include reason for rotating injection site weekly.
4.4	Update to existing warning for 'Epiphyseal disorders'
4.5	Addition of content related to oral estrogen and dosing.
4.8	Addition of ADR lipoatrophy as ADR identified post-marketing. Addition of ADR 'Epiphysiolysis (including slipped capital femoral epiphysis)' with frequency not known.
8	Updated Sponsor website address.