SUMMARY OF PRODUCT CHARACTERISTICS

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

1 NAME OF THE MEDICINAL PRODUCT

Ngenla 60 mg solution for injection in pre-filled pen

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One mL of solution contains 50 mg of somatrogon.

Each pre-filled pen contains 60 mg somatrogon in 1.2 mL solution.

Each pre-filled pen delivers doses from 0.5 mg to 30 mg in a single injection in 0.5 mg increments.

*Produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

The solution is a clear and colourless to slightly light yellow solution with a pH of 6.6.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Ngenla is indicated for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone.

4.2 Posology and method of administration

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

Posology

The recommended dose is 0.66 mg/kg body weight administered once weekly by subcutaneous injection.

Each pre-filled pen is capable of setting and delivering the dose prescribed by the physician. Dose may be rounded up or down based on the physician's expert knowledge of the individual patient needs. When doses higher than 30 mg are needed (i.e. bodyweight > 45 kg), two injections have to be administered.

Starting dose for patients switching from daily growth hormone medicinal products
For patients switching from daily growth hormone medicinal products, the weekly therapy with somatrogon may be initiated at a dose of 0.66 mg/kg/week on the day following their last daily injection.

Dose titration
Somatrogon dose may be adjusted as necessary, based on growth velocity, adverse reactions, body weight and serum insulin-like growth factor 1 (IGF-1) concentrations.

When monitoring for IGF-1, samples should always be drawn 4 days after the prior dose. Dose adjustments should be targeted to achieve average IGF-1 standard deviation score (SDS) levels in the normal range, i.e. between -2 and +2 (preferably close to 0 SDS).

In patients whose serum IGF-1 concentrations exceed the mean reference value for their age and sex by more than 2 SDS, the dose of somatrogon should be reduced by 15%. More than one dose reduction may be required in some patients.

Treatment evaluation and discontinuation
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 levels) and pubertal status. Routine monitoring of serum IGF-1 SDS levels throughout the course of treatment is recommended. More frequent evaluations should be considered during puberty.

Treatment should be discontinued when there is evidence of closure of the epiphyseal growth plates (see section 4.3). Treatment should also be discontinued in patients having achieved final height or near final height, i.e. an annualised height velocity < 2 cm/year or a bone age > 14 years in girls or > 16 years in boys.

Missed dose
Patients should maintain their regular dosing day. If a dose is missed, somatrogon should be administered as soon as possible within 3 days after the missed dose, and then the usual once weekly dosing schedule should be resumed. If more than 3 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 administration can be changed if necessary as long as the time between two doses is at least 3 days. After selecting a new dosing day, the once weekly dosing should be continued.

Special populations

Elderly
The safety and efficacy of somatrogon in patients over the age of 65 years have not been established. No data are available.

Renal impairment
Somatrogon has not been studied in patients with renal impairment. No dose recommendation can be made.

Hepatic impairment
Somatrogon has not been studied in patients with hepatic impairment. No dose recommendation can be made.

Paediatric population
The safety and efficacy of somatrogon in neonates, infants and children less than 3 years of age have not yet been established. No data are available.

Method of administration

Somatrogon is administered by subcutaneous injection.

Somatrogon is to be injected in the abdomen, thighs, buttocks or upper arms. The site of injection should be rotated at each administration to prevent lipoatrophy (see section 4.8). Injections to the upper arms and buttocks should be given by the caregiver.

The patient and caregiver should receive training to ensure understanding of the administration procedure to support self-administration.

If more than one injection is required to deliver a complete dose, each injection should be administered at a different injection site to prevent lipoatrophy.

Somatrogon is to be administered once weekly, on the same day each week, at any time of the day.

Ngenla 24 mg solution for injection in pre-filled pen
The pre-filled pen delivers doses from 0.2 mg to 12 mg of somatrogon in increments of 0.2 mg (0.01 mL).

Ngenla 60 mg solution for injection in pre-filled pen
The pre-filled pen delivers doses from 0.5 mg to 30 mg of somatrogon in increments of 0.5 mg (0.01 mL).

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

4.3 Contraindications

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

Somatrogon must not be used when there is any evidence of activity of a tumour based on experience with daily growth hormone medicinal products. Intracranial tumours must be inactive and antitumour therapy must be completed prior to starting growth hormone (GH) therapy. Treatment should be discontinued if there is evidence of tumour growth (see section 4.4).

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

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 somatrogon (regarding patients undergoing substitution therapy, see section 4.4).

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.

Hypersensitivity

Serious systemic hypersensitivity reactions (e.g. anaphylaxis, angioedema) have been reported with daily growth hormone medicinal products. If a serious hypersensitivity reaction occurs, use of somatrogon should be immediately discontinued; patients should be treated promptly per standard of care and monitored until signs and symptoms resolve (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 somatrogon treatment (see section 4.5). Patients should be monitored for reduced serum cortisol levels and/or need for glucocorticoid dose increases in those with known hypoadrenalism (see section 4.5).

Thyroid function impairment

Growth hormone increases the extrathyroidal conversion of T4 to T3 and may unmask incipient hypothyroidism. Patients with pre-existing hypothyroidism should be treated accordingly prior to the initiation of treatment with somatrogon as indicated based on clinical evaluation. 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 and 4.8).

Prader-Willi syndrome

Somatrogon has not been studied in patients with Prader-Willi syndrome. Somatrogon 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 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.

Glucose metabolism impairment

Treatment with growth hormone medicinal products may reduce insulin sensitivity and induce hyperglycaemia. Additional monitoring should be considered in patients treated with somatrogon who have glucose intolerance, or additional risk factors for diabetes. In patients treated with somatrogon who have diabetes mellitus, hypoglycaemic medicinal products might require adjustment (see section 4.5).

Neoplasm

In patients with previous malignant disease, special attention should be given to signs and symptoms of relapse. Patients with pre-existing tumours or growth hormone deficiency 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 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, ataxia, visual changes, headache, nausea and/or vomiting has been reported in a small number of patients treated with growth hormone medicinal products. Funduscopic examination is recommended at the initiation of treatment and as clinically warranted. In patients with clinical or funduscopic evidence of IH, somatrogon should be temporarily discontinued. At present there is insufficient evidence to give specific advice on the continuation of growth hormone treatment in patients with resolved IH. If treatment with somatrogon is restarted, monitoring for signs and symptoms of IH is necessary.

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%. Based on this information, these types of patients should not be treated with somatrogon. As there is no information available on the safety of growth hormone substitution therapy in acutely critically ill patients, the benefits of continued somatrogon 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 somatrogon must be weighed against the potential risk involved.

Pancreatitis

Although rare in patients treated with growth hormone medicinal products, pancreatitis should be considered in somatrogon-treated patients who develop severe abdominal pain during treatment.

Scoliosis

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

Epiphyseal disorders

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.

Oral oestrogen therapy

Oral oestrogen influences the IGF-1 response to growth hormone. If a female patient taking somatrogon 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 (see section 4.2). In female patients on oral oestrogen-containing therapy, a higher dose of somatrogon may be required to achieve the treatment goal (see section 4.5).

Excipients

Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per dose, that is to say essentially ‘sodium free.’

Metacresol
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 medicinal products without metacresol should be used.

4.5 Interaction with other medicinal products and other forms of interaction

No interactions studies in paediatrics have been performed.

Glucocorticoids

Concomitant treatment with glucocorticoids may inhibit the growth-promoting effects of somatrogon. Patients with adrenocorticotropic hormone (ACTH) deficiency should have their glucocorticoid replacement therapy carefully adjusted to avoid any inhibitory effect on growth. Therefore, 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).

Insulin and hypoglycaemic medicinal products

In patients with diabetes mellitus requiring medicinal product therapy, the dose of insulin and/or oral/injectable hypoglycaemic medicinal products may require adjustment when somatrogon therapy is initiated (see section 4.4).

Thyroid medicinal products

Treatment with daily growth hormone may unmask previously undiagnosed or subclinical central hypothyroidism. Thyroxine replacement therapy may need to be initiated or adjusted (see section 4.4).

Oral oestrogen therapy

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

Cytochrome P450 metabolised products

Drug-drug interaction studies have not been performed with somatrogon. Somatrogon has been shown to induce CYP3A4 mRNA expression *in vitro*. The clinical significance of this is unknown. Studies with other human growth hormone (hGH) receptor agonists performed in growth hormone deficient children and adults, and healthy elderly men, suggest that administration may increase the clearance of compounds known to be metabolised by cytochrome P450 isoenzymes, especially CYP3A. The clearance of compounds metabolised by CYP3A4 (e.g. sex steroids, corticosteroids, anticonvulsants and ciclosporin) may be increased and could result in lower exposure of these compounds.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of somatrogon in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Ngenla is not recommended during pregnancy and in women of childbearing potential not using contraception.

Breast-feeding

It is unknown whether somatrogon/metabolites are excreted in human milk. A risk to the newborns/infants cannot be excluded. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from somatrogon therapy taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Fertility

The risk of infertility in females or males of reproductive potential has not been studied in humans. In a rat study, the fertility in males and females was not affected (see section 5.3).

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile

The commonly reported adverse reactions after treatment with somatrogon are injection site reactions (ISRs) (25.1%), headache (10.7%) and pyrexia (10.2%).

Tabulated list of adverse reactions

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 patients with GHD (see section 5.1). The data reflect exposure of 265 patients to somatrogon administered once weekly (0.66 mg/kg/week).

Table 1 presents the adverse reactions for somatrogon within the system organ class (SOC). The adverse reactions listed in the table below are presented by SOC and

frequency categories, defined 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) or frequency not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

Table 1. Adverse reactions

System organ class	Very common	Common	Uncommon	Rare	Very rare	Frequency not known
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				
General disorders and administration site conditions	Injection site reactions[a] Pyrexia					

* See section 4.2

a Injection site reactions include the following: injection site pain, erythema, pruritus, swelling, induration, bruising, haemorrhage, warmth, hypertrophy, inflammation, deformation, urticaria.

Description of selected adverse reactions

Injection site reaction

In the phase 3 clinical study, reporting of ISRs was actively solicited during the course of the study. In the majority of cases, local ISRs tended to be transient, occurred mainly in the first 6 months of treatment and were mild in severity; ISRs had a mean onset on the day of the injection and a mean duration of < 1 day. Among them, injection site pain, erythema, pruritus, swelling, induration, bruising, hypertrophy, inflammation and warmth were reported in 43.1% of patients treated with somatrogon compared to 25.2% of patients administered daily injections of somatropin.

In the long-term OLE of the clinical phase 3 study, local ISRs were similar in nature and severity, and reported early in subjects switching from somatropin to somatrogon treatment. ISRs were reported in 18.3% of patients originally treated with somatrogon in the main study and continuing treatment in the OLE portion of the study, and likewise, 37% were reported among patients originally treated with somatropin that were switched in the OLE portion of the study to treatment with somatrogon.

Immunogenicity
In the pivotal safety and efficacy study, among 109 subjects treated with somatrogon, 84 (77.1%) tested positive for anti-drug antibodies (ADAs). There were no clinical or safety effects observed with the formation of antibodies.

Other adverse drug reactions for somatropin may be considered class effects, such as:
- Neoplasms benign and malignant: (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, connective tissue, and bone disorders: myalgia.
- Reproductive system and breast disorders: gynaecomastia.
- Skin and subcutaneous tissue disorders: skin rash, urticaria and pruritus.
- General disorders and administration site conditions: peripheral oedema, facial oedema.
- Gastrointestinal disorders: pancreatitis (see section 4.4).

Metacresol
This medicinal product contains metacresol which may contribute to painful injections (see section 4.4).

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Single doses of somatrogon higher than 0.66 mg/kg/week have not been studied.

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

Treatment of overdose with somatrogon should consist of general supportive measures.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatropin and somatropin agonists, ATC code: H01AC08.

Mechanism of action

Somatrogon is a glycoprotein comprised of the amino acid sequence of 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.

Pharmacodynamic effects

In clinical studies, somatrogon increases IGF-1. Pharmacodynamic evaluations performed approximately 96 hours after dose administration in order to assess the mean IGF-1 standard deviation score (SDS) over the dosing interval showed IGF-1 values normalised in treated subjects at one month of treatment.

Water and mineral metabolism
Somatrogon induces the retention of phosphorus.

Clinical efficacy and safety

The safety and efficacy of somatrogon for the treatment of children and adolescents from 3 years of age 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 somatrogon to somatropin administered once daily followed by a single arm OLE period during which all patients were administered somatrogon 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.

The pivotal phase 3 multi-centre non-inferiority study evaluated the safety and efficacy of 0.66 mg/kg/week dose of somatrogon compared to 0.034 mg/kg/day of somatropin in 224 pre-pubertal paediatric patients with GHD. 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 GH levels of ≤ 7 ng/mL, and the mean height was below -2 SDS.

Once weekly somatrogon was non-inferior based on HV at 12 months compared to somatropin administered once daily (see Table 2). Once weekly somatrogon 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 somatrogon compared to somatropin in paediatric patients with GHD at month 12

Treatment parameter	Treatment group		LSM difference (95% CI)
	Somatrogon (N=109)	Somatropin (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.

In the open-label extension of the pivotal phase 3 study, 91 patients received 0.66 mg/kg/week of somatrogon for at least 2 years and provided height data. A progressive gain in height SDS from baseline was observed at 2 years [cumulative change in height SDS mean (SD) = 1.38 (0.78), median = 1.19 (range: 0.2, 4.9)].

In the phase 2, multi-centre safety and dose-finding study, 31 patients received up to 0.66 mg/kg/week of somatrogon for up to 7.7 years. At the last assessment, height SDS [mean (SD)] was -0.39 (0.95) and cumulative change in height SDS [mean (SD)] from baseline was 3.37 (1.27).

Treatment burden
In a phase 3 randomised, open-label, crossover study in 87 paediatric patients with GHD, the impact of somatrogon administered once weekly (0.66 mg/kg/week) on treatment burden was compared to daily somatropin. Somatrogon administered once weekly demonstrated significant improvement (reduction) in treatment burden for the patient, improved (reduced) treatment burden for the caregiver, greater patient convenience, greater intent to comply and greater patient preference.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with Ngenla in all subsets of the paediatric population for the long-term treatment of paediatric patients with growth disturbance due to insufficient secretion of growth hormone (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

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

Absorption

Following subcutaneous 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/week, 0.48 mg/kg/week and 0.66 mg/kg/week. There is no accumulation of somatrogon after once weekly administration. In paediatric patients with GHD, the population PK estimated steady-state peak concentrations following 0.66 mg/kg/week was 636 ng/mL. Patients who tested positive for ADA had an approximately 45% higher steady-state average concentration.

Distribution

In paediatric patients with GHD, the population PK estimated apparent central volume of distribution was 0.728 L/kg and apparent peripheral volume of distribution was 0.165 L/kg.

Biotransformation

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 population PK estimated apparent clearance was 0.0317 L/h/kg. Patients who tested positive for ADA had an approximately 25.8% decrease in apparent clearance. With a population PK estimated effective half-life of 28.2 hours, somatrogon will be present in the circulation for about 6 days after the last dose.

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 dose of 0.66 mg/kg/week provides adequate systemic

exposure to safely achieve efficacy over the weight range evaluated in the clinical studies.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology and repeat-dose toxicity.

Reproductive and developmental toxicity studies were conducted in rats with somatrogon administered subcutaneously at doses up to 30 mg/kg (associated with exposures levels approximately 14 times the maximum recommended human dose based on AUC).

Somatrogon induced an increase in oestrous cycle length, copulatory interval, and number of corpora lutea in female rats but no effects on mating indices, fertility or early embryonic development.

No effects of somatrogon were observed on embryo-foetal development.

In a pre-postnatal development study somatrogon elicited an increase in first generation (F1) mean body weights (both sexes) as well as an increase in the mean copulatory interval in F1 females at the highest dose (30 mg/kg), which was consistent with a longer oestrous cycle length; however, there were no associated effects on mating indices.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trisodium citrate dihydrate

Citric acid monohydrate

L-Histidine

Sodium chloride

m-Cresol

Poloxamer 188

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

Before first use

3 years at 2 °C to 8 °C.

Prior to the first use store Ngenla in a refrigerator. The unopened pre-filled pen may temporarily be held for up to 4 hours at temperatures up to 32 °C.

After first use

28 days.

Store in a refrigerator (2 °C – 8 °C).

Do not freeze.

Keep Ngenla with the pen cap attached in order to protect from light.

Ngenla may be held at room temperature (up to 32 °C) for up to 4 hours with each injection for a maximum of 5 times. Return Ngenla to the refrigerator again after each use. Do not expose Ngenla to temperatures above 32 °C or leave at room temperature for more than 4 hours with each use. The Ngenla pen should be discarded if it has been used 5 times, if it has been exposed to temperatures higher than 32 °C or if it has been removed from the refrigerator for more than 4 hours with each use.

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

Store in a refrigerator (2 °C to 8 °C). Do not freeze. Keep Ngenla in the outer carton in order to protect from light.

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

6.5 Nature and contents of container

This multi-dose disposable pre-filled pen, which consists of a cartridge (Type I clear glass) permanently sealed in a plastic pen, contains 1.2 mL of somatrogon. The cartridge is closed at the bottom with a rubber stopper (Type I rubber closures) shaped as a plunger and at the top with a rubber stopper (Type I rubber closures) shaped as a disc and sealed with an aluminium cap. The pen cap, dose button and label on the pen are coloured blue.

Pack size of 1 pre-filled pen.

6.6 Special precautions for disposal

The solution should appear clear and colourless to slightly light yellow solution and be free of particles. Do not inject the medicinal product if it is cloudy, dark yellow, or contains particulate matter. Do not shake, shaking can damage the medicinal product.

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.

The pre-filled pen should only be used up to 28 days after first use and before the expiry date.

Do not freeze the medicinal product. Do not expose to heat (above 32 °C). Do not use Ngenla if it has been frozen or exposed to heat, discard.

Dose preparation

The pen may be used straight from the refrigerator. For a more comfortable injection, the pre-filled pen containing the sterile solution of somatrogon may be allowed to reach room temperature up to 32 °C for up to 30 minutes. The solution in the pen should be inspected for flakes, particles and colouration. The pen should not be shaken. If flakes, particles or discolouration are observed, the pen should not be used.

Administration

The designated injection site should be prepared as instructed in the Instructions for Use. It is recommended to rotate the injection site at each administration. When in use, always replace the pen cap on the pre-filled pen after each injection. Return Ngenla to the refrigerator again after each use. A new 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 (i.e. liquid does not appear at the needle tip), patients must follow the instructions described in the Instructions for Use accompanying the package leaflet.

Sterile needles are required for administration but are not included. Ngenla can be administered with a needle from 4 mm to 8 mm and between 30G and 32G.

Instructions for the preparation and administration of the product are given in the package leaflet and Instructions For Use.

Disposal

Any unused medicinal product or waste material should be disposed of in accordance with local requirements. If the pre-filled pen is empty, has been exposed to temperatures higher than 32 °C, has been removed from the refrigerator for more than 4 hours with each use, has been used 5 times, or it has been more than 28 days after first use, it should be disposed of even if it contains unused medicinal product. A small amount of the sterile somatrogon solution may remain in the pen after all doses have been correctly given. Patients should be instructed not to use the remaining solution, but to properly discard the pen.

7 MARKETING AUTHORISATION HOLDER

Pfizer Limited,

Ramsgate Road,

Sandwich,

Kent CT13 9NJ,

United Kingdom.

8 MARKETING AUTHORISATION NUMBER(S)

PLGB 00057/1713

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

25/03/2022

10 DATE OF REVISION OF THE TEXT

06/01/2026