Date: 17 November 2022
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

Ngenla

International non-proprietary name: somatrogon
Pharmaceutical form: solution for injection in a pre-filled pen
Dosage strength(s): 24 mg/1.2 mL and 60 mg/1.2 mL
Route(s) of administration: subcutaneous
Marketing Authorisation Holder: Pfizer AG
Marketing Authorisation No.: 68265
Decision and Decision date: approved on 9 September 2022

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Table of contents

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, distribution, metabolism, elimination
AE	Adverse event
ALT	Alanine aminotransferase
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
$AUC_{0\text{-}24h}$	Area under the plasma concentration-time curve for the 24-hour dosing interval
$C_{avg,ss}$	Average concentration of the drug in the steady state
CHO	Chinese hamster ovary
CI	Confidence interval
CL/F	Apparent clearance
C_{max}	Maximum observed plasma/serum concentration of drug
CTP	C-terminal peptide
CYP	Cytochrome P450
DDI	Drug-drug interaction
EMA	European Medicines Agency
ERA	Environmental Risk Assessment
FDA	Food and Drug Administration (USA)
GH	Growth hormone
GHD	Growth hormone deficiency
GHR	Growth hormone receptor
GLP	Good Laboratory Practice
hCG	Human chorionic gonadotropin
hGH	Human growth hormone
hGHR	Human growth hormone receptor
HPLC	High performance liquid chromatography
HT-SDS	Height standard deviation score
HV	Height velocity/Growth velocity
IC/EC_{50}	Half-maximal inhibitory/effective concentration
ICH	International Council for Harmonisation
Ig	Immunoglobulin
IGF-1	Insulin-like growth factor 1
IGFBP-3	Insulin-like growth factor-binding protein 3
INN	International nonproprietary name
ITT	Intention-to-treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
Min	Minimum
MRHD	Maximum recommended human dose
N/A	Not applicable
NO(A)EL	No observed (adverse) effect level
PBPK	Physiology based pharmacokinetics
PD	Pharmacodynamics
pGHD	Paediatric growth hormone deficiency
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population pharmacokinetics
PSP	Pediatric Study Plan (US-FDA)

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Q/F	Apparent inter-compartmental clearance
QoL	Quality of life
rhGH	Recombinant human growth hormone
RMP	Risk Management Plan
SAE	Serious adverse event
SC	Subcutaneous
SDS	Standard deviation score
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TPA	Federal Act of 15 December 2000 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 on Therapeutic Products (SR 812.212.21)
Vc/F	Apparent central volume of distribution
Vp/F	Apparent peripheral volume of distribution

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance somatrogon of the medicinal product mentioned above.

Orphan drug status
The applicant requested Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA.
The Orphan Drug Status was granted on 4 February 2022.

2.2 Indication and Dosage

2.2.1 Requested Indication

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

2.2.2 Approved Indication

Growth disorders in children and adolescents aged 3 years and above in cases of proven growth hormone deficiency.

2.2.3 Requested Dosage

Summary of the requested standard dosage:
The recommended dose is 0.66 mg/kg body weight administered once weekly by subcutaneous (SC) injection.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	2 March 2021
Formal control completed	19 March 2021
List of Questions (LoQ)	16 August 2021
Answers to LoQ	11 November 2021
Preliminary decision	24 January 2022
Answers to Preliminary decision	18 March 2022
Labelling corrections	9 June 2022
Answers to Labelling corrections	7 July 2022
Final Decision	9 September 2022
Decision	approval

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

3 Medical Context

Definition of abbreviations:

GH	= growth hormone
hGH	= human growth hormone
GHD	= growth hormone deficiency
HT-SDS	= height standard deviation score (refers to the deviation in height from the expected age-matched height)
HV	= growth velocity
IGF-1	= insulin-like growth factor 1
IGFBP-3	= insulin-like growth factor-binding protein 3
pGHD	= paediatric growth hormone deficiency
rhGH	= recombinant human growth hormone

Human growth hormone (hGH) is a 191-amino-acid pituitary protein that stimulates production and release of IGF-1 into the systemic circulation and local milieu. hGH and IGF-1 are instrumental in the promotion of linear growth in children and in the control of metabolism and body composition in children and adults. These factors are regulated through complex feedback mechanisms involving hGH, IGFBP-3 and their complexes.

In children, GHD is primarily manifested as abnormal linear growth. GHD also impacts bone, lipid, protein, and glucose metabolism in children, with findings that include decreased bone mineral density, decreased lean body mass, and increased fat mass. In adults, GHD results in decreased lean body mass, increased fat mass, weakness, reduction in exercise capacity, muscle mass/strength, cardiac performance, and bone density, and in neuropsychological disturbances.

Childhood GHD can be congenital, acquired, or idiopathic. Underlying causes for congenital malformation include pituitary dysfunction due to abnormal neurodevelopment in utero of certain brain regions and genetic abnormalities. Aetiology for acquired GHD includes brain tumours in the hypothalamic region, traumatic brain injury, infiltrative disease, cranial irradiation and surgical intervention. The idiopathic origin of GHD is poorly understood but appears to be multifactorial.

Only a small amount of data is available on the incidence and prevalence of GHD. Establishing its frequency is complicated by the fact that the diagnostic criteria are not uniform and that differing methods exist for determining GH. Moreover, the figures stated in the literature depend on whether they refer to childhood GH deficiency exclusively or the prevalence of patients with GH deficiency across all age groups. The prevalence of childhood GH deficiency is thought to be around 1:5,000.

In children, the growth attenuation and short stature resulting from GHD begins in early childhood and continues through attainment of final adult height, which can lead to a reduced quality of life (QoL). This is confounded by delayed puberty and deficits in facial, dental and (in males) genital development. Approximately 5% of children with GHD have episodes of hypoglycaemia, particularly in infancy. pGHD is also associated with a metabolic profile similar to that of metabolic syndrome including dyslipidaemia, insulin resistance, haemostatic alterations, oxidative stress, and chronic inflammation, all of which represent cardiovascular risk factors that, if left untreated, persist into adulthood.

From the patient/caregiver perspective, the burden of GHD on children goes well beyond short stature and its physiological effects. The inability to achieve normal growth and attainment of age- and gender-appropriate height can lead to early onset of psychosocial problems related to short stature, including behavioural and cognitive disturbances. Parents have rated physical health, as well as psychosocial factors, as having a large impact on decisions to seek medical care for their child's short stature.

Growth hormone preparations have been available for the treatment of growth hormone deficiency for more than 50 years. Originally, GH obtained from cadavers was used for this purpose, but following the discovery of Creutzfeldt-Jacob disease, the corresponding preparations were withdrawn from the market. Recombinant GH preparations have since been used for over 30 years to treat tens of thousands of patients (primarily children), and these have proved to be effective and safe.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Treatment of childhood GH deficiency is based on international guidelines (see, in particular, A. Grimberg et al.: Guidelines for growth hormone and insulin-like growth factor-1 treatment in children and adolescents: growth hormone deficiency, idiopathic short stature, and primary insulin-like growth factor-1 deficiency; Horm. Res. Paediatr 2016; 86: 361-397).

rhGH treatment improves growth outcomes, as demonstrated by increased height velocity and normalisation of adult height. rhGH treatment also has positive effects on the metabolic consequences of GHD, including improved body composition (fat/lean mass) and reduction in lipids (total cholesterol, LDL-cholesterol, and triglycerides), and improvements in QoL/psychosocial aspects of pGHD.

The current standard of care for paediatric GHD is daily subcutaneous (SC) injection of rhGH. Treatment response is assessed by measurements of height and growth velocity and is generally continued until final height, epiphyseal closure, or both, have been recorded. Early intervention produces the best outcome as growth potential decreases overtime.

The formulations available to date require a daily subcutaneous injection, and injection pens are used nowadays to simplify administration. Nevertheless, non-compliance remains a major problem. Its frequency described in the literature differs considerably between various studies and depends to some extent on the definition of non-compliance. Furthermore, direct measurement is difficult, and the way of determining compliance differs between various studies. Overall, compliance across several studies was only between 34% and 64%, and it usually declined with increasing treatment duration. Some of these studies have shown a correlation between compliance and growth velocity.

One approach to improving adherence to treatment has been the development of long-acting GH formulations that would require less frequent injections than the current daily injection standard of care. The aim of such long-acting GH formulations is to increase long-term therapeutic success by improving compliance compared to formulations that have to be administered once daily, and to reduce the stress on the patient and his/her family arising from the need for daily injections - while having no relevant influence on efficacy and safety. Several different technological approaches have been evaluated, including sustained-release preparations that utilise microsphere encapsulation (Nutropin Depot, LB03002), pegylated formulations (Jintrolong), non-covalent albumin binding (somapacitan), prodrugs (TransCon), and Fc GH fusion formulations (GX-H9, albutropin). One potential drawback is the IGF-1 profile, which differs from that associated with daily administration, although the extent to which this differing profile may influence efficacy and safety of such formulations in the long term is not known. Last but not least, a relevant factor here is the timing of IGF-1 determination for treatment monitoring.

In Switzerland, no long-acting GH preparation has been authorised to date.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

4 Quality Aspects

4.1 Drug Substance

Somatrogon is a recombinant glycoprotein 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.
Somatrogon is expressed in a Chinese hamster ovary (CHO) cell line, and is manufactured in a production bioreactor. The cell culture fluid is harvested and the drug substance is purified by several chromatographic and filtration steps, including virus inactivation and virus removal steps.
The cell culture and purification process was validated on three batches, demonstrating a consistent manufacturing process that effectively reduces process-related impurities. The impurity clearance validation studies are supported by the impurity levels measured in the drug substance and/or spiking studies. The characterisation of the physicochemical and biological properties of the drug substance and its impurities was performed using state-of-the-art methods.
The specifications for release include relevant tests and limits. Specifications are based on clinical data, batch analysis (release and stability data) and are in conformance with current compendial or regulatory guidelines.
Batch analysis data from development, clinical and process validation batches were provided. All batch release data comply with the drug substance specifications, which were valid at the time of batch release. All specific analytical methods are described and are fully validated.
The drug substance is stored frozen. No changes were observed within the proposed storage conditions. A shelf-life of 36 months has been accepted.

4.2 Drug Product

The finished product Ngenla is available as 24 mg and 60 mg product, which is supplied as sterile liquid in a pre-filled pen. Each pen presentation contains multiple doses of somatrogon drug product solution. The dose is variable and set within the range of 10 to 600 µL. All excipients used comply with the European Pharmacopoeia.
The finished product manufacturing process consists of compounding the drug substance with formulation buffers, sterile filtration, aseptic filling, and inspection steps to obtain drug product solution in a cartridge, followed by assembly of the prefilled pen, labelling and in-process checks.
Process validation studies for the drug product solution were executed at commercial scale using three validation batches of each presentation. Process validation studies for assembly and labelling the prefilled pen were accomplished using three validation batches.
The release and stability specifications include relevant tests and limits. All specific methods are validated in accordance with ICH guidelines.
Batch analysis data from development, clinical and process validation batches were provided. All batch release data comply with the drug product specifications, which were valid at the time of batch release.
The drug product is stored in a 3 mL Type I clear glass cartridge within the pre-filled pen at 2-8°C. Each cartridge is closed with an elastomeric plunger stopper. All components are Ph.Eur. and USP compliant. A shelf-life of 36 months has been accepted.

4.3 Quality Conclusions

The manufacturing processes (drug substance and drug product) are well described and demonstrate a consistent quality of drug substance and drug product. The shelf-life of the drug substance and drug product is supported by data from recommended storage conditions, as well as accelerated and stress studies. Safety concerns with regard to viral and non-viral contaminants were satisfactorily addressed. The risk of adventitious agents is minimised.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

5 Nonclinical Aspects

5.1 Pharmacology

Pharmacodynamics

The binding affinity of somatrogon to the human growth hormone receptor (hGHR) is more than 8-fold lower compared to recombinant GH (somatropin), which served as comparator across the nonclinical studies. The binding affinity of somatrogon to rat GHR was similar to hGHR, but the affinity to monkey GHR was two times lower. In *in vitro* assays, somatrogon was >32-fold less potent than somatropin in inducing cell proliferation, and somatrogon-mediated STAT5b phosphorylation required higher concentrations than somatropin to produce the same effect. Taken together, the results show lower *in vitro* potency of somatrogon compared to somatropin.

Insulin growth factor 1 (IGF-1) served as a marker of biological activity in studies with rats and monkeys. Hypophysectomised rats injected with a single subcutaneous dose of somatrogon showed significantly higher IGF-1 response (3.4 times at C_{max}) compared to rats dosed with the equimolar dose of somatropin. This effect can be explained by the different pharmacokinetics (PK) of somatrogon and somatropin, with somatrogon showing slower absorption (T_{max} 8 h vs. 0.5 h), significantly high exposure, and a 4.5-fold longer half-life ($T_{1/2}$), leading to the sustained activation of the receptor. In the comparative repeated-dose study in rats, somatrogon injected 4 or 7 days apart for 12 days induced a similar weight gain as daily injections of somatropin. The results indicate that, despite reduced somatrogon activity *in vitro*, pharmacological activity of somatrogon is equivalent to somatropin following less frequent injections. Somatrogon showed pharmacological activity in the healthy rats and rhesus monkeys used for the toxicology studies. In rats, a dose-dependent increase in body weight (up to 21%) was observed, which correlated with higher food consumption. IGF-1 levels were continuously increased during the whole treatment period, without a dose-response relationship. Similar results were observed in rhesus monkeys treated every 5 days with somatrogon up to 90 mg/kg for 4 weeks or up to 30 mg/kg for 26 weeks. The lack of dose-response for IGF-1 increase could be related to the physiological IGF-1 production in the animals with normal thyroid function.

Secondary pharmacodynamic studies comparing *in vitro* binding of somatrogon and somatropin to a broad selection of 70 transmembrane and soluble receptors, ion channels and monoamine transporters did not show significant affinity to any of the screened receptors, with the exception of the glutamate. There was no difference in off-target binding of somatrogon and somatropin. The activity on for the prolactin receptor was not assessed. Based on the results of toxicity studies, there are no indications that the fusion of CTP to recombinant human growth hormone (rhGH) affected the off-target binding profile of somatrogon, and no difference to somatropin was observed.

Stand-alone *in vitro* safety pharmacology studies were not conducted, which is in line with ICH S6(R1).

Based on *in vivo* toxicity studies in monkeys, there is no risk of clinically relevant effects of somatrogon on the cardiovascular or central nervous systems, or on respiratory function.

5.2 Pharmacokinetics

The applicant investigated the PK profile of somatrogon after single subcutaneous administration to rats (up to 180 mg/kg) and rhesus monkeys (up to 90 mg/kg). In both species, the exposure increased approximately dose-proportionally, and there were no apparent sex-related differences. Somatrogon exhibited a longer half-life, prolonged time to reach C_{max}, and lower clearance, compared to somatropin. Studies on distribution, metabolism, and excretion were not conducted as somatrogon is expected to be primarily degraded by proteolytic catabolism.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Toxicokinetics was investigated in the repeated-dose toxicity studies in rats and rhesus monkeys following subcutaneous administration. Due to the faster clearance and consequently shorter half-life of somatrogon in rats compared to monkeys and humans, rats were dosed twice weekly and monkeys every five to six days in the toxicity studies. C_{max} and AUC increased dose-proportionally in both species, and there were no large sex differences. In pregnant rats (administered up to 30 mg/kg), the increase in the exposure to somatrogon was approximately dose-proportional. Somatrogon was detected in pooled fetal serum on gestation day (GD) 18 at concentrations ≥ 50-fold lower compared to the maternal serum, indicating placental transfer.
ADAs against CTP (to a lesser extent) and hGH were detected at higher levels in rats than in rhesus monkeys. They were rarely neutralising and did not influence the exposure or biological activity of somatrogon. There was no difference in ADA formation between the somatropin and somatrogon groups, suggesting that the addition of three copies of CTP did not influence the immunogenicity of GH despite high sialylation.

5.3 Toxicology

The toxicity of somatrogon was evaluated in rats (4-week study) and rhesus monkeys (4-week and 26-week studies). Recovery periods of two weeks were included in the studies. Due to the high immunogenicity and possible activation of prolactin receptor by hGH in rats, juvenile rhesus monkeys (2.5-4 years old) were considered the relevant species for the safety evaluation in a chronic repeated -dose study. The age of the monkeys corresponds to puberty in children and does not cover the whole paediatric group.
The animals were treated via the subcutaneous route, identical to the intended clinical route of administration. Dosing frequency was twice weekly in rats and every five-six days in rhesus monkeys which corresponds to different PK profiles in rats and monkeys. The dosing regimen for the monkeys is closer to the one foreseen for humans. Somatropin was used as a comparator in the 26-week study in rhesus monkeys. It was administered once daily at 3.6 mg/kg, which corresponds to 30 mg/kg of somatrogon based on the percentage of hGH.
Somatrogon was well tolerated in both species after single subcutaneous injection up to 180 mg/kg (rats) and 90 mg/kg (monkeys).
In the repeated-dose studies, administration of somatrogon to rats induced effects that were considered directly or indirectly related to its pharmacological mode of action. This included a dose-dependent body weight increase (4-37%) at ≥36 mg/kg that correlated with increased food consumption and an increase in IGF-1 levels. The main target organ in rats was the mammary gland (feminisation). The changes in the mammary gland were not reversible and interpreted as an exaggerated pharmacological effect. Injection site reactions were evident in all somatrogon-treated animals. The high dose level of 180 mg/kg was considered the NOAEL associated with an exposure 150-fold the clinical exposure at the maximum recommended human dose (MRHD).
Injection site reactions were the main findings. Acute inflammation, fibroplasia, and minimal to mild necrosis/degeneration of the underlying skeletal muscle myofibres were observed. These findings were reversible and also occurred in the monkeys treated with somatropin. The NOAEL is considered the highest dose administered (90 and 30 mg/kg), corresponding to more than 65-fold the exposure at the MRHD.
No genotoxicity studies were conducted, which is in line with ICH S6(R1). Carcinogenicity studies were not conducted, which is acceptable considering the high immunogenicity in rodents and prolactin receptor binding in rodents. An adequate carcinogenicity assessment was submitted that included a weight of evidence approach based on the theoretical concerns due to intended pharmacology (literature review). In line with marketed GH products, Ngenla is contraindicated for treatment in the presence of active malignancy and any pre-existing malignancy. An association between growth hormone replacement therapy and an increased long-term risk of developing a malignancy is currently unknown.
The results of the reproductive toxicity studies do not indicate a risk of effects on fertility, pregnancy performance or embryo-foetal development at an exposure 14-fold the exposure at the MRHD. In

females, a significant increase in the number of corpora lutea was observed at 10 and 30 mg/kg, suggesting a superovulatory effect of the drug. The effect on the oestrogen cycle was considered GH specific and was also observed with the other growth hormone products. The clinical relevance is unknown.
In the pre- and postnatal development study in rats dosed up to 30 mg/kg every other day from GD 6 to lactation day 21, no adverse effects on maternal animals or F1 offspring survival and development were observed. F1 rats from the high dose group showed increased body weights and an increased mean copulatory interval (females), which was consistent with a longer oestrus cycle. The relevance of these findings for humans is considered low.
Overall, based on the results of the reproductive toxicity studies, the risk of adverse effects on fertility, pregnancy performance and offspring development at clinically relevant exposures is considered low. Nevertheless, considering differences between the pharmacological activity of hGH in rats and humans and placental or milk transfer in nonclinical species, the use of somatrogon during pregnancy should be avoided.

There is no concern with respect to excipients and impurities.

The description of the safety findings from the nonclinical studies and their evaluation in Module SII of the RMP is accepted. All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.
A significant risk for the environment by the introduction of somatrogon to the market is not expected.

5.4 Nonclinical Conclusions

Overall, the pharmacological and toxicological profiles of somatrogon were adequately characterised in the nonclinical studies. From the nonclinical standpoint, the application is approvable.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The PK of somatrogon in children (3-12 years of age at study entry but up to 15.7 years overall) was characterised in a phase 2 dose finding study and a phase 3 study and evaluated using a PopPK approach.

ADME

Absorption

Following s.c. injection of 0.66 mg/kg, maximal somatrogon serum concentrations were reached by 6-15 hours.

Distribution

The central and peripheral volumes of distribution of somatrogon were estimated at 0.812 L/kg and 0.169 L/kg, respectively.

Elimination

No studies regarding the metabolism of somatrogon have been conducted considering the biological nature of the molecule. The clearance of somatrogon was estimated at 0.0336 L/h/kg, and the effective half-life was estimated at 28 h.

PK after multiple doses and dose linearity

Somatrogon did not accumulate following administration of multiple once weekly doses. The somatrogon exposure increased proportionally with the dose across the dose range of 0.25 – 0.66 mg/kg/week.

Special Populations / Intrinsic Factors

The impact of demographic covariates on the PK of somatrogon in children was assessed as part of the PopPK analysis. The PopPK model was developed using the PK data from the phase 2 study. Although only sparse sampling was conducted on an individual level, the overall sampling scheme in the population covered the PK profile well and allowed the selection of an adequate structural model.

In the phase 3 study, PK samples were mainly trough or 4 days post-dose samples. Therefore, the structural PK parameters (incl. the weight effects) of the initial PopPK model were fixed, and only covariate effects were reassessed.

The PK of somatrogon following s.c. administration in the dose range of 0.25-0.66 mg/kg was adequately described by a two-compartment model with a delayed first order absorption and effects of body weight on the clearance and volume parameters (CL/F, Q/F, Vc/F, and Vp/F). In addition, a time-varying covariate effect of ADA status on clearance (CL/F) was taken into account.

- Positive ADA status decreased CL/F by 25.8%, resulting in the $C_{avg,ss}$ for ADA positive patients, being approximately 45% higher than for ADA negative patients.
- Body weight (range: 10-54 kg) had a significant effect on the clearance and volume parameters. In consequence, older and larger children had a higher clearance and volume of distribution than younger and smaller children: due to the difference in body weight, the $C_{avg,ss}$ for children 6 to 12 years of age was approximately 35% lower than for children 2 to 6 years of age. This effect of body weight on somatrogon exposure was adequately taken into account by the body weight–based dosing recommendation.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Other demographic covariates, such as age (range: 3-15.7 years of age), race (95% Caucasian) and gender (67% male) were not found to have additional significant effects, and no dose adjustments based on these factors are required. Potential effects of impaired hepatic or renal function were not assessed. Therefore, no dose recommendation can be given for subpopulations with impaired hepatic or renal function.

Interactions
No clinical drug-drug interaction studies have been conducted for somatrogon. The interaction potential of somatrogon is expected to be comparable to the interaction potential of recombinant growth hormone for daily administration.

Detailed information and recommendations with regard to the interaction potential are provided in the attached information for healthcare professionals; see Chapter 8 of this report.

Pharmacodynamics

Mechanism of Action and Primary Pharmacology
Somatrogon is comprised of the amino acid sequence of human growth hormone (hGH) with one copy of the C-terminal peptide (CTP) from the β chain of human chorionic gonadotropin (hCG) at the N-terminus and two copies of CTP at the C-terminus. The glycosylation and CTP domains lead to prolongation of half-life.
Somatrogon binds to the growth hormone receptor, ultimately increasing the serum concentration of insulin-like growth factor 1 (IGF-1), which contributes to the clinical efficacy.

Secondary Pharmacology (Safety)
While investigations of this aspect have not been conducted, it is assumed that the corresponding findings applicable to conventional GH also apply to somatrogon. On the one hand, this concerns the possible impact of GH preparations on blood glucose control in diabetics. On the other, conventional GH is also known to inhibit 11βHSD-1, an enzyme that catalyses the conversion of cortisone to cortisol.

6.2 Dose Finding and Dose Recommendation

The conventional GH preparation Genotropin® with daily injection was used as the active comparator in all phase II/III studies.

In a dose-finding study with n=56 treatment-naïve prepubertal patients, three different dosages of somatrogon (0.25mg/kg, 0.48mg/kg und 0.66mg/kg) were compared with conventional GH at a dosage of 0.034mg/kg. The selected dose of the comparator must be considered as relatively high, since its authorised dosage for this indication is 0.025-0.035mg/kg (i.e. at least in some cases, a lower dose would also probably be sufficient). The aim of this study was to determine the somatrogon dose that resulted in findings that most resembled those obtained with the comparator. This ultimately proved to be the dose of 0.66mg/kg, which was therefore investigated further in phase III. However, this dose was not entirely comparable with the recommended dosage of conventional GH in terms of both efficacy and safety.

6.3 Efficacy

To prove efficacy, a pivotal phase III study with n=224 prepubertal patients with GHD was submitted. This is an open-label, randomised, active-controlled, non inferiority study in which the efficacy and safety of somatrogon at a dosage of 0.66mg/kg once a week were compared with those for conventional GH (0.034mg/kg/day) over a treatment period of 12 months. Every three months, the dose was adapted to the patient's new weight.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

If the SDS (standard deviation score) for IGF-1 was >2 on two consecutive measurements, dose had to be reduced by 15%. If 4 weeks later, IGF-1 SDS was still >2, a further dose reduction of 15% was specified. If IGF-1 SDS remained >2 even thereafter, whether the patient should continue receiving treatment and the corresponding dosage was to be decided on a case-by-case basis. A similar dose reduction was also possible in the event of severe AEs.

This study has an open-label extension phase, which is currently still ongoing. Patients remain on treatment until they have reached their final height. Since only limited data are available from the extension phase, the submitted documentation focuses on the efficacy data after 12 months.

A placebo-controlled study, on the other hand, was not conducted for ethical reasons. As a result, the assay sensitivity of the pivotal study cannot be considered as proven, particularly given the lack of placebo-controlled studies also for conventional recombinant GH. Instead, the findings were compared with those from an international database (KIGS, Pfizer International Growth Database).

The study enrolled children aged between 3 and 10 for girls or between 3 and 11 for boys.

The primary endpoint was the annualised height velocity (HV) in cm/year after 12 months. Key secondary endpoints were the HV after 6 months as well as the change in height standard deviation score (HT-SDS) after 6 and 12 months. In addition, IGF-1 and IGFBP-3 levels were determined and bone maturation was monitored. A questionnaire to assess quality of life was also used (QoLISSY). Relevant endpoints in respect of safety included, in particular, IGF-1 serum levels, immunogenicity (i.e. formation of antibodies against somatrogon) and reactions at the injection site. A further focus was glucose metabolism and thyroid function.

According to the study protocol, blood samples for determining IGF-1 had to be collected 96 hours after administration of somatrogon in order to record the average concentration over the full dosage interval in the best possible way. The peak concentrations, instead, were expected after approx. 72 hours. In fact, numerous samples were collected already within the first 72 hours post injection of the test preparation. Premature determination could result in an unwarranted dose reduction.

In addition to the primary analysis of the primary endpoint, several sensitivity analyses (particularly with differing ways of dealing with missing values, even though their number in the study was unusually low) were performed, and all produced comparable findings.

The specified non-inferiority margin was a treatment difference between test preparation and active comparator of -1.8 cm/year. Although this margin cannot be regarded as sufficiently justified, this shortcoming is qualified by the fact that the data would also have met a much stricter margin.

Other covariates considered in the analysis were age, gender, geographical region and peak baseline GH level.

Demographic and baseline characteristics were balanced across both treatment groups. Average age was 7.7 years, and around 60% of patients were older than 7 years. Just under three quarters of the patients were male, while the proportion of girls in the comparator group, at 31%, was slightly higher than the 25% in the somatrogon group.

The average HT-SDS was -2.86. The average baseline GH level was 5.6 ng/ml. Almost half of the patients had a GH level between >3 and ≤7 ng/ml. Around 30% of the patients had a level of >7 ng/ml, while that in the remaining almost 20% was ≤3 ng/ml.

Non-inferiority was clearly met for the primary endpoint. Treatment difference between somatrogon and the active comparator was 0.33 cm/year, with a lower bound of the 95% confidence interval of -0.24 cm/year. However, superiority over the comparator was not demonstrated. The findings for the key secondary endpoints were consistent. Bone age during the observation period did not increase faster than chronological age, and its course over time was likewise comparable in both groups.

IGF-1 SDS reached an average of near zero in both groups after just a month. Subsequently, the average IGF-1 SDS was consistently above zero with somatrogon, whereas it remained at, or just below, zero in the comparator group. While these findings appear to be positive for efficacy, they are also associated with a (safety-related) drawback: the upper limit of the normal range of 2 SDS was exceeded more frequently during somatrogon administration compared to the comparator. After just one month, the upper limit of the range in the somatrogon group was 3.69. The long-term consequences of such exceeding of the normal range are not yet known (see also under "Safety").

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Changes in quality of life were minor overall. As expected, somatrogon emerged slightly more favourably due to the less frequent injections.

A total of n=212 patients, comprising 104 from the somatrogon group and 108 from the comparator group, have been included in the open-label extension phase, during which all patients are treated with somatrogon. In this phase, a further defined endpoint supplementing the endpoints of the pivotal study was final height, but this has been reached only by a small number of study participants to date due to the currently still short observation period. On the whole, the data available from the open-label extensions of this study and from the dose-finding study show that the efficacy of somatrogon is still maintained beyond the first year of treatment. Some of the patients have already reached puberty, and this has not been shown to have any relevant impact on the therapeutic effect.

Overall, most of the data recorded to date originates from treatment-naïve patients, whereas limited data are available on the switching of pretreated patients from conventional GH to somatrogon.

6.4 Safety

Evaluation of safety focuses on data from the pivotal study and the dose-finding study, but data were not pooled due to the differing designs of the two studies. In these studies, a total of n=269 patients were exposed to somatrogon, including 257 who received the proposed dosage. Median duration of exposure up to the data cut-off was approx. 15 months, and the data covered around 477 patient years.

The observed safety profile essentially corresponded to the one already known for GH treatment. The overall incidence of AEs did not show any relevant differences between somatrogon and the comparator. New, unexpected safety signals were not observed.

In the pivotal study, the overall incidence of AEs was 87% for somatrogon versus 84% for the comparator. The corresponding figures for seriou s adverse events (SAEs) were 2.8% vs. 1.7% (corresponding to 3 vs. 2 cases). Overall, only one patient - in the somatrogon group - withdrew from the study due to AEs (erythema and induration at the injection site).

The most frequent AEs (with each incidence for somatrogon versus the comparator stated in brackets) were injection site pain (39% vs. 25%), nasopharyngitis (23% vs. 25%), headache (17% vs. 22%), pyrexia (17% vs. 14%), cough (8% vs. 8%) and vomiting (7% vs. 8%).

All SAEs were classified as unrelated. In the comparator group, these involved one case of tonsillitis and one of urolithiasis. The three SAEs observed for somatrogon were gastroenteritis, pneumonia and chronic tonsillitis.

No fatalities were observed during the paediatric development programme.

Overall, only three relevant differences from conventional therapy were noted:

Reactions at the injection site occurred mainly during the first 6 months of treatment. Their incidence (particularly that of local pain - at 39% for somatrogon) was distinctly higher for somatrogon than for the comparator. This applied primarily to severe reactions. However, comparability of the two groups is limited by the fact that recording of such reactions differed between treatment groups as a result of the differing administration frequencies. Thus, data were recorded for each individual injection of somatrogon, but only for one in every 7 injections for the comparator.

The incidence of antidrug antibodies to somatrogon was much higher than for the comparator, with an incidence of 77% vs. 16% in the pivotal study. There was no evidence of any impact of the antibodies on efficacy or safety. The question of a possible cross-reaction of anti-somatrogon antibodies with conventional recombinant GH preparations cannot be answered on the basis of the available data.

A key difference between treatment groups was also noted for IGF-1. In the pivotal study, n=29 patients showed an IGF-1 SDS >2 at least once, including 26 receiving somatrogon (23.9%) and 3 receiving the comparator (2.6%). During treatment, with somatrogon but not with the comparator, the proportion of cases with elevated values increased over time.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

For somatrogon, IGF-1 values >2 SDS were found in n=14 cases (12.8%) on two consecutive measurements (thus meeting the criterion for a dose reduction). Overall, the IGF-1 tended to be higher for somatrogon than for the comparator.

In adults, an association is known between high IGF-1 levels and an increased risk of malignant tumours. The extent to which this also applies to a paediatric population is unknown.

Moreover, a higher incidence of elevated serum phosphate levels was observed for somatrogon than for the comparator in the pivotal study. Hyperphosphataemia is a known phenomenon in the treatment of GH deficiency. However, the imbalance between the test preparation and comparator is disturbing.

Subgroup analyses of safety data by age (>3-≤7 years vs. >7 years), gender, race, ethnicity, geographical region and baseline severity of the GH deficiency did not reveal any relevant findings. The only finding worth mentioning is the fact that injection site pain was stated more frequently for boys than for girls. This may be relevant for the assessment of the differing incidences of this AE stated for somatrogon and the comparator (see above), since the percentage of boys in the somatrogon group was higher than in the comparator group.

Overall, safety data must still be considered as limited, only allowing a restricted judgement of long-term safety, particularly as regards the possible consequences of the findings for IGF-1 described above. For short-term safety, on the other hand, the data can be deemed sufficient, despite the small sample size, owing to the similarity between somatrogon and conventional GH.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Ngenla is a recombinant GH preparation for subcutaneous use for the treatment of growth disturbances due to GH deficiency. Due to its modified molecular structure, which differs from that of the currently available preparations, it has a longer half-life and therefore only needs to be injected once weekly (instead of daily).

Benefits

The PK of somatrogon has been adequately characterised in paediatric subjects in the age range of 3-12 years of age at study entry and up to 15.7 years overall.

The submitted pivotal study has demonstrated non-inferiority of somatrogon in relation to the active comparator, a conventional GH preparation for daily administration. The somatrogon dose selected for use in this study (based on a preceding dose-finding study) was designed to be as effective as a dose of 0.034mg/kg/day of the comparator. Based on the data from this study, efficacy of Ngenla in the proposed indication for children from 3 years of age can be considered to be sufficiently demonstrated.

Uncertainties regarding benefit

- The PK of somatrogon has not been characterised in older adolescent subjects (>15.7 years of age). However, no substantial differences in the PK of somatrogon are expected in older adolescent subjects compared to the population investigated.
- Only a uniform, weight-based fixed dose was investigated, whereas the dosage recommendations for conventional GH envisage a dose range. As a result, the investigated dosing regimen fails to take account of inter-individual differences in the dosage required. The dose of the comparator selected for the dose-finding study probably resulted in the selection of a rather high dose for somatrogon.
- Since no data are available for doses higher than 0.66 mg/kg, an increase in dosage is not possible in the event of an inadequate response, and treatment may need to be switched to a conventional GH preparation.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

On the other hand, the dose reduction specified in the study protocol in the event of elevated IGF-1 levels or severe side effects should also be implemented accordingly in everyday clinical practice (see Information for healthcare professionals in the Appendix, "Dosage/administration" section).

- No comparable data exist for the parameter crucial for the patient, i.e. final height, since the comparator was administered at most for the first 12 months of the study. Overall, only limited data are available for this endpoint to date. Height velocity investigated as primary endpoint must be viewed as a surrogate parameter in this context. However, extrapolation based on height velocity undertaken by the applicant does appear to be plausible and acceptable.
- Assay sensitivity of the pivotal study cannot be considered as proven due to the lack of placebo control. In an historical comparison, findings for the comparator in this study tended to be slightly worse than in earlier published (but likewise not placebo-controlled) studies.
- As a result of the inclusion criteria for the pivotal study, around 60% of patients represented mild cases. Therefore, the extent to which findings can be applied to patients with more severe GH deficiency (i.e. lower baseline IGF-1) is not known. A striking finding was a certain imbalance in baseline severity. Thus, 44% of patients in the somatrogon group versus just 37% in the comparator group had a baseline IGF-1 <-2.
- Since somatrogon was only investigated in children aged 3 and over, approval has been restricted to this age group.

  Conversely, adequate data exist to date only for prepubertal children. However, there is no evidence from the many years of experience with conventional GH preparations to suggest that a modified response would be expected after puberty, and this experience appears to be transferrable to the long-acting preparation. Basically, HV declines with advancing age. Nevertheless, the treatment does provide a further benefit in terms of HT-SDS.
- Somatrogon was investigated exclusively in patients with "genuine" GH deficiency, but not in other forms of growth disorder for which conventional GH preparations have also been approved (e.g. Prader-Willi syndrome, children with chronic kidney disease or small for gestational age children). For such special situations, for which special precautions are required at least in some cases, somatrogon cannot be approved without submission of corresponding data. Approval has therefore been restricted to patients with confirmed GH deficiency.

Risks

The safety profile of the product essentially corresponds to what can be expected from a GH treatment. However, compared to conventional treatment, injection site reactions (most of which manifested as pain) were documented much more frequently for somatrogon.

Antibody formation was also observed more frequently for somatrogon. Neutralising antibodies were detected only in a few isolated cases.

Compared to conventional GH treatment, the upper limit of normal of 2 SDS for IGF-1 was exceeded more often with somatrogon.

Uncertainties regarding risks

ADAs cause a significantly elevated somatrogon exposure, however, based on the currently available data, the clinical relevance regarding efficacy and safety seems limited.

Variability of IGF-1 is higher for somatrogon than for conventional GH treatment, and it is not yet sufficiently known whether the repeated exceeding of the upper limit of normal may be associated with risks and, if so, what these risks might be.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

Complete IGF-1 profiles over the full dosage interval were not determined for somatrogon, and no data on peak concentrations are available from the pivotal study. Since IGF-1 was determined in this study only after 96 hours, it is also not known how often values >2 SDS can be expected.

In this context, it has not been conclusively clarified at what timepoint in the dosage interval for long-acting GH preparations the IGF-1 levels should be measured for monitoring of treatment and serve as a basis for any dosage adjustment. Nor is it clear, in particular, whether determination of peak levels or average concentrations is more productive, i.e. what role is played by short-term, repeated (poss. weekly) increases above the upper limit of normal. Based on the modelling data, collection of a blood sample on day 4 after injection of the preparation is recommended for Ngenla in order to obtain concentrations that reflect the average exposure during the dosage interval.

Overall, long-term safety data are still limited, although in the studies still ongoing, further data are continuously being generated.

Final risk-benefit profile

Overall, benefit-risk balance is positive for growth disorders with confirmed GH deficiency for children from 3 years of age until epiphyseal closure.

The same precautions as for conventional GH preparations also apply to the use of Ngenla (see Information for healthcare professionals in the Appendix).

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

8 Appendix

Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Ngenla, solution for injection in a pre-filled pen, was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals currently authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

Swissmedic • Hallerstrasse 7 • 3012 Berne • www.swissmedic.ch • Tel. +41 58 462 02 11 • Fax +41 58 462 02 12

▼ 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 new or serious adverse reactions. See the «Undesirable effects» section for advice on the reporting of adverse reactions.

Ngenla®

Composition

Active substances

Somatrogonum (produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells).

Excipients

Acidum citricum monohydricum, L-histidinum, metacresolum, natrii citras dihydricus, poloxamerum 188, natrii chloridum, aqua ad iniectabilia.

Total sodium content per ml: 4.0 mg.

Pharmaceutical form and active substance quantity per unit

Solution for injection in pre-filled pen for subcutaneous injection.

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

Solution for injection in pre-filled pen with 24 mg: Each pre-filled pen contains 24 mg somatrogon in 1.2 ml (= 20 mg/ml) solution that delivers a dose in 0.2 mg increments. Highest single dose that can be set: 12 mg (0.6 ml).

Solution for injection in pre-filled pen with 60 mg: Each pre-filled pen contains 60 mg somatrogon in 1.2 ml (= 50 mg/ml) solution that delivers a dose in 0.5 mg increments. Highest single dose that can be set: 30 mg (0.6 ml).

Indications/Uses

Growth disorders in children and adolescents aged 3 years and above in cases of proven growth hormone deficiency.

Dosage/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).

The recommended dose for both therapy-naive and pre-treated patients is 0.66 mg/kg body weight once weekly as subcutaneous injection. It is always to be administered on the same day each week.

For patients switching from a daily medicinal growth hormone product, administration of Ngenla may be initiated on the day following their last injection of the previous product.

Dose adjustment

If insulin-like growth factor 1 (IGF-1) levels are elevated or if severe adverse effects occur, the dose of Ngenla may be adjusted as follows:

If the IGF-1 standard deviation score (SDS) is >2, a new test should be made 4-6 weeks later. If the value is still >2, the dose should be reduced to 0.56 mg/kg. The next check of IGF-1 should be done 4-6 weeks after the dose reduction. If the value is still >2, the dose should be reduced to 0.48 mg/kg. If the IGF-1 SDS is then still >2, the risk-benefit ratio of continuing the therapy must be weighed individually. In particular, possible causes of the inadequate response should be clarified.

If severe adverse effects occur, dose reduction in equal dose increments is recommended.

Doses >0.66 mg/kg/week have not been studied. A dose increase beyond 0.66 mg/kg/week is therefore not recommended.

A reassessment of the benefit-risk ratio should be carried out at 6-12 months intervals (e.g. by analyzing the hormone concentrations and/or determining the pubertal status). After the onset of puberty, more frequent checks should be considered.

Duration of therapy

After closure of the epiphyseal growth plates, treatment with Ngenla should be discontinued.

IGF-1-Monitoring

When monitoring for IGF-1, samples should always be drawn 4 days after application of the prior dose. The target IGF-1 SDS should be the upper normal range not exceeding 2 SDS.

Mode of administration

Ngenla is administered once weekly at any time of the day by subcutaneous injection (see «Other Information – Instructions for handling» and package leaflet).

Each pre-filled pen can be set to deliver different dosages depending on the patient's body weight. Dose increments of 0.2 mg are possible with the 24 mg pen and 0.5 mg with the 60 mg pen. In each case, the dose closest to the calculated dose should be used.

Ngenla can be given in the abdomen, thighs, buttocks or upper arms. The site of injection should be rotated weekly.

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

The day of weekly administration can be changed if necessary as long as the time between two doses is at least 3 days (>72 hours).

For further instructions on use of the medicinal product, see section «Other Information – Instructions for handling» and Patient Information (package leaflet).

Missed application

If it is noticed within 3 days that a dose was missed, the injection should be made as soon as possible. If more than 3 days have passed since the scheduled time of application, the missed dose should be omitted and the next dose should be administered on the regularly scheduled day. In each case, therapy is then continued on the originally scheduled day of the week with the usual dosing schedule.

Special dosage instructions

Children less than 3 years of age

Safety and efficacy of somatrogon have only been studied in patients 3 years of age and older. No data are available for younger patients and use is not recommended.

Elderly patients

Ngenla is only approved for use in paediatric patients. Safety and efficacy in patients >65 years of age have not been studied.

Patients with hepatic disorders

Somatrogon has not been studied in patients with hepatic impairment. Therefore, no dose recommendation can be made.

Patients with renal disorders

Somatrogon has not been studied in patients with renal impairment specifically. Therefore, no dose recommendation can be made.

Contraindications

Presence of an active tumour and/or active intracranial lesions.

Existing tumour therapy.

Critically ill patients with complications after open-heart or abdominal surgery, polytrauma or acute respiratory insufficiency.

Bloom syndrome.

Fanconi anemia.

Known hypersensitivity to somatrogon or any of its excipients (see «Composition»).

Warnings and precautions

Therapy with Ngenla should only be initiated and monitored by doctors who have appropriate qualifications in the diagnosis and treatment of growth hormone deficiency (GHD).

After closure of the epiphyseal joints, somatrogon is no longer effective for growth promotion and should not be used any further.

The risks described below have been observed with the use of recombinant growth hormone (GH). It is to be expected that they will also apply to somatrogon in a similar way. For somatrogon itself, only limited experience is available so far.

With the use of somatrogon, higher IGF-1 concentrations were observed at the beginning of each dosing interval than with conventional GH therapy with daily administered GH preparations. In particular, the value of 2 SDS was exceeded more frequently than with conventional therapy. It is not known whether this is associated with increased long-term risks (such as tumours or type II diabetes mellitus).

Benign intracranial hypertension

Intracranial hypertension has been reported under therapy with GH. Symptoms usually occurred within the first 8 weeks after initiation of treatment and were generally reversible after discontinuation or dose reduction. In the event of severe or recurrent headaches, visual changes, nausea, and/or vomiting, a fundoscopy should be performed to exclude papilledema. In the presence of papilledema,

benign intracranial hypertension must be considered and Ngenla must be temporarily discontinued. If therapy is resumed at a later date, careful monitoring is required.

Glucose metabolism

Treatment with GH may induce a state of insulin resistance and hyperglycaemia up to manifest diabetes mellitus type II. The risk of developing diabetes during treatment is highest in those patients who already have reduced glucose tolerance and/or other risk factors for type II diabetes mellitus, such as obesity, positive family history or steroid therapy. Therefore, in patients with impaired glucose tolerance or pre-existing diabetes mellitus, therapy with somatrogon should only be carried out under strict medical supervision and laboratory tests. If necessary, the dosage of the anti-diabetic therapy has to be adjusted at the beginning of treatment with GH (see «Interactions»).

Thyroid function

Undiagnosed or untreated, respectively, hypothyroidism may prevent an optimal response to GH therapy. During somatrogon therapy, thyroid function should be monitored. Thyroid hormone may need to be administered in addition to Ngenla.

Adrenocortical insufficiency

Initiation of GH therapy may lead to inhibition of the 11β-hydroxysteroid dehydrogenase 1 (11βHSD-1) and thereby to reduced serum cortisol levels. As a result, latent secondary adrenocortical insufficiency may become manifest, which may require substitution therapy with a glucocorticoid. In addition, patients already treated with glucocorticoid replacement for previously diagnosed hypoadrenalism may require an increase in their maintenance and/or stress doses following initiation of somatrogon treatment (see «Interactions»).

Monitor patients for reduced serum cortisol levels. The need for glucocorticoid dose increases is to be considered especially in patients with known hypoadrenalism.

Skeletal changes

In patients with endocrine disorders, including those with GHD, there is an increased risk of epiphyseolysis of the head of the femur. It is not known whether the risk for such changes is increased by GH therapy. Parents and the attending physician should be vigilant for the possible occurrence of a worsening limp, of hip and knee pain and/or limitation of joint movement. An orthopedic examination may be indicated.

In phases of strong growth, scoliosis may progress in all children. Therefore, during treatment, attention should be paid to signs of scoliosis. However, so far there is no evidence that treatment with GH increases the incidence or severity of scoliosis.

Tumour risk

It is not known to what extent the higher IGF-1 levels observed under somatrogon compared to the daily use of somatropin could promote tumour development. Therefore, patients on GH therapy should always be carefully monitored for the possible development of tumours.

Patients with a history of tumour diseases (including those in whom GHD is a consequence of tumour disease) were excluded from the clinical trials. Ngenla should therefore not be used in these patients as a precaution. If treatment is to be given, the patient must be closely monitored for possible recurrences of the tumour while on somatrogon therapy.

The occurrence of leukaemia has been reported in a small number of children treated with GH. However, there is no evidence that GH therapy increases the incidence of leukaemia in patients without predisposing factors.

Patients on GH therapy should be monitored for increased size or evidence of malignant changes in pre-existing nevi, as increased growth of pre-existing nevi has been reported.

Hypersensitivity

Serious systemic hypersensitivity reactions (e.g., anaphylaxis, angioedema) have been reported with the use of other GH products. If such a reaction occurs, the use of Ngenla must be stopped immediately, appropriate treatment must be initiated and the patient must be monitored until symptoms resolve. Do not use again in patients with previous hypersensitivity to Ngenla (see «Contraindications»).

Injection site reaction

Local injection site reactions (such as pain, erythema, pruritus, swelling, induration, warmth, bruising, hypertrophy or inflammation) were observed during the main period of the pivotal study, particularly early during therapy (during the first six months). Such reactions were reported in 43% of patients treated with somatrogon compared to 25% of patients administered daily injections with somatropin. The most common symptom was local pain (in 39% of patients treated with somatrogon and 25% of patients receiving daily somatropin injections). In both treatment groups, the reactions tended to be transient.

In the long-term open-label extension of the pivotal study, similar reactions were reported. The incidence of local reactions was higher in those patients who had been treated with daily somatropin in the main period of the study and who received somatrogon for the first time during the open-label extension.

Antibody formation

In the pivotal study, antibodies have been detected in 77% of the patients treated with somatrogon. An influence on efficacy or safety was not recognizable within the studies. In patients who do not respond adequately to treatment, antibodies against somatrogon should nevertheless be determined in addition to investigating other possible causes.

To date, no information is available on the question of persistence of antibodies after discontinuation of somatrogon or on possible long-term effects.

Acute critical illness

The use of GH in pharmacological doses has been associated with increased mortality in patients with acute critical illness following open heart or abdominal surgery, or multiple trauma, or with acute respiratory failure (see «Contraindications»). No corresponding data are available for substitution therapy in patients with GHD. In patients treated with Ngenla developing an acute critical illness, the expected benefit of further treatment should be carefully weighed against the potential risk.

Other precautions

In cases of complete or partial anterior pituitary failure, replacement therapy with additional hormones (e.g. glucocorticoids) may be necessary. Because glucocorticoids may reduce the efficacy of GH, in this case, growth must be closely monitored. The dosage of this additional treatment must be carefully adjusted to prevent inhibition of growth.

Pancreatitis has been reported under GH treatment especially in children. If acute severe upper abdominal discomfort occurs in a patient under somatrogon treatment, pancreatitis should be included in the differential diagnosis.

Somatrogon has been studied exclusively in paediatric patients with GHD (so-called pituitary dwarfism). No data are available on other forms of growth disorders such as short stature in Turner syndrome, growth disorders in chronic renal failure, Prader-Willi syndrome or growth disorders in patients with intrauterine short stature (SGA). Ngenla should therefore not be used in these patient groups.

Excipients of particular interest

GH preparations which, like Ngnela, contain the preservative metacresol have in individual cases been associated with myositis. If myalgia or unreasonably severe pain occurs at the injection site, creatine kinase values should be determined. If myositis is diagnosed on the basis of biopsy and elevated creatine kinase values or in any case if some other hypersensitivity reaction to metacresol is suspected, treatment should be switched to a preparation without metacresol.

This medicinal product contains less than 1 mmol sodium (23 mg) per ml, i.e. it is almost «sodium free».

Interactions

No interactions studies have been performed with somatrogon.The following information is based on the corresponding experience with daily applied recombinant GH. It is to be expected that they also apply to somatrogon.

Pharmacokinetic interactions

GH can increase the clearance of substances metabolised by cytochrome P450 isoenzyme 3A4 (e.g. sex hormones, corticosteroids, anticonvulsive agents and ciclosporin). The clinical significance is unclear.

Treatment with GH inhibits the microsomal enzyme 11β-hydroxysteroid dehydrogenase 1 (11βHSD-1), which is required for the conversion of cortisone to its active metabolite cortisol in hepatic and adipose tissue. As a result, the cortisol concentration in the serum decreases (see «Warnings and precautions»).

The conversion of other glucocorticoids like prednisone to their active metabolites also occurs through the activity of 11βHSD-1. This may require a higher dose of prednisone when GH is used at the same time.

Pharmacodynamic interactions

Glucocorticoids

Concomitant treatment with glucocorticoids inhibits the growth-promoting effect of a substitution therapy with GH. The dosage of the glucocorticoid replacement therapy in patients with concurrent adrenocorticoropic hormone (ACTH) deficiency must therefore be carefully adjusted (see «Warnings and precautions»).

Hypoglycaemic agents

In diabetics requiring drug therapy, the dosage of the antidiabetic therapy can require adjustment when somatrogon therapy is initiated (see «Warnings and precautions»).

With concomitant administration of gonadotropins, androgens or anabolic steroids, there may be an additive effect on bone maturation.

Pregnancy, lactation

Pregnancy

There are no studies in pregnant women. Animal studies have shown no reproductive toxicity (see «Preclinical Data»). The effects of a high concentration of GH at specific stages of embryogenesis and foetal growth in humans have not yet been determined. Somatrogon must therefore not be used during pregnancy.

In women of childbearing potential, somatrogon should not be used without reliable contraception, whereby non-hormonal methods should be selected. Therefore, if treatment with somatrogon is continued in girls after menarche, counselling regarding non-hormonal contraceptive methods must be given.

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

Effects of somatrogon on pregnancy test in blood have not been studied at sufficiently high somatrogon concentrations; false negative results can therefore not be ruled out.

Lactation

Lactation studies have not been conducted with somatrogon. It is not known whether somatrogon is excreted in human milk.

As a precautionary measure, a decision should be made to discontinue Ngenla or to refrain from breastfeeding, taking into account the benefits of breastfeeding for the child and the benefits of treatment for the mother.

Fertility

The risk of infertility has not been studied in humans. In a rat study, the fertility in males and females was not affected (see «Preclinical Data»).

There was an increase in oestrous cycle length, copulatory interval, and number of corpora lutea but no effects on mating indices, fertility or early embryonic development in rats (see «Preclinical Data»).

Effects on ability to drive and use machines

No corresponding studies have been conducted. However, an influence of somatrogon on the ability to drive or use machines is not expected.

Undesirable effects

The safety of somatrogon was evaluated in a phase 3 study in 224 paediatric patients with GHD (see «Properties/Effects»).

The most common adverse reactions with somatrogon during the main study period were injection site reactions (43%), headache (19%) and hypersensitivity reactions (19%).

The adverse reactions below are sorted according to MedDRA system organ classes and the conventional frequencies as follows: «very common» (≥1/10), «common» (≥1/100, <1/10), «uncommon» (≥1/1’000, <1/100), «rare» (≥1/10’000, <1/ 1’000), «very rare» (<1/10’000).

Blood and lymphatic system disorders

Common: Anaemia.

Immune system disorders

Very common: Antibody formation against somatrogon (77%; see «Warnings and precautions»), hypersensitivity reactions (19%, e.g. eosinophilia, conjunctivitis allergic, pyrexia).

Endocrine disorders

Common: Hypothyroidism.

Uncommon: Adrenocortical insufficiency.

Metabolism and nutrition disorders

Very common: Increase in serum phosphate (14%).

Nervous system disorders

Very common: Headache (19%).

Skin and subcutaneous tissue disorders

Uncommon: Rash generalised.

Musculoskeletal and connective tissue disorders

Common: Arthralgia, pain in extremity.

General disorders and administration site conditions

Very common: Injection site reactions (43%, see «Warnings and precautions») (This includes for example: injection site pain, erythema, pruritus).

Immunogenicity

In the pivotal study (see «Properties/Effects»), 77% of the 109 patients treated with somatrogon tested positive for anti-drug antibodies (ADAs). An association between antibody status and safety profile has not yet been observed. In addition, efficacy parameters showed comparable findings in patients with and without ADAs.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the ElViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

Doses of somatrogon >0.66 mg/kg/wk have not been studied, and there is no experience with an overdose.

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

A specific antidote does not exist. An overdose with somatrogon should be treated supportively and symptomatically, if necessary.

Properties/Effects

ATC code

H01AC08.

Mechanism of action/Pharmacodynamics

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. The glycosylation and CTP domains result in a half-life extension.

Somatrogon binds to the GH receptor and leads to an increase of the serum concentration of Insulin-like Growth Factor (IGF-1), which contributes to the clinical efficacy. In paediatric patients with GHD, GH and IGF-1 stimulate linear growth and enhance growth velocity.

Clinical efficacy

The efficacy of somatrogon for the treatment of children and adolescents with GHD was evaluated in one multi-centre randomised, open-label active controlled phase 3 study in n=224 paediatric patients. In the 12-month main phase of the study, once weekly administration of somatrogon (0.66 mg/kg/week) was compared with daily use of somatropin (0.034 mg/kg/day).This is followed by a single arm open label extension during which all patients will receive somatrogon once weekly. Pre-pubertal children with proven GH deficiency (i.e. pituitary short stature) aged 3 years to 10 years (girls) or 11 years (boys) who had not previously been treated with recombinant GH were included. Patients with other causes of growth disturbance were excluded from the study. Inclusion criteria were a growth rate below the 25th percentile and an IGF-1 SDS <-1.

The primary efficacy endpoint was annualised height velocity (HV) following 12 months of treatment. Key secondary endpoints were e.g. height SDS and the change in height SDS from baseline.

The mean age at study entry across the treatment groups was 7.7 years (min 3.01, max 11.96), 40% of patients were >3 years to ≤7 years, 60% were >7 years. 72% of patients were male and 28% were female. In this study, 75% of patients were White, 20% were Asian; 1% were Black. Approximately 68% of patients had peak plasma GH levels of ≤7 ng/mL, and the mean height was at -2.86 SDS.

40% of patients included had baseline IGF-1 SDS <-2 (indicating marked GH deficiency), with this proportion slightly higher in the somatrogon group than in the comparator group (44% vs. 36.5%).

In the primary endpoint, non-inferiority of somatrogon administered once weekly versus daily somatropin was demonstrated. Numerically, the height velocity was slightly higher under somatrogon (somatrogon 10.10 cm/year, conventional GH 9.78 cm/year; not significant). The findings of the key secondary endpoints were consistent.

In the open-label extension 91 patients have so far been treated with once-weekly somatrogon for at least 2 years. A progressive gain in height SDS from baseline was observed at 2 years.

Pharmacokinetics

Somatrogon pharmacokinetics was assessed using a population pharmacokinetics approach in 42 paediatric patients with GHD.

Absorption

Following subcutaneous injection, serum concentrations increased slowly, peaking 6-18 hours after dosing.

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

Distribution

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

Metabolism

The metabolism of somatrogon has not been studied in clinical studies. 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 pharmacokinetics estimated apparent clearance was 0.0336 l/h/kg. In patients who tested positive for ADA, the apparent clearance of somatrogon was about 25.8% lower. With mean estimated effective half-life of 28.3 hours, somatrogon will be present in the circulation for about 6 days after the last dose.

Kinetics in specific patient groups

Age, race, gender, body weight

Based on population pharmacokinetic analyses, age (3-15.7 years), sex (66.7% male), and race (95.2% white) 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. A dosing regimen of 0.66 mg/kg/wk provides adequate systemic exposure over the body weight range of 10-54 kg evaluated in the clinical studies.

Preclinical data

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

Somatrogon has been evaluated in single- and repeat-dose toxicity studies in rats and rhesus monkeys. Based on the non-clinical studies conducted, injection site findings have been identified as the only target organ/effect. An anticipated increase in body weight was observed in rats since it is a primary pharmacodynamic effect of GH and associated with secondary effects of increased IGF-1. Other findings related to the pharmacological activity of somatrogon occurred in mammary glands, liver, kidney and spleen in rats.

Genotoxicity and carcinogenicity

Genotoxicity and carcinogenicity studies have not been performed.

Reproductive toxicity

Potential effects of somatrogon on fertility and early embryonic development was evaluated in male and female rats after a subcutaneous somatrogon injection at a dose resulting in 14 times the expected maximum clinical exposure. Somatrogon elicited an increase in oestrous cycle length, copulatory interval, and number of corpora lutea, but there was no impact on mating indices, fertility, number of viable embryos/early embryonic development.

After subcutaneous administration of somatrogon to pregnant rats during organogenesis, at a dose resulting in 14 times the expected maximum clinical exposure, no evidence of fetal damage was identified.

In a pre- and postnatal development study in rats, somatrogon was administered via subcutaneous injection to pregnant rats every 2 days from GD 6 to Lactation Day 20 at doses up to 30 mg/kg. There was no evidence of maternal toxicity and no adverse effects on the first generation (F1) offspring. Somatrogon elicited an increase in F1 mean body weights (both sexes) as well as an increase in the mean copulatory interval in F1 females at the highest dose (14 times the expected maximum clinical exposure), which was consistent with a longer oestrous cycle length; however, there were no associated effects on mating indices.

Other information

Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

Shelf life

Do not use this medicine after the expiry date («EXP») stated on the pack.

Shelf life after opening

After first use

28 days.

Store in a refrigerator (2 °C – 8 °C). Once removed from the refrigerator, Ngenla may be held at room temperature for up to 2 hours with each use.

Do not freeze.

Store Ngenla with the pen cap attached and away from direct sunlight.

Before and after first use

Ngenla may be kept temporarily at room temperature (e.g. warming prior to use for a more comfortable injection). However, Ngenla must be put back into the refrigerator again after each use. It should not be exposed to temperatures above 32 °C and should never be left at room temperature for more than two hours. After five uses, the Ngenla Pen should be discarded. If it has been exposed to

temperatures higher than 32 °C or stored outside the refrigerator for more than 2 hours, it must also be discarded.

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 2-8 °C in between each use.

Special precautions for storage

Store in the refrigerator (2-8 °C).

Do not freeze or expose to heat. Do not use Ngenla if it has been frozen or exposed to heat. In these cases, the pen with the remaining solution must be disposed of immediately.

Keep the container in the outer carton in order to protect the contents from light.

Keep out of the reach of children.

Do not shake.

Always replace the pen cap on the pre-filled pen after each injection.

For storage conditions after first use of the medicinal product, see «Shelf-life after opening».

Instructions for handling

Please refer to the Instruction for Use provided in the Patient Information (package leaflet) for detailed information.

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 solution must be checked for particles, flakes and discoloration before use. Do not use the medicine if it is cloudy or dark yellow or if particles/flakes are visible.

Do not shake, shaking can damage the medicine.

The pre-filled pen should not be used more than 28 days after first use, even if it still contains medicine. It must not be used after the expiry date.

Pen preparation

The pre-filled pen with sterile somatrogon solution may be used straight from the refrigerator. For a more comfortable injection, allow pen to reach room temperature for up to 30 minutes.

Administration

The designated injection site should be prepared as instructed in the Patient Information (package leaflet). It is recommended to rotate the injection site at each administration.

A new sterile 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 or contamination. Put on the protective cap after injection.

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.

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.

Disposal

Any unused product or waste material should be disposed of in accordance with local requirements.

Authorisation number

68265 (Swissmedic).

Packs

Pack with 1 pre-filled pen with 24 mg/1.2 ml [A].

Pack with 1 pre-filled pen with 60 mg/1.2 ml [A].

Needles are not included. Ngenla can be administered with needles ranging in length from 4 mm to 8 mm and sizes from 31 to 32G.

Marketing authorisation holder

Pfizer AG, Zürich.

Date of revision of the text

June 2022.