PUBLIC SUMMARY OF THE RISK MANAGEMENT PLAN

NGENLA (SOMATROGON)

Marketing Authorization Number 68265

Solution for injection in pre-filled pen, 24 mg/1.2 ml and 60 mg/1.2 ml

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
EMA	European Medicines Agency
EPAR	European Public Assessment Report
EU	European Union
GH	Growth Hormone
GHD	Growth Hormone Deficiency
hGH	Human Growth Hormone
IGF	Insulin-like Growth Factor
PASS	Post-authorisation Safety Study
PL	Package Leaflet
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics (Europe)

OVERVIEW

The Risk Management Plan (RMP) is a comprehensive document submitted as part of the application dossier for market approval of a medicine. The RMP summary contains information on the medicine's safety profile and explains the measures that are taken in order to further investigate and follow the risks as well as to prevent or minimise them. The RMP summary for Ngenla is a concise document and does not claim to be exhaustive.

As the RMP is an international document, the summary might differ from the "Arzneimittelinformation / Information sur le médicament" approved and published in Switzerland, e.g., by mentioning risks occurring in populations or indications not included in the Swiss marketing authorization.

Please note that the reference document which is valid and relevant for the effective and safe use of Ngenla in Switzerland is the "Arzneimittelinformation / Information sur le médicament" (see www.swissmedic.ch) approved and authorised by Swissmedic. Pfizer is fully responsible for the accuracy and correctness of the content of the published RMP summary of Ngenla.

SUMMARY OF RISK MANAGEMENT PLAN FOR NGENLA (SOMATROGON)

This is a summary of the RMP for somatrogon. The RMP details important risks of somatrogon, how these risks can be minimised, and how more information will be obtained about somatrogon's risks.

Somatrogon's Summary of Product Characteristics (SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how somatrogon should be used.

This summary of the RMP for somatrogon should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

Important new concerns or changes to the current ones will be included in updates of somatrogon's RMP.

I. The Medicine and What It Is Used For

Somatrogon is indicated for the treatment of children and adolescents from 3 years of age with growth disturbance due to insufficient secretion of growth hormone. It contains somatrogon as the active substance and it is given by subcutaneous injection once weekly.

Injection: 24 mg/1.2 mL or 60 mg/1.2 mL available as:

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

Further information about the evaluation of somatrogon's benefits can be found in somatrogon's EPAR, including in its plain-language summary, which when available, will be placed in the EMA website, under the medicine's webpage.

II. Risks Associated with the Medicine and Activities to Minimise or Further Characterise the Risks

Important risks of somatrogon, together with measures to minimise such risks and the proposed studies for learning more about somatrogon's risks, are outlined below.

Measures to minimise the potential risks identified for medicinal products can be:

- Specific information such as warnings, precautions, and advice on correct use in the proposed PL and proposed SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine's packaging;
- The authorised pack size - the amount of medicine in a pack is chosen to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (eg, with or without a prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation measures*.

In addition to these measures, information about AEs is collected continuously and regularly analysed so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

II.A. List of Important Risks and Missing Information

Important risks of somatrogon are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of somatrogon. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (eg, on the long-term use of the medicine).

Table 1. List of important risks and missing information

Important identified risks	None
Important potential risks	Benign and malignant neoplasia (New first neoplasm, Second neoplasm in childhood cancer survivors, Recurrence or progression of a pre-existing tumour)
	Diabetes mellitus type 2
	Medication errors (resulting in under or overdosing of this long-acting formulation)
	Immunogenicity specifically related to long term clinical impact on lack of efficacy and safety (especially in relation to severe injections site reactions).
Missing information	None

II.B. Summary of Important Risks

Table 2. Important Potential Risk - Benign and Malignant Neoplasia (New first neoplasm, Second neoplasm in childhood cancer survivors, Recurrence or progression of a pre-existing tumour)

Evidence for linking the risk to the medicine	Post-marketing safety surveillance of marketed GH products. Literature of marketed GH products.
Risk factors and risk groups	Patients with a previous neoplasm have an increased risk of relapse of the same tumour type without treatment due to the biology of the disease. In addition, regardless of underlying diagnosis, paediatric patients with prior neoplasm are at an increased risk of developing second neoplasm when treated with growth hormone especially if they had received prior radiotherapy.

Table 2. Important Potential Risk - Benign and Malignant Neoplasia (New first neoplasm, Second neoplasm in childhood cancer survivors, Recurrence or progression of a pre-existing tumour)

Risk minimisation measures	Routine risk minimisation measures: Proposed SmPC Section 4.3 where a contraindication concerning any evidence of activity of a tumour is included. Proposed SmPC Section 4.4 where a warning is included on neoplasms. Proposed PL Section 2, where information is included on tumours. Somatrogon is a restricted prescription-only medicine, prescribed by physicians who are qualified and experienced in the diagnosis and management of paediatric patients with GHD. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Non-interventional PASS is planned to monitor the long-term safety of somatrogon among paediatric patients to characterize the risk of neoplasms, diabetes mellitus type 2, medication errors, and immunogenicity. See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 3. Important Potential Risk - Diabetes Mellitus Type 2

Evidence for linking the risk to the medicine	A large observational study of patients treated with GH in childhood concluded that the patients had an increased risk of developing type 2 diabetes mellitus compared with the general population. However, most patients had diabetes risk factors and certain patient populations receiving GH treatment are inherently at risk of developing type 2 diabetes mellitus. Due to the low number of subjects exposed to somatrogon in the completed clinical trials, the strength of evidence for the risk of development of type 2 diabetes mellitus in somatrogon-treated subjects is limited.
Risk factors and risk groups	Hyperglycemia/new onset diabetes can be serious if not diagnosed and treated appropriately. At-risk groups include a family history of diabetes mellitus, pre-existing diabetes, type 1 or type 2 diabetes mellitus, insulin resistance, glucose intolerance, and obesity.
Risk minimisation measures	Routine risk minimisation measures: Proposed SmPC Section 4.4 where a warning is included on glucose metabolism impairment. Proposed PL Section 2, where information is included on high blood sugar. Somatrogon is a restricted prescription-only medicine, prescribed by physicians who are qualified and experienced in the diagnosis and management of paediatric patients with GHD. Additional risk minimisation measures: No risk minimisation measures.

Table 3. Important Potential Risk - Diabetes Mellitus Type 2

Additional pharmacovigilance activities	Additional pharmacovigilance activities: Non-interventional PASS is planned to monitor the long-term safety of somatrogon among paediatric patients to characterise the risk of neoplasms, diabetes mellitus type 2, medication errors, and immunogenicity. See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 4. Important Potential Risk - Medication Errors (resulting in under or overdosing of this long-acting formulation)

Evidence for linking the risk to the medicine	Patients who administer GH injections daily may continue to do so, and as such, are at risk of overdose. Conversely, patients who are not used to the somatrogon pen may self-administer a lower dose than prescribed.
Risk factors and risk groups	Patients switching from daily to weekly dosing.
Risk minimisation measures	Routine risk minimisation measures: Proposed SmPC Section 4.2, where information is included concerning appropriately qualified and experienced physicians should initiate and monitor somatrogon treatment. In addition, Section 4.2 provides clear instructions on once-weekly dose, how to change dosing day, steps to follow when a dose is missed, switching between daily GH to weekly therapy, and monitoring IGF-1 to support dose adjustments. Proposed labelling Section 5 (carton) and Section 2 (pen), where 'once weekly' is printed on the carton and the preloaded pen. Proposed PL Section 3, where information is included regarding how and when to use somatrogon. Proposed Instructions for Use, which provide detailed information on how to use the somatrogon pen. Somatrogon is a restricted prescription-only medicine, prescribed by physicians who are qualified and experienced in the diagnosis and management of paediatric patients with GHD. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Non-interventional PASS is planned to monitor the long-term safety of somatrogon among paediatric patients to characterise the risk of neoplasms, diabetes mellitus type 2, medication errors, and immunogenicity. See Section II.C of this summary for an overview of the post-authorisation development plan.

Table 5. Important Potential Risk - Immunogenicity Specifically Related to Long Term Clinical Impact on Lack of Efficacy and Safety (especially in relation to severe injections site reactions)

Evidence for linking the risk to the medicine	Somatrogon has given rise to the formation of antibodies in approximately 77% of children and adolescent patients. The binding activity of these antibodies has been low and no clinical consequences have been associated with their formation.
Risk factors and risk groups	There are currently no reliable predictors of patients who may or may not develop ADAs, as antibodies develop to varying degrees during treatment with human proteins including growth hormone.
Risk minimisation measures	Routine risk minimisation measures: Proposed SmPC Section 4.8 Undesirable effects. Somatrogon is a restricted prescription-only medicine, prescribed by physicians who are qualified and experienced in the diagnosis and management of paediatric patients with GHD. Additional risk minimisation measures: No risk minimisation measures.
Additional pharmacovigilance activities	Additional pharmacovigilance activities: Non-interventional PASS is planned to monitor the long-term safety of somatrogon among paediatric patients to characterise the risk of neoplasms, diabetes mellitus type 2, medication errors, and immunogenicity. See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C. Post-Authorisation Development Plan

II.C.1. Studies which are Conditions of the Marketing Authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of somatrogon.

II.C.2. Other Studies in Post-Authorisation Development Plan

PASS Summary

Study short name and title:

An Active Surveillance Study to Monitor the Real-World Long-Term Safety of Somatrogon Among Paediatric Patients in Europe.

Purpose of the study:

The purpose of this study will be to assess the long-term safety of somatrogon, a long-acting hGH, under routine clinical care and is intended to reflect outcomes that occur in real-world clinical practice.

Primary Objective:

- Estimate the incidence rates of neoplasms, and diabetes mellitus type 2, the primary safety events of interest, in paediatric patients treated with somatrogon, and

paediatric patients treated with once daily somatropin, in the course of routine clinical care.

Secondary Objectives:

- Estimate the incidence rates of clinical endpoints related to immunogenicity, medication errors, the secondary safety events of interest, in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

- Evaluate long-term efficacy by measuring IGF-1 levels, and height in paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

- Estimate the hazard ratios of the neoplasms, and diabetes mellitus type 2, the primary safety events of interest, between paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.

- Estimate the hazard ratios of the clinical endpoints related to immunogenicity, the secondary safety event of interest, between paediatric patients treated with somatrogon, and paediatric patients treated with once daily somatropin, in the course of routine clinical care.