Summary of risk management plan for Increlex (mecasermin)

This is a summary of the risk management plan (RMP) for Increlex. The RMP details important risks of Increlex, how these risks can be minimised, and how more information will be obtained about Increlex 's risks and uncertainties (missing information).

Increlex's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Increlex should be used.

This summary of the RMP for Increlex 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 Increlex's RMP.

I. The Medicine and What it is Used For

Increlex is authorised for long-term treatment of growth failure in children and adolescents from 2 to 18 years with severe primary insulin-like growth factor-1 deficiency (primary IGFD; see SmPC for the full indication). It contains mecasermin as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Increlex's benefits can be found in Increlex's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

https://www.ema.europa.eu/medicines/human/EPAR/increlex

II. Risks associated with the medicine and activities to minimise or further characterise the risk

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

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and 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 so to ensure that the medicine is used correctly;
- The medicine's legal status - the way a medicine is supplied to the patient (e.g. with or without prescription) can help to minimise its risks.

Together, these measures constitute routine risk minimisation measures.

In the case of Increlex, these measures are supplemented with additional risk minimisation measures mentioned under relevant important risks, below.

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

If important information that may affect the safe use of Increlex is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of Increlex 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 Increlex. 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 (e.g. on the long-term use of the medicine).

List of Important Risks and Missing Information	
Important identified risks	• Hypoglycaemia • Lipohypertrophy • Tonsillar hypertrophy and associated AEs • Intracranial hypertension • Hypersensitivity • Scoliosis • Cardiomegaly • Benign and malignant neoplasia.
Important potential risks	• Immunogenicity (potential reduced effect) • Slipped capital femoral epiphysis
Missing information	• None

II.B Summary of important risks

Important identified risk - Hypoglycaemia	
Evidence for linking the risk to the medicine	The evidence for the classification of this risk comes from exposure in the clinical development programme and in the postmarketing setting. Hypoglycaemia occurred very commonly (≥1/10) in the clinical development programme and has also been observed in the postmarketing setting.
Risk factors and risk groups	Younger age group, severity of short stature and a previous history of spontaneous hypoglycaemia are considered risk factors for hypoglycaemia in patients on IGF therapy based on an analysis of 62 treatment-naïve subjects with IGF-I deficiency due to GH insensitivity treated for at least 1 year with rhIGF-I. In the EU Increlex Registry, predictive factors for hypoglycaemia were presence of Laron Syndrome at treatment initiation and history of hypoglycaemia at treatment initiation (p=0.001 and p=0.041, respectively).

Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.2 • SmPC Section 4.4 • SmPC Section 4.5 • SmPC Section 4.7 • SmPC Section 4.8 • SmPC Section 4.9 • SmPC Section 5.1 • SmPC Section 5.3 • PL Section 2 • PL Section 3 • PL Section 4. **Additional risk minimisation measures** • Physician Information Pack (SmPC, Physician Leaflet, Hypoglycaemia Leaflet, Dosing Guide with Dose Calculator) • Patient Information Pack (Patient Leaflet, Increlex Instructions for Use)
Additional pharmacovigilance activities	• Global Increlex Registry (Study number: 2-79-52800-002 amendment #8) : Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)

IGF-1=insulin-like growth factor-1; EU=European Union; GH=growth hormone; PL=package leaflet; rhIGF-1=recombinant insulin-like growth factor-1; SmPC=Summary of Product Characteristics

Important identified risk - Lipohypertrophy	
Evidence for linking the risk to the medicine	The evidence for the classification of this risk comes from exposure in the clinical development programme and in the postmarketing setting. Lipohypertrophy occurred uncommonly (≥ 1/1000, <1/100) in the clinical development programme overall, but occurred at a frequency of 35% in Study 1419 and has also been observed in the postmarketing setting. Additionally, it has been noted as a frequent event associated with IGF-1 therapy in the published literature .
Risk factors and risk groups	A clinical study in which 430 outpatients injecting insulin filled in a questionnaire regarding their injection technique before examination of their injection sites for the presence of hypertrophy found that failure to rotate injection sites and use of needles more than five times (i.e. reuse of needles) were risk factors for lipohypertrophy.
Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.2 • SmPC Section 4.8 • PL Section 3 • PL Section 4. **Additional risk minimisation measures** • Physician Information Pack (SmPC, Physician Leaflet, Hypoglycaemia Leaflet, Dosing Guide with Dose Calculator) • Patient Information Pack (Patient Leaflet, Increlex Instructions for Use)
Additional pharmacovigilance activities	• Global Increlex Registry (Study number: 2-79-52800-002 amendment #8) : Global Patient Registry to Monitor Long-

	term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)

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Important identified risk - Tonsillar hypertrophy and associated AEs	
Evidence for linking the risk to the medicine	The evidence for the classification of this risk comes from exposure in the clinical development programme and in the postmarketing setting. Tonsillar hypertrophy occurred commonly (≥1/100 to <1/10) in the clinical development programme and has also been observed in the postmarketing setting.
Risk factors and risk groups	No specific risk groups or risk factors for tonsillar hypertrophy and associated AEs attributable to rhIGF-1 therapy have been identified.
Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4. **Additional risk minimisation measures** • Physician Information Pack (SmPC, Physician Leaflet, Hypoglycaemia Leaflet, Dosing Guide with Dose Calculator) • Patient Information Pack (Patient Leaflet, Increlex Instructions for Use).
Additional pharmacovigilance activities	• Global Increlex Registry (Study number: 2-79-52800-002 amendment #8) : Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)

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Important identified risk - Intracranial hypertension	
Evidence for linking the risk to the medicine	The evidence for the classification of this risk comes from exposure in the clinical development programme and in the postmarketing setting. Intracranial hypertension was reported in the clinical development programme, albeit uncommonly (≥1/1000, <1/100), and has also been observed in the postmarketing setting. In addition, intracranial hypertension has been reported in association with IGF-1 treatment in the published literature .
Risk factors and risk groups	In a review of paediatric idiopathic intracranial hypertension by Rangwala and Liu, various risk factors for developing idiopathic intracranial hypertension are discussed. However, the risk factor profile is not well understood and may differ between young children and adolescents or adults. No specific risk groups or risk factors for intracranial hypertension attributable to rhIGF-1 therapy have been identified.
Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4. **Additional risk minimisation measures** • Physician Information Pack (SmPC, Physician Leaflet, Hypoglycaemia Leaflet, Dosing Guide with Dose Calculator) • Patient Information Pack (Patient Leaflet, Increlex Instructions for Use).
Additional pharmacovigilance activities	• Global Increlex Registry (Study number: 2-79-52800-002 amendment #8) : Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)

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Important identified risk - Hypersensitivity	
Evidence for linking the risk to the medicine	The evidence for the classification of this risk comes from exposure in the clinical development programme and in the postmarketing setting. Hypersensitivity (either systemic and/or local to the injection site) occurred in 8% of subjects in the clinical development programme and has also been observed in the postmarketing setting.
Risk factors and risk groups	Subjects with a congenital protein deficiency are less likely to recognise a therapeutic protein as "self" and are therefore more likely to mount an immune response. In the context of mecasermin therapy, patients who produce no IGF-1 of their own are more likely to generate antibodies towards rhIGF-1 as the protein is more likely to be recognised as foreign. Patients who are atopic and/or who have underlying allergic conditions, such as eczema, asthma and allergic rhinitis, are considered to be at increased risk of anaphylaxis.
Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4. **Additional risk minimisation measures** • Physician Information Pack (SmPC, Physician Leaflet, Hypoglycaemia Leaflet, Dosing Guide with Dose Calculator) • Patient Information Pack (Patient Leaflet, Increlex Instructions for Use).
Additional pharmacovigilance activities	• Global Increlex Registry (Study number: 2-79-52800-002 amendment #8) : Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)

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Important identified risk - Scoliosis	
Evidence for linking the risk to the medicine	The evidence for the classification of this risk comes from exposure in the clinical development programme and in the postmarketing setting. Scoliosis is known to occur in patients who experience rapid growth and was commonly observed in the clinical development programme (≥1/100 to <1/10) and there have been some cases reported from solicited and clinical trials sources since marketing approval.
Risk factors and risk groups	No specific risk groups or risk factors for scoliosis attributable to rhIGF-1 therapy have been identified. However, established biological risk factors are growth velocity and potential residual spinal growth.
Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 2 • PL Section 4.

	Additional risk minimisation measures • Physician Information Pack (SmPC, Physician Leaflet, Hypoglycaemia Leaflet, Dosing Guide with Dose Calculator) • Patient Information Pack (Patient Leaflet, Increlex Instructions for Use).
Additional pharmacovigilance activities	• Global Increlex Registry (Study number: 2-79-52800-002 amendment #8) : Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)

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Important identified risk - Cardiomegaly	
Evidence for linking the risk to the medicine	Cardiomegaly is considered to be an Important identified risk based on the fact that the published literature suggests IGF-1 may lead to increased myocyte mass and volume together with the fact that some cases of cardiomegaly were observed in clinical studies, albeit uncommonly (≥1/1000, <1/100). Cardiomegaly is not considered to be associated with untreated severe IGFD. Genetic aetiology accounts for about one half of presumed sporadic cases and nearly two thirds of familial cases of childhood onset cardiac hypertrophy. Increased cardiac mortality is seen in GH and IGF-1 deficient states and animal studies suggest protection of cardiac myocytes by IGF-1.
Risk factors and risk groups	No specific risk groups or risk factors for cardiomegaly attributable to rhIGF-1 therapy have been identified.
Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.4 • SmPC Section 4.8 • PL Section 4. **Additional risk minimisation measures** • Physician Information Pack (SmPC, Physician Leaflet, Hypoglycaemia Leaflet, Dosing Guide with Dose Calculator)
Additional pharmacovigilance activities	• Global Increlex Registry (Study number: 2-79-52800-002 amendment #8) : Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)

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Important identified risk - Benign and malignant neoplasia	
Evidence for linking the risk to the medicine	The evidence for the classification of this risk comes from exposure in the clinical development programme and in the postmarketing setting. IGF-1 is a growth factor, and therefore has the potential to increase the risk of developing neoplasias. Melanocytic naevus was a common (≥1/100 to <1/10) event in the clinical development programme and has also been observed in the postmarketing setting. Additional spontaneous reports of benign and malignant neoplasia have also been reported in the postmarketing setting. To date the frequency of these events is unknown.
Risk factors and risk groups	Individuals at the high end of the normal range of serum IGF-1 concentration have been found to have more than double the risk of developing prostate, breast and colorectal cancers than those at the lower end. One suggestion is that higher levels of IGF-1 may result in early undetected carcinogenic lesions progressing to clinically significant manifestations. Nevertheless, some review papers refer to other studies that have failed to find an association between higher IGF-1 levels and increased risk of certain cancers. However, an association between normalising IGF-1 levels and cancer in children treated with rhIGF-1 has not been reported in these publications.
Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.2 • SmPC Section 4.3 • SmPC Section 4.4 • SmPC Section 4.8 • SmPC Section 4.9 • PL Section 2 • PL Section 4 **Additional risk minimisation measures** • Physician Information Pack (SmPC, Physician Leaflet, Hypoglycaemia Leaflet, Dosing Guide with Dose Calculator) • Patient Information Pack (Patient Leaflet, Increlex Instructions for Use) • Direct healthcare professional communication.
Additional pharmacovigilance activities	• Global Increlex Registry (Study number: 2-79-52800-002 amendment #8) : Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)

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Important potential risk - Immunogenicity (potential reduced effect)	
Evidence for linking the risk to the medicine	The evidence for the classification of this risk comes from exposure in the clinical development programme. Positive IGF-1 antibody tests were observed in a large number of subjects in the clinical studies. Potential clinical consequences of immunogenicity are a decrease in mecasermin efficacy, allergic reactions and induction of autoimmunity including antibodies to the endogenous form of the protein. However, the risk of immunogenicity for mecasermin is not yet well established, therefore, Immunogenicity (potential reduced effect) is considered to be an important potential risk.
Risk factors and risk groups	Subjects with a congenital protein deficiency are less likely to recognise a therapeutic protein as "self" and are therefore more likely to mount an immune response. In the context of mecasermin therapy, patients who produce no IGF-1 of their own are more likely to generate antibodies towards rhIGF-1 as the protein is more likely to be recognised as foreign. The immunogenicity of biologic agents is influenced by the molecule itself, the route of delivery, the degree of exposure, and the simultaneous use of immunosuppressive agents during administration, as well as other factors. No specific risk groups or risk factors for immunogenicity attributable to rhIGF-1 therapy have been identified.
Additional pharmacovigilance activities	• Global Increlex Registry (Study number: 2-79-52800-002 amendment #8) : Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)
Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.4 • SmPC Section 4.8. **Additional risk minimisation measures** • Physician Information Pack (SmPC, Physician Leaflet, Hypoglycaemia Leaflet, Dosing Guide with Dose Calculator).

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Important potential risk- Slipped capital femoral epiphysis	
Evidence for linking the risk to the medicine	It is known that slipped capital femoral epiphysis can occur in patients who experience rapid growth. However, there were no reports of slipped capital femoral epiphysis/avascular necrosis in any of the clinical studies and a single case in the US Increlex Registry (no cases in the EU Increlex Registry).
Risk factors and risk groups	No specific risk groups or risk factors for slipped capital femoral epiphysis attributable to rhIGF-1 therapy have been identified. However, established biological risk factors are male gender (male to female ratio is approximately 1.5), race (higher prevalence rate in the black population, Hispanics, Polynesians, and Native Americans when compared with Caucasians), geographic location (higher rates in the north and western parts of the United States). The age of onset of slipped capital femoral epiphysis is approximately 12.7 to 13.5 years for boys and 11.2 to 12 years for girls. Obesity may also be a risk factor for slipped capital femoral epiphysis as well as certain abnormal morphologies of the proximal femur.
Risk minimisation measures	**Routine risk minimisation measures** • SmPC Section 4.4 • PL Section 2. **Additional risk minimisation measures** • Physician Information Pack (SmPC, Physician Leaflet, Hypoglycaemia Leaflet, Dosing Guide with Dose Calculator) • Patient Information Pack (Patient Leaflet, Increlex Instructions for Use).
Additional pharmacovigilance activities	• Global Increlex Registry (Study number: 2-79-52800-002 amendment #8) : Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)

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II.C Post-authorisation development plan

II.C.1 Studies which are conditions of the marketing authorisation

The following studies are conditions of the marketing authorisation:

Global registry: (Study number : 2 79 52800 002, amendment #8)

Global Patient Registry to Monitor Long-term Safety and Effectiveness of Increlex® in Children and Adolescents with Severe Primary Insulin-like Growth Factor-1 Deficiency (SPIGFD)

Purpose :

Primary Objective:

• To collect safety data in children and adolescents receiving Increlex® for the treatment of SPIGFD.

Secondary Objectives:

• To describe long-term safety data, for at least 5 years after the end of Increlex® therapy, in children and adolescents who have received Increlex® therapy, regardless of treatment duration and adult height;

• To describe long-term safety data at 2 and 5 years after the end of Increlex® therapy, for a subset of children and adolescents who have been exposed to Increlex® therapy for at least 3 cumulative years excluding interruptions, regardless of adult height;

• To describe Increlex® effectiveness throughout the study until the participant reaches adult height;

• To identify predictive factors of the main effectiveness parameters by modelisation of height velocity, final adult height (FAH), height standard deviation score (SDS) change, timing and progression of puberty, bone age development;

• To evaluate Increlex® therapy exposure and compliance;

• To assess quality of life (QoL) during Increlex® therapy and in the post-treatment period (using EQ-5D version EQ-5D-Y (paediatric questionnaire));

• To describe the timeframe of the occurrence of neoplasia (benign and malignant) and hypoglycaemia.

• To determine the LED defined as the cut-off dose under which there is no further effect on the height velocity (short-term evaluation: 1-year height velocity).

Long-term safety follow-up extension of the Global Increlex Registry (SOB 002)

Purpose:

To perform one long-term safety study where mecasermin treatment is initiated in the early phase of childhood and continued to adulthood in order to investigate:

•Long-term toxicity in subjects undergoing developmental changes

•Possible occurrence of malignancies as well as other risks.

Complementary analysis of data from the Global Increlex Registry to determine the lowest effective dose of mecasermin (MEA 020.3(previously FUM 020))

Purpose:

Main effectiveness parameters (height SDS, height velocity) will be described according to average dose received over the course of the study and according to dose ranges (i.e. 4 dose ranges (≤50,]50-80],]80-110], > 110 µg/kg BID)). This analysis will support the description of the lowest effective dose.

II.C.2 Other studies in post-authorization development plan

None