SUMMARY OF PRODUCT CHARACTERISTICS

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

1 NAME OF THE MEDICINAL PRODUCT

INCRELEX 10 mg/ml solution for injection

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains 10 mg of mecasermin*.
Each vial of 4 ml contains 40 mg of mecasermin*.
*Mecasermin is a recombinant DNA-derived human insulin-like growth factor-1(IGF-1) produced in *Escherichia coli*.

Excipient with known effect:
One ml contains 9 mg of benzyl alcohol.
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Solution for injection (injection).

Colourless to slightly yellow and clear to slightly opalescent liquid.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the long-term treatment of growth failure in children and adolescents from 2 to 18 years with confirmed severe primary insulin-like growth factor-1 deficiency (Primary IGFD).

Severe Primary IGFD is defined by:

- height standard deviation score ≤ –3.0 and
- basal IGF-1 levels below the 2.5th percentile for age and gender and
- GH sufficiency.
- Exclusion of secondary forms of IGF-1 deficiency, such as malnutrition, hypopituitarism, hypothyroidism, or chronic treatment with pharmacologic doses of anti-inflammatory steroids.

Severe Primary IGFD includes patients with mutations in the GH receptor (GHR), post-GHR signaling pathway, and IGF-1 gene defects; they are not GH deficient, and therefore, they cannot be expected to respond adequately to exogenous GH treatment. In some cases, when deemed necessary, the physician may decide to assist in the diagnosis by performing an IGF-I generation test.

4.2 Posology and method of administration

Treatment with mecasermin should be directed by physicians who are experienced in the diagnosis and management of patients with growth disorders.

Posology

The dose should be individualised for each patient. The recommended starting dose of mecasermin is 0.04 mg/kg of body weight twice daily by subcutaneous injection. If no significant adverse reactions occur for at least one week, the dose may be raised in increments of 0.04 mg/kg to the maximum dose of 0.12 mg/kg given twice daily. Doses greater than 0.12 mg/kg twice daily should not be exceeded as this may increase the risk of neoplasia (see section 4.3, 4.4 and 4.8).

If the recommended dose is not tolerated by the patient, treatment with a lower dose can be considered. Treatment success should be evaluated based on height velocities. The lowest dose that was associated with substantial growth increases on an individual basis was 0.04 mg/kg twice daily (BID).

Paediatric population

The safety and efficacy of mecasermin in children below age of 2 have not been established (see section 5.1). No data are available.
Therefore, this medicinal product is not recommended in children below age of 2.

Special Populations

Hepatic impairment

There are limited data concerning the pharmacokinetics of mecasermin in children with hepatic impairment, in this specific population of severe primary IGFD patients. It is recommended that the dose be individualised for each patient as described under posology

Renal impairment

There are limited data concerning the pharmacokinetics of mecasermin in children with renal impairment, in this specific population of severe primary IGFD patients. It is recommended that the dose be individualised for each patient as described under posology

Method of administration

INCRELEX should be administered by subcutaneous injection shortly before or after a meal or snack. If hypoglycaemia occurs with recommended doses, despite adequate food intake, the dose should be reduced. If the patient is unable to eat, for any reason, this medicinal product should be withheld.

Pre-prandial glucose monitoring is recommended at treatment initiation and until a well-tolerated dose is established. If frequent symptoms of hypoglycaemia and/or severe hypoglycaemia occur, blood glucose monitoring should continue regardless of pre-prandial condition and if possible at the time of the event.

The dose of mecasermin should never be increased to make up for one or more omitted doses.

Injection sites should be rotated to a different site with each injection to help prevent lipohypertrophy.

INCRELEX should not be administered intravenously.

Precaution to be taken before manipulating or administering the medicinal product
The solution should be clear immediately after removal from the refrigerator. If the solution is cloudy, or contains particulate matter, it must not be injected.

INCRELEX should be administered using sterile disposable syringes and injection needles. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

INCRELEX is contraindicated in children and adolescents with active or suspected neoplasia, or any condition or medical history which increases the risk of benign or malignant neoplasia.
Therapy should be discontinued if evidence of neoplasia develops.

As INCRELEX contains benzyl alcohol, it must not be given to premature babies or neonates.

4.4 Special warnings and precautions for use

Benign and malignant neoplasms

There is an increased risk of benign and malignant neoplasia in children and adolescents treated with INCRELEX, since IGF-1 plays a role in the initiation and progression of benign and malignant tumours.

There have been post-marketing reports of both benign and malignant neoplasms in children and adolescents who have received treatment with INCRELEX. These cases represented a variety of different malignancies and included rare malignancies usually not seen in children (see section 4.8). The increased risk of neoplasia may be higher in patients who receive INCRELEX for unapproved uses or at higher than recommended doses. Current knowledge of IGF-1 biology suggests that IGF-1 plays a role in malignancies in all organs and tissues. Physicians should therefore be vigilant of any symptoms of potential malignancy.
If benign or malignant neoplasia develops, INCRELEX treatment should be discontinued definitely and appropriate expert medical care sought.

Mecasermin is not a substitute for GH treatment.

Mecasermin should not be used for growth promotion in patients with closed epiphyses.

Mecasermin should be administered shortly before or after a meal or snack, because it may have insulin-like hypoglycaemic effects. Special attention should be paid to young children, children with a history of hypoglycaemia and children with inconsistent food intake. Patients should avoid engaging in any high-risk activities within 2-3 hours after dosing, particularly at the initiation of mecasermin treatment, until a well-tolerated dose of INCRELEX has been established. If a person with severe hypoglycemia is unconscious or otherwise unable to ingest food normally, an injection of glucagon may be required. Persons with a history of severe hypoglycemia should have glucagon available. At the time of initial prescription, physicians should educate parents on the signs, symptoms and treatment of hypoglycaemia, including injection of glucagon.

Doses of insulin and/or other hypoglycaemic medicinal products may need to be reduced for diabetic subjects using this medicinal product.

Echocardiogram is recommended before initiation of mecasermin treatment in all patients. Patients who terminate treatment should also have an echocardiogram. Patients with abnormal echocardiogram findings or cardiovascular symptoms should be followed regularly with echocardiogram procedures.

Lymphoid tissue (e.g., tonsillar) hypertrophy associated with complications, such as snoring, sleep apnoea, and chronic middle-ear effusions have been reported with the use of this medicinal product. Patients should have examinations periodically and at the occurrence of clinical symptoms to rule out such potential complications or to initiate appropriate treatment.

Intracranial hypertension (IH) with papilloedema, visual changes, headache, nausea and/or vomiting has been reported in patients treated with mecasermin, as has been reported with therapeutic GH administration. IH-associated signs and symptoms resolved after interruption of dosing. Funduscopic examination

is recommended at the initiation, periodically during the course of mecasermin therapy and at the occurrence of clinical symptoms.

Slipped capital femoral epiphysis (with the potential to lead to avascular necrosis) and progression of scoliosis can occur in patients who experience rapid growth. These conditions and other symptoms and signs known to be associated with GH treatment in general should be monitored during mecasermin treatment. Any patient with the onset of a limp or complaint of hip or knee pain should be evaluated.

In post-marketing experience in patients treated with INCRELEX, cases of hypersensitivity, urticaria, pruritus and erythema have been reported. These have been observed both as being systemic and/or local to the injection site. A small number of cases indicative of anaphylaxis requiring hospitalisation have been reported. Parents and patients should be informed that such reactions are possible and that if a systemic allergic reaction occurs, treatment should be interrupted, and prompt medical attention should be sought.

Treatment should be reconsidered if after a year patients remain non-responsive.

Persons who have allergic reactions to injected IGF-1, who have unexpectedly high blood values of IGF-1 after injection, or who fail to show a growth response without any identified cause may be having an antibody response to injected IGF-1. This may be through the production of anti-IGF-1 IgEs, sustaining antibodies or neutralizing antibodies respectively. In such instances, instructions for antibody testing should be considered.

Excipients
INCRELEX contains 9 mg/ml benzyl alcohol as a preservative.

Benzyl alcohol may cause toxic reactions and anaphylactoid reactions in infants and children up to 3 years old.

This medicine contains less than 1 mmol sodium (23 mg) per vial, that is to say essentially ‘sodium-free’.

Traceability
In order to improve the traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Doses of insulin and/or other hypoglycaemic medicinal products may need to be reduced (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
A negative pregnancy test is recommended for all women of child bearing potential prior to treatment with mecasermin. It is also recommended that all women of childbearing potential use adequate contraception during treatment.

Pregnancy
There are no or limited amount of data for the use of mecasermin in pregnant women.

Animal studies are insufficient with respect to reproductive toxicity (see section 5.3). The potential risk for humans is unknown.

This medicinal product should not be used during pregnancy.

Breast-feeding
Breast-feeding while taking INCRELEX is not recommended, because there is insufficient information on the excretion of mecasermin in human milk.

Fertility
Mecasermin has been tested in a rat teratology study with no effects on fœtus up to 16 mg/kg (20 fold the maximum recommended human dose (MRHD) based on body surface area) and in a rabbit teratology with no effects on foetus at dose of 0.5 mg/kg (2 fold the MRHD based on body surface area). Mecasermin has no effects on fertility in rats using intravenous doses 0.25, 1, and 4 mg/day (up to 4 times the clinical exposure with the MRHD based on AUC).

The effects of mecasermin on the unborn child have not been studied. Therefore, there is insufficient medical information to determine whether there are significant risks to a foetus. Studies have not been conducted with mecasermin in breast-feeding mothers. INCRELEX should not be given to pregnant or nursing women. A negative pregnancy test and adequate contraception is required in all pre-menopausal women receiving INCRELEX.

4.7 Effects on ability to drive and use machines

INCRELEX may have a major influence on the ability to drive or use machines in case of a hypoglycaemic episode. Hypoglycaemia is a very common adverse reaction.

4.8 Undesirable effects

Summary of the safety profile
Adverse reaction data was taken from a total of 413 clinical trial patients with IGFD, including 92 patients with severe primary IGFD. Data was also collected from post-marketing sources.

The most frequently reported adverse reactions from the clinical trials were headache (44%), hypoglycaemia (28%), vomiting (26%), injection site hypertrophy (17%), and otitis media (17%).

Intracranial hypertension/increased intracranial pressure occurred in 4 (0.96%) of patients from the clinical trials and occurred in 7 – 9 year old treatment naïve subjects.

During clinical trials in other indications totaling approximately 300 patients, reports of local and/or systemic hypersensitivity were received for 8% of patients. There were also reports of systemic hypersensitivity from post-marketing use, of which some cases were indicative of anaphylaxis. Post-marketing reports of local allergic reactions were also received.

Some patients may develop antibodies to mecasermin. No attenuation of growth was observed as a consequence of the development of antibodies.

Tabulated list of adverse reactions

Table 1 contains very common (≥ 1/10), common (≥ 1/100 to < 1/10) and uncommon (≥ 1/1000, < 1/100) adverse reactions which occurred in clinical trials. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. Other adverse reactions have been identified during post approval use of INCRELEX. As these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency (not known).

Table 1: Adverse reactions

SYSTEM ORGAN CLASS	**Reactions observed in the clinical trials**	**Reactions observed from the post-marketing environment**
Blood and lymphatic system disorders	Common: Thymus hypertrophy	
Immune system disorders		Not known: Systemic hypersensitivity (anaphylaxis, generalized urticaria, angioedema, dyspnoea), local allergic reactions at the injection site (pruritus, urticaria)
Metabolism and nutrition disorders	Very common: Hypoglycaemia Common: Hypoglycaemic seizure, hyperglycaemia	
Psychiatric disorders	Uncommon: Depression, nervousness	
Nervous system disorders	Very common: Headache Common: Convulsions, dizziness, tremor Uncommon: Benign	

	intracranial hypertension	
Eye disorders	Common: Papilloedema	
Ear and labyrinth disorders	Very common: Otitis media Common: Hypoacusis, ear pain, middle ear effusion	
Cardiac disorders	Common: Cardiac murmur, tachycardia Uncommon: Cardiomegaly, ventricular hypertrophy, mitral valve incompetence, tricuspid valve incompetence	
Respiratory, thoracic and mediastinal disorders	Common: Sleep apnoea syndrome, adenoidal hypertrophy, tonsillar hypertrophy, snoring	
Gastrointestinal disorders	Very common: Vomiting, upper abdominal pain Common: Abdominal pain	
Skin and subcutaneous tissue disorders	Common: Skin hypertrophy, abnormal hair texture	Not known: alopecia
Musculoskeletal and connective tissue disorders	Very common: Arthralgia, pain in extremity Common: Scoliosis, myalgia	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Common: Melanocytic naevus	Not known: Benign and malignant neoplasms
Reproductive system and breast disorders	Common: Gynaecomastia	
General disorders and administration site conditions	Very common: Injection site hypertrophy, injection site bruising Common: Injection site pain, injection site reaction, injection site haematoma, injection site erythema, injection site induration, injection site haemorrhage, injection site irritation Uncommon: Injection site rash, injection site swelling, lipohypertrophy	
Investigations	Uncommon: Increased weight	
Surgical and medical procedures	Common: Ear tube insertion	

Description of selected adverse reactions

Neoplasms

There have been post-marketing reports of benign and malignant neoplasms in children and adolescents who have received treatment with INCRELEX. These cases represented a variety of different malignancies and included rare malignancies usually not seen in children (see section 4.4 and 4.3).

Systemic/local hypersensitivity
Clinical Trial
During clinical trials in other indications (totaling approximately 300 patients) 8% of patients reported a local and/or systemic hypersensitivity reactions. All cases were mild or moderate in severity and none was serious.
Post-marketing reports
Systemic hypersensitivity included symptoms such as anaphylaxis, generalized urticaria, angioedema and dyspnoea. The symptoms in the cases indicative of anaphylaxis included hives, angioedema and dyspnoea. Some patients required hospitalization. Upon re-administration, symptoms did not re-occur in all patients. There were also reports of local allergic reactions at the injection site. Typically these were pruritus and urticaria.

Hypoglycaemia
Of the 115 (28%) subjects who experienced one or more episode of hypoglycaemia, 6 subjects experienced a hypoglycaemic seizure on one or more occasion. Symptomatic hypoglycaemia was generally avoided when a meal or snack was consumed either shortly before or after the administration of INCRELEX.

Injection site hypertrophy
This reaction occurred in 71 (17%) subjects from the clinical trials and was generally associated with lack of proper rotation of injections. When injections were properly dispersed, the condition resolved.

Tonsillar hypertrophy
This was noted in 38 (9%) subjects, particularly in the first 1 to 2 years of therapy with lesser tonsillar growth in subsequent years.

Snoring
This occurred generally in the first year of treatment and was reported in 30 subjects (7%).

Intracranial hypertension/increased intracranial pressure
This occurred in 4 subjects (0.96%); in two subjects INCRELEX was discontinued and not restarted; in two subjects the event did not recur after restarting INCRELEX at a reduced dose. All 4 subjects recovered from the event without sequelae.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed below:

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

4.9 Overdose

Acute overdose could lead to hypoglycaemia. Treatment of acute overdose of mecasermin should be directed at alleviating any hypoglycaemic effects. Oral glucose or food should be consumed. If the overdose results in loss of consciousness, intravenous glucose or parenteral glucagon may be required to reverse the hypoglycaemic effects.

Long-term overdose may result in signs and symptoms of acromegaly or gigantism. Overdosing may lead to supraphysiological IGF-1 levels and may increase the risk of benign and malignant neoplasm.

In case of an acute or a chronic overdose, Increlex must be discontinued immediately. If Increlex is restarted, the dose should not exceed the recommended daily dosage (see section 4.2)

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Pituitary and hypothalamic hormones and analogues, somatropin and somatropin agonists, ATC code: H01AC03

Mecasermin is a human insulin-like growth factor-1 (rhIGF-1) produced by recombinant DNA technology. IGF-1 consists of 70 amino acids in a single chain with three intramolecular disulfide bridges and a molecular weight of 7649 daltons. The amino acid sequence of the product is identical to that of endogenous human IGF-1. The rhIGF-1 protein is synthesised in bacteria (*E. coli*) that have been modified by the addition of the gene for human IGF-1.

<u>Mechanism of action</u>
Insulin-like growth factor-1 (IGF-1) is the principal hormonal mediator of statural growth. Under normal circumstances, growth hormone (GH) binds to its receptor in the liver and other tissues and stimulates the synthesis/secretion of IGF-1. In target tissues the Type 1 IGF-1 receptor, which is homologous to the insulin receptor, is activated by IGF-1, leading to intracellular signalling which stimulates multiple processes leading to statural growth. The metabolic

actions of IGF-1 are in part directed at stimulating the uptake of glucose, fatty acids, and amino acids so that metabolism supports growing tissues.

Pharmacodynamic effects
The following actions have been demonstrated for endogenous human IGF-1:

Tissue Growth
Skeletal growth is accomplished at the epiphyseal plates at the ends of a growing bone. Growth and metabolism of epiphyseal plate cells are directly stimulated by GH and IGF-1.
Organ growth: treatment of IGF-1 deficient rats with rhIGF-1 results in whole body and organ growth.
Cell growth: IGF-1 receptors are present on most types of cells and tissues. IGF-1 has mitogenic activity that leads to an increased number of cells in the body.

Carbohydrate Metabolism
IGF-1 suppresses hepatic glucose production, stimulates peripheral glucose utilization, and can reduce blood glucose and cause hypoglycaemia.
IGF-1 has inhibitory effects on insulin secretion.

Bone/Mineral Metabolism
Circulating IGF-1 plays an important role in the acquisition and maintenance of bone mass. IGF-1 increases bone density.

Clinical efficacy and safety
Five clinical studies (4 open-label and 1 double-blind, placebo-controlled) were conducted with INCRELEX. Subcutaneous doses of mecasermin, generally ranging from 60 to 120 μg/kg given twice daily (BID), were administered to 92 paediatric subjects with severe Primary IGFD. Patients were enrolled in the studies on the basis of extreme short stature, slow growth rates, low IGF-1 serum concentrations and normal GH secretion. Eighty-three (83) out of 92 patients were naïve to INCRELEX at baseline and 81 completed at least one year of INCRELEX treatment. Baseline characteristics for the 81 patients evaluated in the primary and secondary efficacy analyses from the combined studies were (mean ± SD): chronological age (years): 6.8 ± 3.8; age range (years): 1.7 to 17.5; height (cm): 84.1 ± 15.8; height standard deviation score (SDS): -6.9 ± 1.8; height velocity (cm/yr): 2.6 ± 1.7; height velocity SDS: -3.4 ± 1.6; IGF-1 (ng/ml): 24.5 ± 27.9; IGF-1 SDS: -4.2 ± 2.0; and bone age (years): 3.8 ± 2.8. Of these, 72 (89%) had Laron syndrome-like phenotype; 7 (9%) had GH gene deletion, 1 (1%) had neutralizing antibodies to GH and 1 (1%) had isolated genetic GH deficiency. Forty-six (57%) of the subjects were male; 66 (81%) were Caucasian. Seventy-four (91%) of the subjects were prepubertal at baseline.

Annual results for height velocity, height velocity SDS, and height SDS until year 8 are shown in Table 2. Pre-treatment height velocity data were available for 75 subjects. The height velocities at a given year of treatment were compared by paired t-tests to the pre-treatment height velocities of the same subjects completing that treatment year. The height velocities for years 2

through 8 remained statistically greater than baseline. For the 21 treatment naïve subjects with near-adult height, the mean (± SD) of the difference between observed increase in height versus that expected from Laron was approximately 13 cm (± 8 cm) after an average of 11 years of treatment.

Table 2: Annual Height Results by Number of Years Treated with INCRELEX

	Pre-Tx	**Year 1**	**Year 2**	**Year 3**	**Year 4**	**Year 5**	**Year 6**	**Year 7**	**Year 8**
Height Velocity (cm/yr)									
N	75	75	63	62	60	53	39	25	19
Mean (SD)	2.6 (1.7)	8.0 (2.3)	5.9 (1.7)	5.5 (1.8)	5.2 (1.5)	4.9 (1.5)	4.8 (1.4)	4.3 (1.5)	4.4 (1.5)
Mean (SD) for change from pre-Tx		+5.4 (2.6)	+3.2 (2.6)	+2.8 (2.4)	+2.5 (2.5)	+2.1 (2.1)	+1.9 (2.1)	+1.4 (2.2)	+1.3 (2. 8)
P-value for change from pre-Tx [1]		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0042	0.0486
Height Velocity SDS									
N	75	75	62	62	58	50	37	22	15
Mean (SD)	-3.4 (1.6)	1.7 (2.8)	-0.0 (1.7)	-0.1 (1.9)	-0.2 (1.9)	-0.3 (1.7)	-0. 2 (1. 6)	-0. 5 (1.7)	-0.2 (1.6)
Mean (SD) for change from pre-Tx		+5.2 (2.9)	+3.4 (2.4)	+3.3 (2. 3)	+3.2 (2.1)	+3.2 (2.1)	+3.3 (2.0)	+3.0 (2.1)	+3.3 (2.7)
P-value for change from pre-Tx [1]		<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001	<0.0001	0.0003
Height SDS									
N	81	81	67	66	64	57	41	26	19
Mean (SD)	-6.9 (1.8)	-6.1 (1.8)	-5.6 (1.7)	-5.3 (1.7)	-5.1 (1.7)	-5.0 (1.7)	-4.9 (1.6)	-4.9 (1.7)	-5.1 (1.7)
Mean (SD) for change from pre-Tx		+0.8 (0.6)	+1.2 (0.9)	+1.4 (1.1)	+1.6 (1.2)	+1. 7 (1.3)	+1. 8 (1.1)	+1. 7 (1.0)	+1.7 (1.0)
P-value for change from pre-Tx [1]		<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	0.0001	<0.0001

Pre-Tx = Pre-treatment; SD = Standard Deviation; SDS = Standard Deviation Score

[1] P-values for comparison versus pre-Tx values were computed using paired t-tests.

For subjects with bone age available for at least 6 years after treatment initiation, the mean increase in bone age was comparable to the mean increase in chronological age; for these subjects, there does not appear to be any clinically significant advance of bone age relative to chronological age.

Efficacy is dose dependent. The dose of 120 μg/kg given subcutaneously (SC) and twice daily (BID) was associated with the greatest growth responses.

Among all subjects included for safety evaluation (n=92), 83% of the subjects reported at least one adverse event during the course of the studies. There was no death during the studies. No subject discontinued the studies due to adverse events.

Hypoglycaemia was the most frequently reported adverse event and a proper attention has to be given to meals in relation to dosing.

This medicinal product has been authorised under "exceptional circumstances".

This means that due to the rarity of the disease it has not been possible to obtain complete information on this medicinal product.

The European Medicines Agency will review any new information which may become available every year and this SmPC will be updated as necessary.

5.2 Pharmacokinetic properties

Absorption

The absolute subcutaneous bioavailability of mecasermin in severe Primary IGFD subjects has not been determined. The bioavailability of mecasermin after subcutaneous administration in healthy subjects has been reported to be approximately 100%.

Distribution

In blood, IGF-1 is bound to six IGF binding proteins (IGFBPs), with ~80% bound as a complex with IGFBP-3 and an acid-labile subunit. IGFBP-3 is reduced in subjects with severe Primary IGFD, resulting in increased clearance of IGF-1 in these subjects relative to healthy subjects. The total IGF-1 volume of distribution (mean ± SD) after subcutaneous administration of INCRELEX in 12 subjects with severe Primary IGFD is estimated to be 0.257 (± 0.073) l/kg at a mecasermin dose of 0.045 mg/kg, and is estimated to increase as the dose of mecasermin increases. Limited information is available on the concentration of unbound IGF-1 after the administration of INCRELEX.

Biotransformation

Both the liver and the kidney have been shown to metabolise IGF-1.

Elimination

The mean terminal $t_{1/2}$ of total IGF-1 after single subcutaneous administration of 0.12 mg/kg in three paediatric subjects with severe Primary IGFD is estimated to be 5.8 hours. Clearance of total IGF-1 is inversely proportional to serum IGFBP-3 levels and total IGF-1 systemic clearance (CL/F) is estimated to be 0.04 l/hr/kg at 3 mg/l IGFBP-3 in 12 subjects.

Special populations

Elderly
The pharmacokinetics of INCRELEX have not been studied in subjects greater than 65 years of age.

Children
The pharmacokinetics of INCRELEX have not been studied in subjects younger than 12 years of age.

Gender
In adolescents with Primary IGFD and in healthy adults there were no apparent differences between males and females in the pharmacokinetics of INCRELEX.

Race
No information is available.

Renal impairment
No studies have been conducted in children with renal impairment.

Hepatic impairment
No studies have been conducted to determine the effect of hepatic impairment on the pharmacokinetics of mecasermin.

5.3 Preclinical safety data

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

Adverse reactions not observed in clinical studies, but seen in animals at exposure levels similar to clinical exposure levels and with possible relevance to clinical use were as follows:

Toxicity to reproduction
In rats and rabbits reproductive toxicity was studied after intravenous but not after subcutaneous application (the normal clinical route). These studies did not indicate direct or indirect harmful effects with respect to fertility and pregnancy, but due to the different route of application the relevance of these findings is unclear. Placental transfer of mecasermin was not studied.

Carcinogenic potential
Mecasermin was administered subcutaneously to Sprague Dawley rats at doses of 0, 0.25, 1, 4, and 10 mg/kg/day for up to 2 years. An increased incidence of adrenal medullary hyperplasia and pheochromocytoma was observed in male rats at doses of 1 mg/kg/day and above (≥ 1 times the clinical exposure with the maximum recommended human dose [MRHD] based on AUC) and female rats at all dose levels (≥ 0.3 times the clinical exposure with the MRHD based on AUC).

An increased incidence of keratoacanthoma in the skin was observed in male rats at doses of 4 and 10 mg/kg/day (≥ 4 times the exposure with the MRHD based on AUC). An increased incidence of mammary gland carcinoma in both male and female rats was observed in animals treated with 10 mg/kg/day (7 times the exposure with the MRHD based on AUC). Excess mortality secondary to IGF-1 induced hypoglycaemia was observed in the carcinogenesis studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Benzyl alcohol
Sodium chloride
Polysorbate 20
Glacial acetic acid
Sodium acetate
Water for injections

6.2 Incompatibilities

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

6.3 Shelf life

5 years

After opening
Chemical and physical in-use stability has been demonstrated for 30 days at 2°C to 8°C.
From a microbiological point of view, once opened, the medicinal product may be stored for a maximum of 30 days at 2°C to 8°C.

6.4 Special precautions for storage

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

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

6.5 Nature and contents of container

5 ml vial (type I glass) closed with a stopper (chloro-butyl/isoprene polymer) and a seal (Coloured plastic).

Each vial contains 4 ml of solution.

Pack size of 1 vial.

6.6 Special precautions for disposal

INCRELEX is supplied as a multi-dose solution.
Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Esteve Pharmaceuticals S.A.
Passeig de la Zona Franca 109 Planta 4
08038 Barcelona
Spain

8 MARKETING AUTHORISATION NUMBER(S)

PL 08498/0041

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/01/2021

10 DATE OF REVISION OF THE TEXT

27/06/2025