ANNEX I

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 or severe hypoglycaemia occur, blood glucose monitoring should continue regardless of pre-prandial condition and if possible, in case of hypoglycaemic symptoms.

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 in Appendix V.

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.

Mechanism of action
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 and other handling

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)

EU/1/07/402/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03 August 2007
Date of latest renewal: 16 June 2017

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Lonza AG
Lonzastrasse
CH-3930 Visp
Switzerland

Name and address of the manufacturers responsible for batch release

Tjoapack Netherlands B.V.
Nieuwe Donk 9
4879 AC Etten-Leur
The Netherlands

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH must ensure that, at launch, all physicians who are expected to prescribe INCRELEX are provided with a “physician information pack” containing the following:

- Product information
- Physician information about INCRELEX (information card, dosing guide, and a dose calculator)
- Patient information pack

The physician information about INCRELEX should contain the following key elements:

- To document severe primary IGF-1 deficiency diagnosis.
- To educate parents on the signs, symptoms and treatment of hypoglycaemia, including injection of glucagon.
- To advise parents regarding the benefit of INCRELEX versus the increased risk of benign and malignant neoplasia.
- INCRELEX is contraindicated in case of active or suspected neoplasia, or any condition or medical history which increases the risk of benign or malignant neoplasia , and therapy should be discontinued definitely if evidence of neoplasia develops.
- To document assessment of patient history and risk factors for malignancy to ensure contraindications are excluded.
- To inform parents that they should monitor for development of any new growth or signs and symptoms potentially related to benign or malignant neoplasm and report immediately to an appropriate healthcare professional in case of suspicion.
- To prevent overdose by strictly following the label and manage any overdose effects by discontinuation of the treatment or dose reduction
- That patients should have examinations of the ears, nose and throat periodically and at the occurrence of clinical symptoms to rule out such potential complications or to initiate appropriate treatment.
- To perform a routine funduscopic examination prior to beginning treatment and periodically during treatment or at the occurrence of clinical symptoms.
- Slipped capital femoral epiphysis and progression of scoliosis can occur in patients who experience rapid growth. These conditions should be monitored during INCRELEX treatment.
- To inform parents and patients that systemic allergic reactions are possible and that if this occurs treatment should be interrupted, and prompt medical attention should be sought.
- Immunogenicity sampling information.

The patient information about INCRELEX should contain the following information:

- That INCRELEX should be administered shortly before or after a meal or snack because it has insulin-like hypoglycaemic effects.
- The signs and symptoms of hypoglycaemia. Instructions on the treatment of hypoglycaemia. That parents and caregivers should always ensure that the child has a source of sugar. Instructions on the administration of glucagon should severe hypoglycaemia occur.
- INCRELEX should not be administered if the patient is unable to eat for any reason. The dose of INCRELEX should not be doubled to make up for one or more omitted doses.
- To avoid engaging in any high-risk activities (such as vigorous physical activity) within 2 - 3 hours after dosing, particularly at the initiation of INCRELEX treatment, until a well-tolerated dose of INCRELEX has been established.
- The patients or parents should report immediately to the appropriate healthcare professional as soon as there is a suspicion of the patient developing a benign or malignant neoplasm.
- Instructions to change and rotate the site of injection for each injection to avoid the development of lipohypertrophy.
- Instructions to report the onset or worsening of snoring that may indicate an increase in growth of tonsils and/or adenoids following the beginning of treatment with INCRELEX.
- To report the onset of severe headache, blurred vision and associated nausea and vomiting to their physician.
- To report any onset of a limp or complaint of hip or knee pain to their physician so it can be evaluated.

In addition there will be a dosing guide, and a dose calculator, for use by physician and patients to include information on the individualised dose escalation to minimise the risk of medication errors and hypoglycaemia.

E. SPECIFIC OBLIGATION TO COMPLETE POST-AUTHORISATION MEASURES FOR THE MARKETING AUTHORISATION UNDER EXCEPTIONAL CIRCUMSTANCES

This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the following measures:

Description	Due date
Non-interventional PASS: In order to assess the long-term safety of mecasermin initiated in early phase of childhood and continued into adulthood, the MAH should conduct and submit the results of a non-interventional safety study (Global Increlex Patient Registry):	N/A, annual study reports will be submitted with the annual reassessment

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

INCRELEX 10 mg/ml solution for injection
mecasermin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ml contains 10 mg of mecasermin.
Each vial contains 40 mg of mecasermin.

3. LIST OF EXCIPIENTS

Other ingredients: benzyl alcohol, sodium chloride, polysorbate 20, glacial acetic acid, sodium acetate and water for injections.
See the package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Solution for injection.
One multi-use vial of 4 ml.
40mg/4ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP
After first opening, use within 30 days.

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
Do not freeze.
Keep vial in the outer carton in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/402/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

INCRELEX

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

INCRELEX 10 mg/ml injection
mecasermin
SC

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

40mg/4ml

6. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the user

INCRELEX 10 mg/ml solution for injection
Mecasermin

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What INCRELEX is and what it is used for
2. What you need to know before you use INCRELEX
3. How to use INCRELEX
4. Possible side effects
5. How to store INCRELEX
6. Contents of the pack and other information

1. What INCRELEX is and what it is used for

- INCRELEX is a liquid that contains mecasermin which is a man-made insulin-like growth factor-1 (IGF-1), which is similar to the IGF-1 made by your body.
- It is used to treat children and adolescents from 2 to 18 years old who are very short for their age because their bodies do not make enough IGF-1. This condition is called primary IGF-1 deficiency.

2. What you need to know before you use INCRELEX

Do not use INCRELEX
- If you currently have any tumour or growth, either cancerous or non-cancerous
- if you have had cancer in the past
- if you have any conditions which may increase the risk of cancer
- if you are allergic to mecasermin or any of the other ingredients of this medicine (listed in section 6).
- in premature babies or neonates because it contains benzyl alcohol.

Warnings and precautions
There is an increased risk of tumours and growths (both cancerous and non-cancerous) in children and adolescents treated with INCRELEX. If any new growth, skin lesion or any unexpected symptom occurs during treatment or after treatment, see your doctor immediately since mecasermin may play a role in cancer development.

Talk to your doctor or pharmacist before using INCRELEX
- if you have a curved spine (scoliosis). You should be monitored for progression of scoliosis.
- if you develop a limp or hip or knee pain
- if you have enlarged tonsils (tonsillar hypertrophy). You should have examinations periodically.

- if you have symptoms of increased pressure in the brain (intracranial hypertension), such as visual changes, headache, nausea and/or vomiting, contact the doctor for advice.
- if you have a localised reaction at the injection site or generalised allergic reaction with INCRELEX. Call the doctor as soon as possible if you get a localised rash. Get medical help immediately if you have a generalised allergic reaction (hives, trouble breathing, faintness or collapse and feeling generally unwell).
- if you have finished growing (the bone growth plates are closed). In this case INCRELEX cannot help you grow and should not be used.

Children under 2 years old

The use of this medicine has not been studied in children under 2 years of age and is therefore not recommended.

Other medicines and INCRELEX

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Especially tell the doctor if you take insulin or other anti-diabetes medicines. A dose adjustment may be needed for these medicines.

Pregnancy, breast-feeding and fertility

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

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.

Mecasermin therapy should be discontinued if pregnancy occurs.

Mecasermin should not be administered to a breast-feeding mother.

Driving and using machines

Mecasermin may cause hypoglycaemia (very common side effect, see section 4) that may impair your ability to drive and use machines because your ability to concentrate or react may be reduced.

You should avoid engaging in any high-risk activities (e.g., driving, etc.) within 2-3 hours after dosing, particularly at the start of INCRELEX treatment, until a dose of INCRELEX has been found which does not cause side effects that make these activities risky.

INCRELEX contains benzyl alcohol and sodium

INCRELEX contains benzyl alcohol as a preservative which may cause toxic reactions and allergic 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’.

3. How to use INCRELEX

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The typical dose is 0.04 to 0.12 mg/kg of patient weight administered twice a day. See the 'Instructions for Use' at the end of this leaflet.

Inject INCRELEX just under your skin shortly before or after a meal or snack because it may have insulin-like hypoglycaemic effects and so it may decrease blood sugar levels (see hypoglycaemia in section 4). Do not inject your dose of INCRELEX if you cannot eat for any reason. Do not make up the missed dose by giving two doses the next time. The next dose should be taken as usual, with a meal or snack.

Inject INCRELEX just below the skin in your upper arm, upper leg (thigh), stomach area (abdomen), or buttocks. Change the injection site for each injection. Never inject it into a vein or muscle.

Only use INCRELEX that is clear and colourless.

Treatment with mecasermin is a long-term therapy. For further information ask the doctor.

If you use more INCRELEX than you should

Mecasermin, like insulin, may lower blood sugar levels (see hypoglycaemia in section 4).

If more INCRELEX than recommended was injected, contact your doctor immediately.

Acute overdose could lead to hypoglycaemia (low blood sugar).

Treatment of acute overdose of mecasermin should be directed at reversing hypoglycaemia. Sugar-containing fluids or food should be consumed. If the patient is not awake or alert enough to drink sugar-containing fluids, an injection of glucagon into the muscle may be necessary to reverse the low blood sugar. Your doctor or nurse will instruct you how to give the injection of glucagon.

Long-term overdose may result in enlargement of certain body parts (e.g., hands, feet, parts of the face) or excessive growth of the whole body. If you suspect long-term overdose, contact your doctor immediately.

If you forget to use INCRELEX

Do not use a double dose to make up for a forgotten dose.
If a dose is skipped, the next dose should not be made larger to compensate. The next dose should be taken as usual, with a meal or snack.

If you stop using INCRELEX

A disruption or early ending of treatment with mecasermin may impair the success of the growth therapy. Please ask the doctor for advice before stopping the treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

The most frequently occurring side effects with mecasermin are: low blood sugar (hypoglycemia), vomiting, injection site reactions, headache and middle ear infections. Serious allergic reactions have

also been reported with INCRELEX. If you develop any of these events, please follow the advice given for each event in the sections below.

Frequency not known (frequency cannot be estimated from the available data)
Cancerous and non-cancerous tumours
An increase in both cancerous and non-cancerous tumours has been reported in patients treated with INCRELEX. The risk of such tumours may be higher if INCRELEX is used for condition other than what is stated in Section 1 or used at higher than recommended dose as per Section 3.

Serious allergic reactions (anaphylaxis)
Generalised hives, difficulty in breathing, dizziness, swelling of the face and/or throat have been reported following mecasermin use. Stop INCRELEX immediately and seek urgent medical advice if you develop a serious allergic reaction.
Local allergic reactions at the injection site (itching, hives) have also been reported.

Hair loss (alopecia)
Hair loss has also been reported following mecasermin use.

Very common (may affect more than 1 in 10 people)
Low blood sugar (hypoglycaemia)
Mecasermin may lower blood sugar levels. Signs of low blood sugar are: dizziness, tiredness, restlessness, hunger, irritability, trouble concentrating, sweating, nausea and fast or irregular heartbeats.

Severe hypoglycaemia may cause unconsciousness, seizures/fits or death. Stop INCRELEX immediately and seek urgent medical advice if you develop seizures/fits or become unconscious.

If you take INCRELEX, you should avoid participating in high risk activities (such as vigorous physical activity) within 2 to 3 hours after INCRELEX injection, especially at the beginning of INCRELEX treatment.

Before beginning treatment with INCRELEX the doctor or nurse will explain to you how to treat hypoglycaemia. You should always have a source of sugar such as orange juice, glucose gel, sweets, or milk available in case symptoms of hypoglycaemia occur. For severe hypoglycaemia, if you are not responsive and cannot drink sugar-containing fluids, you should give an injection of glucagon. The doctor or nurse will instruct you how to give the injection. Glucagon raises the blood sugar when it is injected. It is important that you have a well-balanced diet including protein and fat such as meat and cheese in addition to sugar-containing foods.

You should be monitored at fingertip for blood sugar (glucose) before each meal at treatment initiation and until a well-tolerated dose is established. If frequent symptoms of hypoglycaemia or severe hypoglycaemia occur, blood sugar monitoring should continue regardless of eating condition and if possible, in case of hypoglycaemic symptoms.

Injection site hypertrophy (tissue at injection site increases in size) and bruising
These can be avoided by changing the injection site at each injection (injection site rotation).

Digestive system
Vomiting and pain in the upper belly have occurred with mecasermin treatment.

Infections
Infections of the middle ear have been observed in children with mecasermin treatment.

Musculoskeletal system
Joint pains and pains in the limbs have occurred with mecasermin treatment.

Nervous system
Headache has occurred with mecasermin treatment.

Common (may affect up to 1 in 10 people)
Seizures
Seizures (fits) have been observed with mecasermin treatment.
Dizziness and tremor have also been reported with mecasermin treatment.

Heart abnormalities
A fast heart rate and abnormal heart sounds have been reported with mecasermin treatment.

Increased blood sugar (hyperglycaemia)
Increased blood sugar has also been observed with mecasermin treatment.

Enlarged tonsils/adenoids
Mecasermin may enlarge your tonsils/adenoids. Some signs of enlarged tonsils/adenoids include: snoring, difficulty breathing or swallowing, sleep apnoea (a condition where breathing stops briefly during sleep), or fluid in the middle ear, as well as infections of the ear. Sleep apnea can cause excessive daytime sleepiness. Call the doctor should these symptoms bother you. The doctor should regularly examine your tonsils/adenoids.

Enlarged thymus
An enlarged thymus (a specialized organ of the immune system) has been observed with mecasermin treatment.

Papilloedema
A swelling at the back of the eye (due to increased pressure within the brain) may be observed by a doctor or optician during mecasermin treatment.

Hypoacusis (hearing loss)
Hypoacusis (hearing loss), ear pain and fluid in the middle ear have been observed with mecasermin treatment. Tell the doctor if you develop hearing problems.

Worsened scoliosis (caused by rapid growth)
If you have scoliosis, you will need to be checked often for an increase in the curve of the spine.
Pain in muscles has also been seen with mecasermin treatment.

Reproductive system
Breast enlargement has been observed with mecasermin treatment.

Digestive system
Pain in the belly has occurred with mecasermin treatment.

Skin and hair changes
Skin thickening, moles and abnormal hair texture have been seen with mecasermin treatment.

Reactions at the injection site
Reactions including pain, irritation, bleeding, bruising, redness and hardening have been reported with INCRELEX treatment. Injection site reactions can be avoided by changing the injection site at each injection (injection site rotation).

Uncommon (may affect up to 1 in 100 people)
Increased pressure in the brain (intracranial hypertension)
INCRELEX can sometimes cause a temporary increase in pressure within the brain. The symptoms of intracranial hypertension can include visual changes, headache, nausea and/or vomiting. Tell the doctor immediately if you have any of these symptoms. Your doctor can check to see if intracranial

hypertension is present. If it is present, your doctor may decide to temporarily reduce or discontinue mecasermin therapy. Mecasermin may be started again after the episode is over.

Heart abnormalities
In some patients treated with mecasermin, an ultrasound examination of the heart (echocardiogram) showed an increased size of the heart muscle and abnormalities of heart valve function. Your doctor may perform an echocardiogram before, during and after mecasermin treatment.

Reactions at the injection site
Reactions including rash, swelling and fatty lumps have been reported with INCRELEX treatment. Injection site reactions can be avoided by changing the injection site at each injection (injection site rotation).

Weight increase
Weight increase has been observed with mecasermin treatment.

Other uncommon side effects seen with mecasermin treatment include depression, nervousness.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store INCRELEX

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and label after EXP. The expiry date refers to the last day of the month.

Store in a refrigerator (2°C - 8°C). Do not freeze.
Keep the vial in the outer carton in order to protect from light.
After first use, the vial may be stored for up to 30 days at 2°C to 8ºC.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What INCRELEX contains
- The active substance is mecasermin. One ml contains 10 mg of mecasermin. Each vial contains 40 mg of mecasermin.
- The other ingredients are: benzyl alcohol, sodium chloride, polysorbate 20, glacial acetic acid, sodium acetate and water for injections (see section 2 "INCRELEX contains benzyl alcohol and sodium").

What INCRELEX looks like and contents of the pack

INCRELEX is a colourless to slightly yellow and clear to slightly opalescent solution for injection (injection) supplied in a glass vial closed with a stopper and a seal. The vial contains 4 ml of solution.

Pack size of 1 vial.

Marketing Authorisation Holder and Manufacturer

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

Manufacturer:
Tjoapack Netherlands B.V.
Nieuwe Donk 9
4879 AC Etten-Leur
The Netherlands

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

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Luxembourg/Luxemburg
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Medis RO S.R.L.
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This leaflet was last revised in

This medicine has been authorised under ‘exceptional circumstances’. This means that because of the rarity of this disease it has been impossible to get complete information on this medicine.
The European Medicines Agency will review any new information on this medicine every year and this leaflet will be updated as necessary.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

This leaflet is available in all EU/EEA languages on the European Medicines Agency website.
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INSTRUCTIONS FOR USE

INCRELEX should be administered using sterile disposable syringes and injection needles which could be provided by your doctor, pharmacist or nurse. The syringes should be of small enough volume that the prescribed dose can be withdrawn from the vial with reasonable accuracy.

Preparing the dose

1. Wash your hands before getting INCRELEX ready for your injection.

2. Use a new disposable needle and syringe every time you give a dose. Use syringes and needles only once. Throw them away properly in a sharps container (such as a biohazard container), hard plastic container (such as a detergent bottle), or metal container (such as an empty coffee can). **Never** share needles and syringes.

3. Check the liquid to make sure it is clear and colourless. Do not use after the expiry date (which is stated on the label after EXP and it refers to the last day of the month) or if it is cloudy or if you see bits. If a vial freezes, dispose appropriately. Ask your pharmacist how to throw away medicines you no longer use.

4. If you are using a new vial, remove the protective cap. Do not remove the rubber stopper.

5. Wipe the rubber stopper of the vial with an alcohol swab to prevent contamination of the vial by germs that may be introduced by repeated needle insertions (see Figure 1).

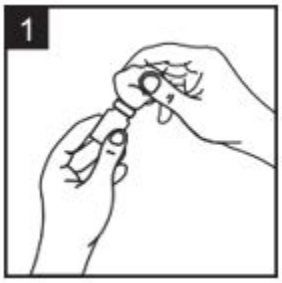


Figure 1: Wipe top with alcohol

6. Before putting the needle into the vial, pull back on plunger to draw air into the syringe equal to the prescribed dose. Put the needle through the rubber top of the vial and push the plunger to inject air into the vial (see Figure 2).

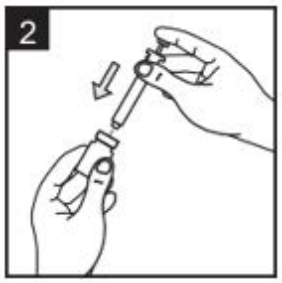


Figure 2: Inject air into vial

7. Leave the syringe in the vial and turn both upside down. Hold the syringe and vial firmly (see Figure 3).

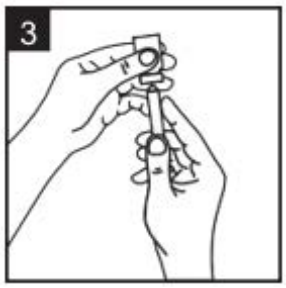


Figure 3: Prepare for extraction

8. Make sure the tip of the needle is in the liquid (see Figure 4). Pull the plunger to withdraw the correct dose into the syringe (see Figure 5).

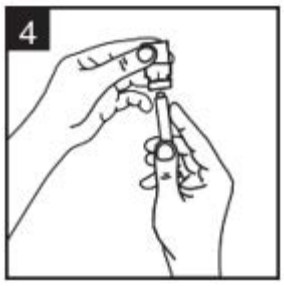


Figure 4: Tip in liquid

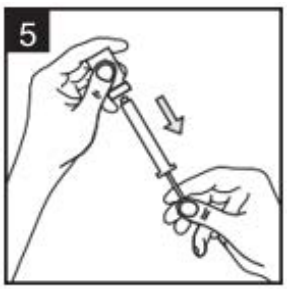


Figure 5: Extract correct dose

9. Before you take the needle out of the vial, check the syringe for air bubbles. If bubbles are in the syringe, hold the vial and syringe with needle straight up and tap the side of the syringe until the bubbles float to the top. Push the bubbles out with the plunger and draw liquid back in until you have the correct dose (see Figure 6).

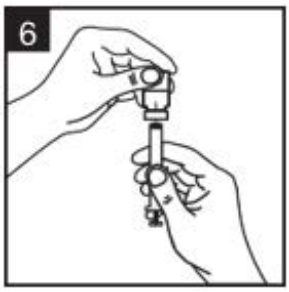


Figure 6: Remove air bubbles and refill syringe

10. Remove the needle from the vial and replace the protective cap. Do not let the needle touch anything. You are now ready to inject (see Figure 7).

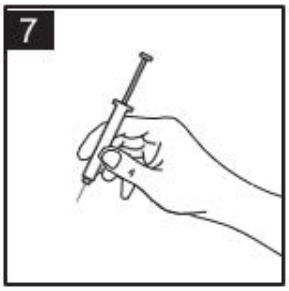
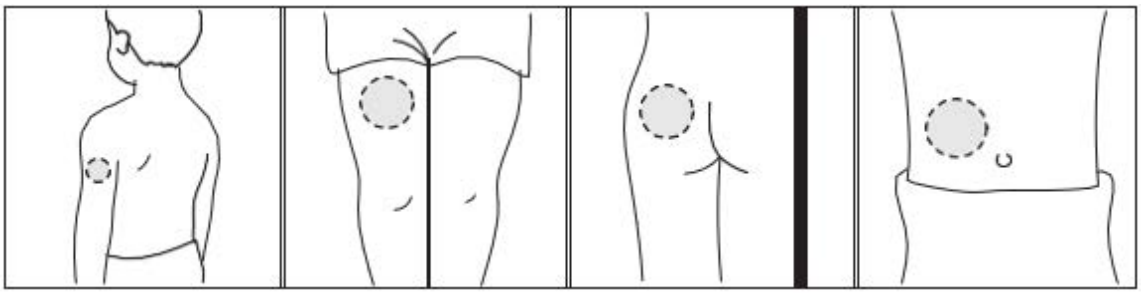


Figure 7: Ready to inject

Injecting the dose:

Inject INCRELEX as instructed by the doctor.
Do not give the injection if you are unable to eat shortly before or after the injection.

1. Decide on an injection area – upper arm, thigh, buttock, or abdomen (see below). The injection site should be changed for each injection (rotate the injection site) , to avoid formation of a lump of fatty tissue under your skin (lipohypertrophy) caused by repeated injections in the same place.



Upper arm Thigh Buttock Abdomen

2. Use alcohol or soap and water to clean the skin where you are going to inject you. The injection site should be dry before you inject.

3. Lightly pinch the skin. Insert the needle in the way the doctor showed you. Release the skin (see Figure A).

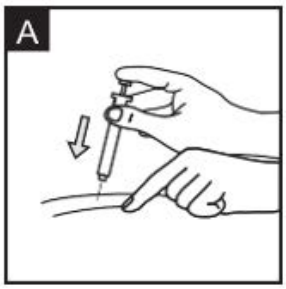


Figure A: Lightly pinch the skin and inject as instructed

4. Slowly push in the plunger of the syringe all the way, making sure you have injected all the liquid. Pull the needle straight out and gently press on the spot where you injected you with gauze or a cotton ball for a few seconds. **Do not rub the area** (see Figure B).

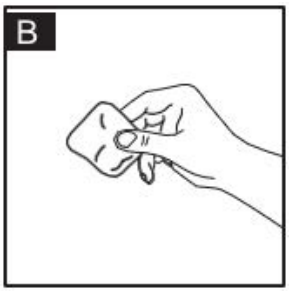


Figure B: Press (don’t rub) with gauze or cotton

5. Follow the doctor’s instructions for throwing away the needle and syringe. Do not recap the syringe. Used needle and syringe should be placed in a sharps container (such as a biohazard container), hard plastic container (such as a detergent bottle), or metal container (such as an empty coffee can). Such containers should be sealed and disposed of properly in the way your doctor described.