ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS
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 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).
Aqueous, clear and colourless solution.

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 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, 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. It is recommended to confirm the diagnosis by conducting an IGF-1 generation test.

4.2 Posology and method of administration

Treatment with INCRELEX 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 given twice daily have not been evaluated in children with severe Primary IGFD.

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 BID.

Paediatric population

The safety and efficacy of INCRELEX in children below age of 2 have not been established. No data are available. Therefore INCRELEX is not recommended in children below age of 2.

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, INCRELEX should be withheld. 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.

INCRELEX should not be administered intravenously.

Precaution to be taken before manipulating or administering the 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 (see section 6.6).

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.

Active or suspected 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

 Thyroid and nutritional deficiencies should be corrected before initiating INCRELEX treatment.

INCRELEX is not a substitute for GH treatment.

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

INCRELEX 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 INCRELEX 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 INCRELEX.

Echocardiogram is recommended before initiation of INCRELEX 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 INCRELEX. 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 INCRELEX, 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 INCRELEX 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 INCRELEX 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 may be having an antibody response to injected IGF-1. In such instances, instructions for antibody testing should be followed.

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 medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. essentially ‘sodium-free’.

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 INCRELEX. 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.

INCRELEX should not be used during pregnancy unless clearly necessary.

**Breast-feeding**
Breast-feeding while taking INCRELEX is not recommended.

**Fertility**
INCRELEX has been tested in a rat teratology study with no effects on foetus up to 16 mg/kg (20 fold the 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). INCRELEX 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 INCRELEX on 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 INCRELEX in nursing 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**
Hypoglycaemia is a very common adverse reaction. In case of a hypoglycaemic episode INCRELEX may have major influence on the ability to drive or use machines.

**4.8 Undesirable effects**

**Summary of the safety profile**
Adverse reaction data was taken from a pivotal clinical study of 76 subjects with severe Primary IGFD treated for a mean duration of 4.4 years and representing 321 subject-years. Data was also collected from post-marketing sources.

The most frequently reported adverse reactions from the pivotal clinical trial were hypoglycaemia (47%), injection site hypertrophy (32%), snoring (22%), hypoacusis (20%), headache (18%) and tonsillar hypertrophy (16%).

Intracranial hypertension occurred in 4% of patients from the pivotal clinical trial.

During clinical trials in other indications totalling 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 INCRELEX. Anti-IGF-1 antibodies were observed in 11 of 23 children with severe Primary IGFD tested during the first year of therapy. 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) and common (≥ 1/100 to < 1/10) 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. Because these reactions are reported voluntarily from a population of uncertain size, it is not possible to reliably estimate their frequency.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Reactions observed in the pivotal clinical trial</th>
<th>Reactions observed from the post-marketing environment</th>
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<tbody>
<tr>
<td>Infections and infestations</td>
<td>Common: Febrile infection*, upper respiratory tract infection*, otitis media, otitis media serous, chronic otitis media serous <em>, otitis externa</em>, pharyngitis*, tonsillitis, ear infection, oral candidiasis*</td>
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<tr>
<td>Blood and lymphatic system disorders</td>
<td>Very common: Thymus hypertrophy  Common: Lymphadenopathy*</td>
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<td>Immune system disorders</td>
<td>Not known: Systemic hypersensitivity (anaphylaxis, generalized urticaria, angioedema, dyspnoced)</td>
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<tr>
<td>Metabolism and nutrition disorders</td>
<td>Very common: Hypoglycaemia  Common: Hypoglycaemic seizure, hyperglycaemia, hyperlipidaemia*, obesity*</td>
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<tr>
<td>Psychiatric disorders</td>
<td>Common: Depression*, sleep terror, nervousness, abnormal behaviour*, disorientation*</td>
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<tr>
<td>Nervous system disorders</td>
<td>Very common: Headache  Common: Convulsions, febrile convulsion*, benign intracranial hypertension, loss of consciousness*, sleep apnoea syndrome, dizziness, tremor*, restless leg syndrome*</td>
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<tr>
<td>Eye disorders</td>
<td>Common: Papilloedema, reduced visual acuity*, myopia*</td>
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<tr>
<td>Ear and labyrinth disorders</td>
<td>Very common: Hypoacusis  Common: Otorrhoea, ear disorder*, middle ear disorder*, tympanic membrane disorder*, ear pain, ear congestion*, fluid in middle ear</td>
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<tr>
<td>Cardiac disorders</td>
<td>Common: Cardiomegaly, ventricular hypertrophy, atrial hypertrophy*, tachycardia, tachycardia paroxysmal*, mitral valve incompetence*, tricuspid valve incompetence*</td>
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<td>Respiratory, thoracic and mediastinal disorders</td>
<td>Very common: Tonsillar hypertrophy, snoring  Common: Adenoidal hypertrophy, nasal turbinate hypertrophy*</td>
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<tr>
<td>Medical Condition</td>
<td>Common:</td>
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<tr>
<td>Gastrointestinal disorders</td>
<td>Dyspnoea*, nasal mucosal disorder*, obstructive airway disorder*, abnormal respiration*, nasal congestion, mouth breathing</td>
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<td>Skin and subcutaneous tissue disorders</td>
<td>Common: Skin hypertrophy, acrochordons*, abnormal hair texture</td>
<td>Alopecia</td>
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<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Common: Arthralgia, pain in extremity, myalgia, scoliosis*, spinal deformity*, soft tissue disorder*, muscle cramp*, flank pain*, musculoskeletal stiffness*</td>
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<tr>
<td>Renal and urinary disorders</td>
<td>Common: Nephrolithiasis*, hydronephrosis*, renal colic*</td>
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<tr>
<td>Reproductive system and breast disorders</td>
<td>Common: Gynaecomastia, ovarian cyst</td>
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<tr>
<td>Congenital, familial and genetic disorders</td>
<td>Common: Congenital jaw malformation, pigmented naevus*</td>
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<tr>
<td>General disorders and administration site conditions</td>
<td>Very common: Injection site hypertrophy</td>
<td>Local allergic reactions at the injection site (pruritus, urticaria)</td>
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<tr>
<td>Investigations</td>
<td>Common: Cardiac murmur, abnormal tympanometry, abnormal echocardiogram, increased alanine aminotransferase*, increased aspartate aminotransferase*, increased weight</td>
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<tr>
<td>Surgical and medical procedures</td>
<td>Common: Adenotonsillectomy*, adenoidectomy, ear tube insertion</td>
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</table>

* = occurred in only 1 subject (1%)

Description of selected adverse reactions

Systemic/local hypersensitivity
Clinical Trial: During clinical trials in other indications (totalling 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 36 (47%) subjects who experienced one or more episode of hypoglycaemia, 4 subjects experienced a hypoglycaemic seizure on one or more occasion. Twelve of the 36 subjects (33%) had a history of hypoglycaemia prior to beginning treatment. The frequency of hypoglycaemia was highest in the first month of treatment, and episodes were more frequent in younger children. 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 24 (32%) subjects from the pivotal clinical trial 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 12 (16%) 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 17 subjects (22%).

**Intracranial hypertension**
This occurred in three subjects (4%). In two subjects the events resolved without interruption of INCRELEX treatment. INCRELEX treatment was discontinued in the third subject and resumed later at a lower dose without recurrence. Fourteen subjects (18%) had headache considered related to study drug.

**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. Long-term overdose may result in signs and symptoms of acromegaly or gigantism.

Treatment of acute overdose of mecamasermin 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.

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 signaling 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 76 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. Baseline characteristics for the patients evaluated in the primary and secondary efficacy analyses from the combined studies were (mean ± SD): chronological age (years): 6.8 ± 3.8; height (cm): 85.0 ± 15.3; height standard deviation score (SDS): -6.7 ± 1.8; height velocity (cm/yr): 2.8 ± 1.8; height velocity SDS: -3.3 ± 1.7; IGF-1 (ng/ml): 21.9 ± 24.8; IGF-1 SDS: -4.4 ± 2.0; and bone age (years): 3.9 ± 2.8. Sixty-two subjects had at least one year of treatment. Of these, 53 (85%) had Laron syndrome-like phenotype; 7 (11%) had GH gene deletion, and 1 (2%) had neutralizing antibodies to GH. Thirty-eight (61%) of the subjects were male; 49 (79%) were Caucasian. Fifty-six (90%) of the subjects were prepubertal at baseline.

Annual results for height velocity, height velocity SDS, and height SDS are shown in Table 2. Pre-treatment height velocity data were available for 59 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.
Table 2: Annual Height Results by Number of Years Treated with INCRELEX

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<th>Year 1</th>
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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.

Forty-seven subjects were included in an analysis of the effects of INCRELEX on bone age advancement. The mean ± SD change in chronological age was 5.1 ± 3.0 years and the mean ± SD change in bone age was 5.8 ± 2.9 years.

Efficacy is dose dependent. For subjects receiving doses between 100 and 120 μg/kg BID, the mean first year height velocity was approximately 8.7 cm/yr.

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

General characteristics

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 children over 12 years old 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 mecaneserin 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
Acetic acid, glacial
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

3 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 product may be stored for a maximum of 30 days at 2°C to 8°C. Other in-use storage times and conditions are the responsibility of the user.
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

4 ml of solution in a 5 ml vial (type I glass) closed with a stopper (bromobutyl/isoprene polymer) and a seal (lacquered plastic).

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

INCRELEX is supplied as a multi-dose solution.

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 (see section 4.2).

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

7. MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65, quai Georges Gorse
92100 Boulogne-Billancourt
France

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/07/402/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 03/08/2007
Date of latest renewal: 03/08/2012

10. DATE OF REVISION OF THE TEXT

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION
A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Lonza Biologics, Inc.
97 South Street
Hopkinton, Massachusetts 01748
USA

Name and address of the manufacturer responsible for batch release

Beaufour Ipsen Industrie
Rue d'Ette Virton
28100 Dreux
France

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

Pharmacovigilance system

The MAH must ensure that the system of pharmacovigilance, as presented in Module 1.8.1. of the Marketing Authorisation, is in place and functioning before and whilst the medicinal product is on the market.

Risk Management Plan (RMP)

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

PSURs

The PSUR cycle for the medicinal product should follow the yearly cycle until otherwise agreed by the CHMP.
• CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

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 educate parents on the signs, symptoms and treatment of hypoglycaemia, including injection of glucagon.
- 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.
- INCRELEX is contraindicated in the presence of active or suspected neoplasia, and therapy should be discontinued if evidence of neoplasia develops.
- 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.
- 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.

• 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:

Clinical aspects

- To develop and validate an immunogenicity assay for assessing anti-IGF-I antibodies.
- To perform one long-term safety study where mecasermin treatment is initiated in early phase of childhood and continued to adulthood in order to investigate:
  - Long-term toxicity in patients undergoing developmental changes
  - Possible occurrence of malignancies as well as other risks

The next interim report shall be submitted by 31/12/2013, and subsequent interim reports will be submitted every two years until the final patient is followed for 5 years.
ANNEX III

LABELLING AND PACKAGE LEAFLET
A. LABELLING
### PARTICULARS TO APPEAR ON THE OUTER PACKAGING

#### CARDBOARD BOX

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.

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 APPLICABLE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Ipsen Pharma
65, quai Georges Gorse
92100 Boulogne-Billancourt
France

12. MARKETING AUTHORIZATION NUMBER(S)

EU/1/07/402/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

INCRELEX
# MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

## VIAL

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<tr>
<td><strong>1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION</strong></td>
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<tr>
<td>INCRELEX 10 mg/ml injection</td>
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<tr>
<td>Mecasermin</td>
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<td>SC</td>
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<td><strong>2. METHOD OF ADMINISTRATION</strong></td>
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<td><strong>3. EXPIRY DATE</strong></td>
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<td><strong>4. BATCH NUMBER</strong></td>
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<td><strong>5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT</strong></td>
<td>4 ml</td>
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<td><strong>6. OTHER</strong></td>
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</table>
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.
- INCRELEX 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 are allergic to mecasermin or any of the other ingredients of this medicine (listed in section 6).
- if you have cancer.
- in premature babies or neonates because it contains benzyl alcohol.

Warnings and precautions
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**

A negative pregnancy test is recommended for all women of child bearing potential prior to treatment with INCRELEX. It is also recommended that all women of childbearing potential use adequate contraception during treatment.

INCRELEX therapy should be discontinued if pregnancy occurs.

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

**Driving and using machines**

INCRELEX may cause hypoglycaemia (very common side effect) 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**

INCRELEX contains 9 mg per ml of benzyl alcohol as a preservative.

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

This medicinal product contains less than 1 mmol sodium (23 mg) per vial, i.e. 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. Never inject it into a vein or muscle. Change the injection site for each injection.

Only use INCRELEX that is clear and colourless.

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

**If you use more INCRELEX than you should**

INCRELEX, 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). 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.

Treatment of acute overdose of INCRELEX 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.

**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 INCRELEX 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 INCRELEX are: low blood sugar (hypoglycemia), injection site reaction, snoring, hearing loss, headache and enlarged tonsils. 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)**

**Serious allergic reactions (anaphylaxis)**

Can cause generalised hives, difficulty in breathing, dizziness, swelling of the face and/or throat have been reported. 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 INCRELEX use.
Very common (may affect more than 1 in 10 people)
Low blood sugar (hypoglycaemia)
INCRELEX 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.

Enlarged tonsils/adenoids
INCRELEX may enlarge your tonsils/adenoids. Some signs of enlarged tonsils/adenoids include: snoring, difficulty breathing or swallowing, sleep apnea (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. An infection of the tonsils has also been observed. The doctor should regularly examine your tonsils/adenoids. Swelling inside the nose, enlarged thymus and lymph nodes have been seen with INCRELEX treatment.

Hypoacusis (hearing loss)
Tell the doctor if you develop hearing problems.

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

Common (may affect up to 1 in 10 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 INCRELEX therapy. INCRELEX may be started again after the episode is over.

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

Also, a racing pulse and heart valve abnormalities have been reported with INCRELEX treatment.

Seizures/fits associated with a high temperature (Febrile seizures)
Febrile seizures/fits have been observed with INCRELEX treatment.

Increased blood sugar (hyperglycaemia)
Increased blood sugar has also been observed with INCRELEX treatment.
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 and stiffness in muscles or joints, as well as jaw malformations, have also been seen with INCRELEX treatment.

Infections
Infections of the mouth, throat and the upper airways have been observed in children with INCRELEX treatment. Such infections may be associated with fever.

Kidney disorders
Kidney stones have been reported, as well as associated pain and kidney swelling.

Reproductive system
Breast enlargement, as well as cysts in the ovaries, have been observed.

Digestive system
Stomach-ache, difficulties swallowing, retching and vomiting have occurred with INCRELEX treatment. Weight gain/obesity have also been reported, as have increases in blood fat and in liver enzyme values.

Skin and hair changes
Skin thickening, moles, skin tags, and abnormal hair texture have been seen with INCRELEX treatment.

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

Other common side effects seen with INCRELEX treatment include restless legs, chest pain, depression, sleep terror, nervousness, abnormal behaviour and disorientation.

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 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 to 8°C.

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.
What INCRELEX looks like and contents of the pack

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

Pack size of 1 vial.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder:
Ipsen Pharma
65, quai Georges Gorse
92100 Boulogne-Billancourt
France

Manufacturer:
Beaufour Ipsen Industrie
Rue d'Eté Virton
28100 Dreux
France

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

België/Belgique/Belgien, Luxembourg/Luxembourg
Ipsen NV
Guldensporenpark 87
B-9820 Merelbeke
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România, България
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Ipsen Pharma, o.s.
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Tel: + 420 242 481 821

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Institut Produits Synthèse (IPSEN) AB
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Färögatan 33
SE- 164 51 Kista
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Ipsen SpA
Via A. Figinio, 16
I-20156 Milano
Tel: + 39 - 02 - 39 22 410

Latvija
Ipsen Pharma
Kalnciema iela 33-5
Riga LV 1046
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Lietuva, Hrvatska
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9-ojo Forto 47
LT-48100 Kaunas
Tel. + 370 37 337854

Magyarország
Ipsen Pharma SAS Magyarországi Kereskedelmi Képviselet
Árbóc utca 6.
H-1133 Budapest
Tel.: + 36 1 555 5930
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.
INSTRUCTIONS FOR USE

INCRELEX should be administered using sterile disposable syringes and injection needles which could be provided by physician / pharmacist / 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](image)

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](image)
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).

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).
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](image)

**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).

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.
Annex IV

Scientific conclusions and grounds recommending the variation to the terms of the Marketing Authorisation
Scientific conclusions

Taking into account the PRAC Assessment Report on the PSUR for mecasermin, the scientific conclusions of CHMP are as follows:

A search of the MAHs Global Safety Database cumulative to 20 January 2015 identified 1 unique case of treatment emergent femoral epiphysiolyis and 3 unique cases of treatment emergent avascular necrosis (AVN) of the femoral head.

Given (i) the medical importance of AVN, (ii) that AVN is a recognised complication of slipped capital femoral epiphysis (SCFE), (iii) that the risk of SCFE is higher in patients with growth hormone (GH) abnormalities, (iv) and that both SCFE and AVN are noted in Section 4.4 Special warnings and precautions for use and/or Section 4.8 Undesirable effects of UK SmPCs for human Growth Hormone, it is considered necessary to revise the wording of Section 4.4 of the EU SmPC.

Therefore, in view of available data regarding mecasermin, the PRAC considered that changes to the product information were warranted.

Furthermore, the MAH is asked to address this issue in the relevant sections of the EU RMP in the next regulatory procedure affecting the RMP.

The CHMP agrees with the scientific conclusions made by the PRAC.

Grounds recommending the variation to the terms of the Marketing Authorisation

On the basis of the scientific conclusions for mecasermin the CHMP is of the opinion that the benefit-risk balance of the medicinal product containing mecasermin is favourable subject to the proposed changes to the product information.

The CHMP recommends that the terms of the Marketing Authorisation should be varied.