Recombinant IGF1 Therapy In Children With Severe Primary IGF-1 Deficiency (SPIGFD)

Formulated by the UK IGF-1 User’s Group

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Scope Of Guidance – To guide UK pediatric endocrinologists who are considering the use of rhIGF-1 for SPIGFD.

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A. Background
Primary insulin-like growth factor 1 (IGF-1) deficiency is characterized by an inadequate production of IGF-1, in spite of sufficient secretion of growth hormone (GH). This leads to a serious growth disorder. The classic form of severe primary IGF-1 deficiency (SPIGFD) is Laron syndrome, where a genetic defect in the GH receptor (GHR) leads to low or undetectable IGF-1 levels in the body. More recently, genetic abnormalities in the GH signal transduction (STAT5b) and in the IGF-1 gene, which also lead to primary IGF-1 deficiency and very small stature, were described. SPIGFD (height <-3 SD, serum IGF-1 <2.5th centile, GH normal) is a licensed indication by the European Medicines Agency since 2007 for the use of rhIGF-1 in the UK.

B. Treatment objective
Long-term improvement of adult height of children with SPIGFD.

C. Diagnosis of SPIGFD
1. Diagnosis of primary IGF-1 deficiency does not necessarily require a GH stimulation test or an IGF-1 generation test when the presentation is clearly classical (positive family history, consanguineous pedigree, extreme short stature, features of Laron’s syndrome, high baseline GH and low or undetectable IGF-1).
2. In the above classic cases, genetic analysis of GHR is recommended for understanding the condition and confirming the clinical diagnosis. In case of any difficulty in identifying a suitable lab, contact the User Group.
3. In those cases that do not have a mutation in GHR, genetic analysis of other downstream candidate genes may be performed. In these cases, it would be useful to have biochemical data for IGFBP3, ALS and if possible, GHBP. In case of any difficulty in identifying a suitable lab, contact the User Group.
4. Pretreatment serum samples should be stored in local clinical biochemistry departments for later analysis for the above markers if necessary.
5. Children with suspected SPIGFD who do not have the classical features but have abnormal auxology and features of growth failure may need detailed endocrine evaluation including analysis of the GH-IGF-1 axis. This should include a GH stimulation test.
6. An IGF-1 generation test may also be included; however, the clinical utility of this test in reaching a diagnosis of SPIGFD is unclear. A recommended protocol is GH 0.033 mg/kg daily x 4 with IGF-I (± IGFBP-3) before the first injection and 12 hours after the 4th injection.
7. As experience and awareness of SPIGFD increases, it is possible that paediatric endocrinologists may start encountering more cases of SPIGFD that have non-classical clinical or biochemical features. Chronic inflammatory diseases and ongoing systemic therapy with drugs such as glucocorticoids may be associated with secondary IGF1 deficiency and such conditions need to be excluded.
8. It is possible that some children with classical SPIGFD may present late as the extreme short stature may be attributed to failure to thrive or familial short stature.
D. Initiating Therapy
1. Contraindications to rhIGF-1 therapy include hypersensitivity for the active substance or the excipients and active or suspected neoplasia.
2. Given the relative rarity of rhIGF-1 therapy, the patient should be managed by a paediatric endocrinologist with experience of managing children with complex growth disorders.
3. Shared care guidelines would allow involvement of GPs and referring paediatricians (Under development).
4. In those situations where the prescriber is encountering any difficulty in seeking approval, the clinician can approach the Chair or the other members of the User Group. Guidance in building a case for support is currently under development.
5. Initiation of rhIGF-1 therapy may require a short admission, particularly in younger children because of a potential risk of hypoglycaemia.
6. After a starting dose of 40μg/kg bd, aim to increase the dose at regular (for example, weekly) increments to the maintenance dose of 120μg/kg bd by around 3 months.
7. After an increase in dose, it is advisable to measure capillary blood glucose (CBG) before breakfast and evening meal, coinciding with the injections, for at least 2 days.
8. RhIGF-1 should be administered shortly 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, no rhIGF-1 should be administered.
9. Following informed consent, children on rhIGF-1 should be entered onto the web-based post-marketing surveillance Registry.
10. Children and their parents should be provided with an information leaflet and any other educational aids that may be available.
11. The following list details procedures and checks that need to be considered at baseline.

<table>
<thead>
<tr>
<th>Baseline assessment</th>
<th>Standard</th>
<th>Optional</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enter patient on IGFD Register</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Physical examination: height, weight, sitting height, pubertal stage, blood pressure, fundoscopy, tonsils</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Echocardiography</td>
<td>+</td>
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<tr>
<td>Bone age</td>
<td>+</td>
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<tr>
<td>Photograph of the face (frontal and lateral)</td>
<td>+</td>
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<tr>
<td>Dietary advice</td>
<td>+</td>
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<tr>
<td>First injection as in-patient</td>
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<tr>
<td>Fasting cholesterol (HDL, LDL and total), triglycerides</td>
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<tr>
<td>DXA – whole body and lumbar spine</td>
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<td>+</td>
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<tr>
<td>Arrange home care and nursing support</td>
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<td>+</td>
</tr>
</tbody>
</table>

E. Maintenance of Therapy
1. Clinic visits should occur 3-4 monthly and an annual review should be performed.
2. Clinic visits should enquire of the targeted adverse events (TAE) listed below and should be reported through the yellow card scheme as well as the IGFD Registry
   - Hypoglycaemia
   - Lymphoid Hyperplasia
   - Intracranial hypertension
   - SCFE
   - Scoliosis
   - Coarsening of face
   - Allergic reaction
   - Lipohypertrophy
   - Hypoacusis
   - Tachycardia
   - Overweight
   - Hyperandrogenism
   - Cardiac hypertrophy
3. More detailed assessment may be required in those cases where clinical history is positive, for instance, a clinical history of sleep disordered breathing may require pulse oximetry or sleep studies.
4. Routine measurement of serum IGF-1 is not advised but may be useful in those cases where adherence to therapy is questionable.
5. Hypoglycaemia is defined as capillary blood glucose testing as less than 3.5mmol or symptoms of hypoglycaemia.
6. Dietary advice needs to be considered at an early stage if there are concerns about lack of weight gain or excessive weight gain.
7. Regular nursing support should be considered to check injection technique and ensure adherence.
8. Involvement of occupational therapy and clinical psychology may need to be considered in those cases where marked short stature persists despite therapy.
9. GnRH agonist therapy may be indicated in pubertal children who are markedly short and in who have not had a sufficiently long period of treatment with rhIGF-1. There is little evidence for the efficacy of this regimen in this context for improving growth and final height and treatment may be guided by the personal preferences of the young person.
10. Treatment with rhIGF-1 should be reconsidered if after a year the patient has an increase in height velocity of less than 30%.
11. The following tests are recommended to be performed at clinic visits and/or annually.

<table>
<thead>
<tr>
<th>Test</th>
<th>Every Clinic Visit</th>
<th>Annually</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enter data on IGFD Register</td>
<td>+</td>
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</tr>
<tr>
<td>Physical examination: height, weight, sitting height, pubertal stage, blood pressure, fundoscopy, tonsils</td>
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<tr>
<td>Echocardiography</td>
<td>+</td>
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<tr>
<td>Bone Age</td>
<td>+</td>
<td></td>
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<tr>
<td>Examination of injection sites</td>
<td>+</td>
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<tr>
<td>Photograph of the face (frontal and lateral)</td>
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<td></td>
</tr>
<tr>
<td>DXA – whole body and lumbar spine*</td>
<td>+</td>
<td></td>
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<tr>
<td>Audiology*</td>
<td>+</td>
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</tbody>
</table>

* These investigations are not considered to be standard but may provide objective data on changes in hearing and body composition

**G. Further Details Of TAEs**

1. RhIGF-1 can have insulin-like hypoglycaemic effects. Special attention should be paid to young children, children with a history of hypoglycaemia or children with an irregular eating pattern. At the start of the treatment, strenuous activities 2 to 3 hours following the administration of rhIGF-1 should be avoided, until a well-tolerated dose is determined. The frequency of hypoglycaemia is the highest in the first month of treatment. Parents should be educated about symptoms of hypoglycaemia and on its management.

2. The use of rhIGF-1 has been associated with hypertrophy of the lymphoid tissue (adenoids and tonsils), notably in the first 1 to 2 years of treatment. In case of a medical history suspected for adenoid or tonsil hypertrophy (snoring, poor feeding pattern, apnoea, reduced hearing) or associated physical examination, an ENT specialist should be consulted.

3. Intracranial hypertension, associated with papilloedema, visual changes, headache, nausea and/or vomiting have been reported. If this is diagnosed, rhIGF-1 should be stopped. These symptoms disappear after discontinuing rhIGF-1, which can be restarted using a lower dose initially after the symptoms and signs have disappeared.

4. In case of fast growth, SCFE and progression of scoliosis can occur, associated with limping or pain.

5. Coarsening of the face has been observed and can be documented by regular photographs.

6. Local or systemic allergic reactions may occur. In post-marketing experience, cases of hypersensitivity, urticaria, pruritis and erythema have been reported, both as systemic and/or local to the injection site. A small number of cases indicative of anaphylaxis requiring hospitalisation have been reported. Patients and parents should be informed of this, and that if a systemic allergic reaction occurs, treatment should be interrupted and prompt medical attention should be sought. Antibodies against the injected IGF-1 may be produced. In case of suspicion of antibody formation, the Ipsen Medical Information Department should be contacted for antibody testing on 01753 627777 or medical.information.uk@ipsen.com.
7. Lipohypertrophy of the injection site usually occurs when injection sites are not alternated appropriately.
8. Adverse events should be recorded within the IGFD Registry. In addition, reporting forms and information regarding reporting to the MHRA can be found at www.yellowcard.gov.uk. Adverse events should also be reported to the Ipsen Medical Information department on 01753 627777 or medical.information.uk@ipsen.com

H. Literature


7. www.medicines.org.uk/EMC/medicine/20054/SPC/Increlex+10mg+ml+solution+for+injection/Template letter


I. The UK IGF-1 User’s Group
The group consists of consultant paediatric endocrinologists and specialist paediatric endocrine nurses who are currently treating a child with rhIGF-1. The group held its first meeting in Feb 2010 and aims to meet twice a year. The general remit of the group is to maintain high standards of practice in the field of rhIGF-1 therapy. Its meetings are used to:-
• Discuss new cases of SPIGFD
• Develop a uniform system of assessment and monitoring of cases
• Provide a summary of all the UK cases of SPIGFD that are on the IGFD Register
• Discuss practical issues around diagnosis, initiating treatment and supporting the child and family

Membership Of The IGF-1 User’s Group:-
Prof Faisal Ahmed, Glasgow (Chair), Dr Rakesh Amin, London, Dr Charles Buchanan, London, Dr Louise Denvir, Nottingham, Dr Khalid Hussain, London, Dr Helen Johnstone, Newcastle, Sr Ethel McNeil, Glasgow, Dr Talat Mushtaq, Leeds, Dr Leena Patel, Manchester, Dr Stephen Rose, Birmingham, Prof Martin Savage, London, Dr Nick Shaw, Birmingham, Sr Amanda Whitehead, Leeds, Dr Caroline Brain, London, Dr Mo Didi/Jo Blair, Liverpool

The group is grateful for the support of Ipsen UK.

Appendix 1 – Summary of Product Characteristics for Increlex
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*.

Excipients:
One ml contains 9 mg of benzyl alcohol.
For a full list of excipients, see section 6.1.

3. **PHARMACEUTICAL FORM**

Solution for 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 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.

The dose should be individualised for each patient. The recommended starting dose of mecasermin is 0.04 mg/kg twice daily by subcutaneous injection. If no significant treatment-related adverse events 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 subject, 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.

INCRELEX should be administered 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 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.

INCRELEX is not recommended for use in children below age 2 due to a lack of data on safety and efficacy (see section 5.1).

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

Intravenous administration.

Active or suspected neoplasia. Therapy should be discontinued if evidence of neoplasia develops.

Benzyl alcohol 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 agents 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 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 hospitalization 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, follow the instructions for antibody testing.

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.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Pregnancy and lactation

A negative pregnancy test and education about adequate contraception are recommended for all women of child bearing potential prior to treatment with INCRELEX.

There are no adequate data for the use of mecasermin in pregnant women.

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

INCRELEX should not be used during pregnancy unless clearly necessary.

Breast-feeding while taking INCRELEX is not recommended.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed. However, hypoglycaemia may impair the ability to drive or use machines.
4.8 Undesirable effects

An integrated safety database from clinical studies contains 76 subjects with severe Primary IGFD treated for a mean duration of 4.4 years and representing 321 subject-years.

Hypoglycaemia is the most frequently reported adverse drug reaction. The thirty-six subjects (47%) who had one or more episodes of hypoglycaemia included 4 subjects who had hypoglycaemic seizure on one or more occasion. Of the 36 subjects, 12 (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 occurred in 24 subjects (32%). This reaction was generally associated with lack of proper rotation of injections. When injections were properly dispersed, the condition resolved.

Tonsillar hypertrophy was noted in 12 (16%) subjects, particularly in the first 1 to 2 years of therapy with lesser tonsillar growth in subsequent years.

Snoring, generally beginning in the first year of treatment, was reported in 17 subjects (22%).

Hypoacusis was reported in 15 subjects (20%).

Intracranial hypertension 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.

During clinical trials in other indications totalling approximately 300 patients, reports of local and/or systemic hypersensitivity were received for 8% of patients. All cases were mild or moderate in severity and none was serious.

As with all protein pharmaceuticals, 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.

Table 1 contains very common (≥ 1/10) and common (≥ 1/100 to < 1/10) adverse reactions for which there is at least a reasonable suspicion of a causal relationship to INCRELEX treatment which occurred in clinical trials. Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.
<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>Adverse Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Common</td>
</tr>
<tr>
<td>Investigations</td>
<td>Cardiac murmur, abnormal tympanometry, abnormal echocardiogram, increased alanine aminotransferase*, increased aspartate aminotransferase*, increased weight</td>
</tr>
<tr>
<td>Cardiac Disorders</td>
<td>Cardiomegaly, ventricular hypertrophy, atrial hypertrophy*, tachycardia, tachycardia paroxysmal*, mitral valve incompetence*, tricuspid valve incompetence*</td>
</tr>
<tr>
<td>Congenital, Familial and Genetic Disorders</td>
<td>Congenital jaw malformation, pigmented naevus*</td>
</tr>
<tr>
<td>Blood and Lymphatic System Disorders</td>
<td>Thymus hypertrophy</td>
</tr>
<tr>
<td></td>
<td>Lymphadenopathy*</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td>Headache</td>
</tr>
<tr>
<td></td>
<td>Convulsions, febrile convulsion*, benign intracranial hypertension, loss of consciousness*, sleep apnoea syndrome, dizziness, tremor*, restless leg syndrome*</td>
</tr>
<tr>
<td>Eye Disorders</td>
<td>Papilloedema, reduced visual acuity*, myopia*</td>
</tr>
<tr>
<td>Ear and Labyrinth Disorders</td>
<td>Hypoacusis</td>
</tr>
<tr>
<td></td>
<td>Otorrhoea, ear disorder*, middle ear disorder*, tympanic membrane disorder*, ear pain, ear congestion*, fluid in middle ear</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal</td>
<td>Tonsillar hypertrophy, snoring</td>
</tr>
<tr>
<td>Disorders</td>
<td>Adenoidal hypertrophy, nasal turbinate hypertrophy*, dyspnoea*, nasal mucosal disorder*, obstructive airway disorder*, abnormal respiration*, nasal congestion, mouth breathing</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Adverse Reaction</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td>Vomiting, retching*, abdominal pain*, upper abdominal pain*, abdominal distension*, dysphagia*</td>
</tr>
<tr>
<td>Renal and Urinary Disorders</td>
<td>Nephrolithiasis*, hydronephrosis*, renal colic*</td>
</tr>
<tr>
<td>Skin and Subcutaneous Tissue Disorders</td>
<td>Skin hypertrophy, acrochordons*, abnormal hair texture*</td>
</tr>
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<td>Arthralgia, pain in extremity, myalgia, scoliosis*, spinal deformity*, soft tissue disorder*, muscle cramp*, flank pain*, musculoskeletal stiffness*</td>
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<td></td>
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<td>Surgical and Medical Procedures</td>
<td>Adenotonsillectomy*, adenoidecctomy, ear tube insertion</td>
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<tr>
<td>General Disorders and Administration</td>
<td>Injection site hypertrophy</td>
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<tr>
<td>Site Conditions</td>
<td>Mucosal membrane hyperplasia, hypertrophy, injection site pain, injection site bruising, injection site fibrosis*, injection site reaction*, injection site swelling*, injection site induration*, injection site pigmentation changes*, mucosal oedema*, asthenia*, lethargy*, chest discomfort*</td>
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<tr>
<td>Reproductive System and Breast Disorders</td>
<td>Gynaecomastia, ovarian cyst*</td>
</tr>
<tr>
<td>System Organ Class</td>
<td>Adverse Reaction</td>
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<tr>
<td>---------------------------</td>
<td>----------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td>Depression*, sleep terror, nervousness, abnormal behaviour*, disorientation*</td>
</tr>
</tbody>
</table>

* = occurred in only 1 subject (1%)

The following 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.

- **Systemic hypersensitivity:** anaphylaxis, generalized urticaria, angioedema, 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.
- **Local allergic reactions at the injection site:** pruritis, urticaria.

### 4.9 Overdose

No case of overdose has been reported.

Acute overdose could lead to hypoglycaemia. Long-term overdose may result in signs and symptoms of acromegaly or gigantism.

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.

### 5. PHARMACOLOGICAL PROPERTIES

#### 5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Somatropin and agonists, ATC code: H01AC03

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 (EMEA) will review any new information which may become available every year and this SPC will be updated as necessary.

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.

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.
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**

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

<table>
<thead>
<tr>
<th>Height Velocity (cm/yr)</th>
<th>Pre-Tx</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
<th>Year 7</th>
<th>Year 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>59</td>
<td>59</td>
<td>54</td>
<td>48</td>
<td>39</td>
<td>21</td>
<td>20</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.8 (1.8)</td>
<td>8.0 (2.2)</td>
<td>5.8 (1.4)</td>
<td>5.5 (1.9)</td>
<td>4.7 (1.4)</td>
<td>4.7 (1.6)</td>
<td>4.8 (1.5)</td>
<td>4.6 (1.5)</td>
<td>4.5 (1.2)</td>
</tr>
<tr>
<td>Mean (SD) for change from pre-Tx</td>
<td>+5.2 (2.6)</td>
<td>+3.0 (2.3)</td>
<td>+2.6 (2.3)</td>
<td>+1.6 (2.1)</td>
<td>+1.5 (1.8)</td>
<td>+1.5 (1.7)</td>
<td>+1.0 (2.1)</td>
<td>+0.9 (2.4)</td>
<td></td>
</tr>
<tr>
<td>P-value for change from pre-Tx [1]</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0015</td>
<td>0.0009</td>
<td>0.0897</td>
<td>0.2135</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Height Velocity SDS</th>
<th>Pre-Tx</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
<th>Year 7</th>
<th>Year 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>59</td>
<td>59</td>
<td>53</td>
<td>47</td>
<td>38</td>
<td>19</td>
<td>18</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-3.3 (1.7)</td>
<td>1.9 (2.9)</td>
<td>-0.2 (1.6)</td>
<td>-0.3 (2.0)</td>
<td>-0.7 (1.9)</td>
<td>-0.6 (2.1)</td>
<td>-0.4 (1.4)</td>
<td>-0.4 (1.9)</td>
<td>-0.3 (1.8)</td>
</tr>
<tr>
<td>Mean (SD) for change from pre-Tx</td>
<td>+5.1 (3.1)</td>
<td>+3.2 (2.2)</td>
<td>+3.1 (2.4)</td>
<td>+2.5 (2.1)</td>
<td>+2.5 (2.2)</td>
<td>+2.7 (2.1)</td>
<td>+2.5 (2.1)</td>
<td>+2.8 (2.7)</td>
<td></td>
</tr>
<tr>
<td>P-value for change from pre-Tx [1]</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>0.0001</td>
<td>0.0003</td>
<td>0.0041</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Height SDS</th>
<th>Pre-Tx</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Year 4</th>
<th>Year 5</th>
<th>Year 6</th>
<th>Year 7</th>
<th>Year 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>62</td>
<td>62</td>
<td>57</td>
<td>51</td>
<td>41</td>
<td>22</td>
<td>20</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-6.7 (1.8)</td>
<td>-5.9 (1.7)</td>
<td>-5.6 (1.8)</td>
<td>-5.3 (1.8)</td>
<td>-5.3 (1.8)</td>
<td>-5.5 (1.8)</td>
<td>-5.4 (1.8)</td>
<td>-5.2 (1.9)</td>
<td>-5.2 (1.9)</td>
</tr>
<tr>
<td>Mean (SD) for change from pre-Tx</td>
<td>+0.8 (0.5)</td>
<td>+1.1 (0.8)</td>
<td>+1.4 (1.0)</td>
<td>+1.4 (1.1)</td>
<td>+1.4 (1.3)</td>
<td>+1.4 (1.2)</td>
<td>+1.4 (1.1)</td>
<td>+1.6 (1.1)</td>
<td></td>
</tr>
<tr>
<td>P-value for change from pre-Tx [1]</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td>0.0001</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

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.

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.

**Metabolism**

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

**Excretion**

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.

**CHARACTERISTICS IN SPECIAL POPULATIONS**

**Geriatric**

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 insufficiency**

No studies have been conducted in children with renal impairment.

**Hepatic insufficiency**

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:

Reproductive toxicity

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.

Carcinogenesis

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

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.

6.5 Nature and contents of container

4 ml of solution in a 5 ml vial (type I glass) closed with a latex-free 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 sterile solution with preservative for multiple use.

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.

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

10. DATE OF REVISION OF THE TEXT
ANNEX II

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER
A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURING AUTHORISATION HOLDER 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(s) responsible for batch release

Beaufour Ipsen Industrie
Rue d'Ethe Virton
28100 Dreux
France

B. CONDITIONS OF THE MARKETING AUTHORISATION

• CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER

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

• 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.

**OTHER CONDITIONS**

*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 product is on the market.

*Risk Management plan*

The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in Version 2 of 1.9. of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation Application and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, the updated RMP should be submitted at the same time as the next Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation activities
- Within 60 days of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the EMEA
C. SPECIFIC OBLIGATIONS TO BE FULFILLED BY THE MARKETING AUTHORISATION HOLDER

The Marketing Authorisation Holder shall complete the following programme of studies within the specified time frame, the results of which shall form the basis of the annual reassessment of the benefit/risk profile.

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 31/12/2011, and subsequent interim reports will be submitted every two years until the final patient is followed for 5 years.
ANNEX III
LABELING AND PACKAGE LEAFLET
A. LABELING
<table>
<thead>
<tr>
<th>PARTICULARS TO APPEAR ON THE OUTER PACKAGING</th>
</tr>
</thead>
<tbody>
<tr>
<td>CARDBOARD BOX</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>1. NAME OF THE MEDICINAL PRODUCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCRELEX 10 mg/ml solution for injection.</td>
</tr>
<tr>
<td>Mecasermin</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. STATEMENT OF ACTIVE SUBSTANCE(S)</th>
</tr>
</thead>
<tbody>
<tr>
<td>One ml contains 10 mg of mecasermin.</td>
</tr>
<tr>
<td>Each vial contains 40 mg of mecasermin.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>3. LIST OF EXCIPIENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other ingredients: benzyl alcohol, sodium</td>
</tr>
<tr>
<td>chloride, polysorbate 20, glacial acetic</td>
</tr>
<tr>
<td>acid, sodium acetate and water for injections.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. PHARMACEUTICAL FORM AND CONTENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Solution for injection.</td>
</tr>
<tr>
<td>One multi-use vial of 4 ml.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. METHOD AND ROUTE(S) OF ADMINISTRATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subcutaneous use.</td>
</tr>
<tr>
<td>Read the package leaflet before use.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Keep out of the reach and sight of children.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>7. OTHER SPECIAL WARNING(S), IF NECESSARY</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>8. EXPIRY DATE</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
<tr>
<td>After first opening, use within 30 days.</td>
</tr>
</tbody>
</table>
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

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 AUTHORISATION 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**

<table>
<thead>
<tr>
<th>1. Name of the Medicinal Product and Route(s) of Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>INCRELEX 10 mg/ml injection</td>
</tr>
<tr>
<td>Mecasermin</td>
</tr>
<tr>
<td>SC</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2. Method of Administration</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>3. Expiry Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXP</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>4. Batch Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lot:</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>5. Contents by Weight, by Volume or by Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 ml</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>6. Other</th>
</tr>
</thead>
</table>
B. PACKAGE LEAFLET
INCRELEX 10 mg/ml solution for injection
Mecasermin

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, please ask the doctor or pharmacist.
- This medicine has been prescribed for you/your child. Do not pass it on to others. It may harm them, even if their symptoms are the same.
- If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell the doctor or pharmacist.

In this leaflet:

1. What INCRELEX is and what it is used for
2. Before you use INCRELEX
3. How to use INCRELEX
4. Possible side effects
5. How to store INCRELEX
6. Further information

1. WHAT INCRELEX IS AND WHAT IT IS USED FOR

- INCRELEX is a liquid that contains 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 or adolescents 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. BEFORE YOU USE INCRELEX

Do not use INCRELEX
- if you/your child is allergic (hypersensitive) to mecasermin or any of the other ingredients of INCRELEX.
- if you/your child has cancer.
- by injecting directly into a vein.
- Benzyl alcohol must not be given to premature babies or neonates.

Take special care with INCRELEX
- if you/your child has a curved spine (scoliosis). They should be monitored for progression of their scoliosis.
- if you/your child has enlarged tonsils (tonsillar hypertrophy). They should have examinations periodically.
- if you/your child has symptoms of increased pressure in the brain (intracranial hypertension), such as headache with vomiting, contact the doctor for advice.
- if you/your child has a localised reaction at the injection site or generalised allergic reaction with INCRELEX. Call the doctor as soon as possible if you/your child get a localised rash. Get medical help immediately if you/your child has a generalised allergic reaction (hives, trouble breathing, faintness or collapse and feeling generally unwell).
- if you/your child has finished growing (the bone growth plates are closed).
- the use of INCRELEX has not been studied in children under 2 years of age and is therefore not recommended.
Using other medicines

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

Please tell the doctor or pharmacist if you/your child is taking or has recently taken any other medicines, including medicines obtained without a prescription, herbal medicines and vitamin supplements.

Taking INCRELEX with food and drink

INCRELEX should be administered shortly before or after eating, because it may have insulin-like hypoglycaemic effects and so it may decrease blood sugar levels.

The doses should be withheld when a meal or snack is omitted. The dose should never be increased to make up for one or more omitted doses.

Pregnancy and breast-feeding

INCRELEX therapy should be discontinued if pregnancy occurs.

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

Driving and using machines

No studies of the effects of INCRELEX on the ability to drive and use machines have been performed. However, hypoglycaemia may impair the ability to drive and use machines.

Patients should avoid engaging in any high-risk activities (e.g., driving, etc.) within 2-3 hours after dosing, particularly at the initiation of INCRELEX treatment, until a dose of INCRELEX has been established without occurrence of significant treatment-related adverse events.

Important information about some of the ingredients of INCRELEX

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

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

3. HOW TO USE INCRELEX

Always use INCRELEX exactly as your/your child’s doctor has told you. You should check with your/your child’s 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/your child’s skin shortly before or after a meal or snack. Do not give you/your child’s dose of INCRELEX if you/your child cannot eat for any reason. Do not make up the missed dose by giving two doses the next time.

Inject INCRELEX just below the skin in your/your child’s 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

If more INCRELEX than recommended was injected, please tell the doctor.

Acute overdosage 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 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 product, ask the doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, INCRELEX can cause side effects, although not everybody gets them.

If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell the doctor or pharmacist.

The very common side effects (likely to occur in more than 1 out of 10 patients) which occurred in clinical trials are listed below.

Hypoglycaemia (Low Blood Sugar):
INCRELEX, like insulin, 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 or death. If you/your child take INCRELEX, you/your child 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/your child 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/your child is 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/your child have a well-balanced diet including protein and fat such as meat and cheese in addition to sugar-containing foods.

Increased blood sugar has also been observed with INCRELEX treatment.
Reactions at the Injection Site:
Injecting INCRELEX can cause local lipoatrophy (loss of fat), lipohypertrophy (increase of fat), or pain, redness or bruising at the injection site. Injection site reactions can be avoided by changing the injection site at each injection (injection site rotation).

Enlarged tonsils:
INCRELEX may enlarge you/your child’s tonsils. Some signs of enlarged tonsils 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/your child. An infection of the tonsils has also been observed. The doctor should regularly examine your/your child’s tonsils. Swelling inside the nose, enlarged thymus and lymph nodes have been seen with INCRELEX treatment.

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

The common side effects (likely to occur in fewer than 1 out of 10 patients) which occurred in clinical trials are listed below.

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.

Intracranial hypertension (increased pressure in the brain):
INCRELEX, like growth hormone, can sometimes cause a temporary increase in pressure within the brain. The symptoms of intracranial hypertension can include headache and nausea with vomiting. Tell the doctor if you/your child has headache with vomiting. 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.

Vision disturbances have also been reported.

Slipped capital femoral epiphysis:
This is a situation where the top of the upper leg (femur) slips apart. Get medical attention for you/your child immediately if you/your child develops a limp or has hip or knee pain.

Worsened scoliosis (caused by rapid growth):
If you/your child has scoliosis, you/your child 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 pain, difficulties swallowing, retching and vomiting have occurred with INCRELEX treatment. Weight gain has 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.

Other reported adverse events include lack of energy, depression, nervousness, disorientation, chest discomfort, dizziness, trembling and restless legs.

During post-marketing experience the following adverse events have been reported: serious allergic reactions (anaphylaxis) which can cause generalised hives, difficulty in breathing, dizziness, swelling of the face and/or throat. Local allergic reactions at the injection site (itching, hives) have also been reported. The frequency of these events occurring cannot be estimated from the available data. Tell the doctor if you/your child develops serious allergic reactions.

5. **HOW TO STORE INCRELEX**

Keep out of the reach and sight of children.

Do not use INCRELEX 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.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **FURTHER 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 supplied in a glass vial closed with a stopper and a seal. The vial contains 4 ml of liquid.

INCRELEX is supplied as a pack containing one glass vial.

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This leaflet was last approved 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 (EMEA) will review any new information on the medicine every year and this leaflet will be updated as necessary.

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

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INSTRUCTIONS FOR USE

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.

Preparing the Dose:

1. Wash your hands before getting INCRELEX ready for your/your child’s 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. Never share needles and syringes.

3. Check the liquid to make sure it is clear and colourless. Do not use after the expiry date or if it is cloudy or if you see particles. If a vial freezes, dispose appropriately.

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).

![Figure 4: Tip in liquid](image1)

![Figure 5: Extract correct dose](image2)

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](image3)
10. Remove the needle from the vial. 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/your child is 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).

   - Upper arm
   - Thigh
   - Buttock
   - Abdomen

2. Use alcohol or soap and water to clean the skin where you are going to inject you/your child. 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](image)

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/your child 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](image)

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.